Global Burden and Significance of Multiple Micronutrient Deficiencies in Pregnancy

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Abstract

Maternal mortality, low birthweight infants and childhood stunting continue to be major global public health problems, part of a recurring cycle of disadvantage. Maternal undernutrition in particular is one of the most neglected aspects of nutrition in public health. One possible low-cost public health intervention that might help address these problems is the antenatal provision of multiple micronutrient supplements. If the evidence base could be established, cost-effectiveness found to be acceptable and safety ensured, supplementation could ameliorate the impact of poor nutrition and diets, high disease burdens and the sociocultural factors contributing to these problems. There have been good studies in over a dozen countries addressing some of these issues but with conflicting results. Consequently, at least three meta-analyses have been undertaken to establish significant findings that could help guide policies and programs. They concluded that multimicronutrient supplementation improves birthweight and likely reduces the number of infants born low birthweight. Supplementation with iron-folic acid or multimicronutrients also appears to have positive longer-term impacts on the health and development of the offspring. There remain concerns about possible increased infant mortality in some populations. Given the results of the meta-analyses, cautious scaling-up of country effectiveness trials appears justified with careful monitoring and evaluation.

Introduction

High levels of maternal mortality, infants of low birthweight (LBW) and childhood stunting remain major public health problems, especially in resource-
Micronutrient Deficiencies in Women of Reproductive Age

Concurrent deficiencies of micronutrients are well documented among young pregnant women (and young children), especially in low- and moderate-income countries [3–5]. The commonest deficiency is iron, but often there is at least one other deficiency [4]. These deficiencies in maternal micronutrient status are a result of poor-quality diets, high fertility rates, repeated pregnancies, and short inter-pregnancy intervals, increased physiological needs, as well as inadequate health systems with poor capacity, poverty and inequities, and sociocultural factors such as early marriage and adolescent pregnancies and some traditional dietary practices [6]. A systematic review identifying all studies that had been published between 1988 and 2008 reporting on micronutrient intakes in women living in resource-poor environments showed that, except for vitamin A (29%), vitamin C (34%), and niacin (34%), the reported mean/median intakes in over 50% of the studies were below the estimated average requirements, demonstrating that inadequate intakes of multiple micronutrients are common amongst women living in resource-poor settings [7], including urban settings [8].

Data on vitamin and mineral metabolism and requirements during pregnancy are surprisingly imprecise, largely because of the complexity of maternal metabolism during pregnancy. Requirements for many, but not all, micronutrients increase during pregnancy. Studies of micronutrient status in adolescents, including when pregnant, have found poor micronutrient intakes and status [9], including in the UK [10], and increased risk of small for gestational age (SGA) and LBW infants at birth [6].
Global Burden

Information on the burden of diseases can help countries assess their comparative importance in causing premature death, loss of health and disability, and so assist countries in deciding health policies and programs [11]. Although the numbers of pregnant women affected by micronutrient deficiencies, especially iron deficiency and anemia, are considerable, the actual global burden of multiple micronutrient deficiencies during pregnancy has not been estimated [3, 11]. It would be difficult to estimate as the burden rests not only on women’s mortality, morbidity and reproductive health outcomes [1], but also inter-generational effects that affect both the mother and her neonate’s immediate burden and that of her children, especially in terms of intellectual and physical development and the later incidence of noncommunicable diseases [5, 12–16].

The micronutrients, for which the global burden is reported upon, are iodine deficiency, vitamin A deficiency, and iron deficiency anemia, and an estimate for zinc has also been made [3, 11]. However, while the numbers of those affected may be great, e.g. up to two billion for iron deficiency or those living in areas of poor iodine availability, the burden (as measured by disability-adjusted life years – DALYs) on women of child-bearing age (15–59 years) is limited. Except for anemia, most of the impact is on the infants and children, e.g. the number of child deaths attributed to zinc, vitamin A and iron deficiencies was estimated in 2002 to be 19% of all child deaths or just over two billion children [3]. In total, micronutrient deficiencies were estimated in the 2002 World Health Report to cause about 6% of global DALYs [3]. Since then, progress has continued to be made in the prevention and control of iodine deficiency and vitamin A deficiency, where the burden of disease for females caused by iodine and vitamin A deficiency is only 0.2% and 0.0% of the global total of DALYs, respectively [3, 11]. By contrast, little progress has been made with iron deficiency, and estimates attribute it causing a fifth of early neonatal mortality and a tenth of maternal mortality, along with the additional morbidity of reduced cognitive development in children and work performance in adolescents and adults. About 800,000 deaths and 2.4% of global DALYs were attributed to iron deficiency in 2002 [3] with the global figures, based on 2004 estimates, in table 1, with updated figures due this year (2011) [11].

Although the global burden for reproductive-aged women from deficiencies of a range of vitamins and minerals is not estimated as such, WHO does give estimates of the three most prevalent micronutrient deficiencies by gender and by WHO region, and which show marked differences. The impact on women of poor micronutrient status is double that of males, and is far greater in low-income countries, so that the burden (as measured by DALYs) of iron deficiency anemia in low-income countries e.g. is 12.5 times that of high-income countries [11]. In the eastern Mediterranean, South Asia (SEAR) and Sub-Saharan Africa (AFR), 3 out of every 10 deaths are due to ‘communicable, reproductive or nutritional
conditions’ [11]. Most of the deaths from iron deficiency anemia in women (15–59 years) occur in low-income countries (about 70,000 poorer women annually to virtually none in high-income countries) contributing an estimated 5,792,000 DALYs (or about 1.6%) [11]. By region, SEAR bears 4.1% of the global burden for iron deficiency anemia, 3.8% in the eastern Mediterranean and 3.0% in AFR. The burden of maternal conditions in AFR and SEAR is responsible for 8% of the total global burden in women aged 15–59 years [11]. Almost all of this loss of healthy years of life is avoidable. In equivalent years of healthy life lost for women from anemia, the number in low- and middle-income countries for women is 2.4% or 7.4 million women [11]. There is no information on the probably fairly small contribution to the global burden of disease from other micronutrients of public health importance such as folate, vitamin B12 and other B vitamins and selenium, although the total number of women deficient in two or more of these is considerable, e.g. 46% of rural Ethiopian women are said to have folate deficiency.

Another way of looking at this is the global burden of prematurity and LBW (to which maternal nutrition and health contribute importantly), which is 2.9% of total DALYs, and which again rises to 3.9% in low-income countries [11].

### Table 1.

Deaths and burden of disease (as measured by DALYs) as percent of total deaths and total DALYs, by nutritional cause and by female sex (based on [3] and tables A1, A2, and A5a in Annexes of WHO [11])

<table>
<thead>
<tr>
<th>Nutritional cause</th>
<th>Deaths as % of total (n)</th>
<th>Burden by DALYs as % of total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>both sexes¹</td>
<td>females²</td>
</tr>
<tr>
<td>Protein-energy malnutrition</td>
<td>0.4 (251)</td>
<td>0.4 (16)</td>
</tr>
<tr>
<td>Iodine deficiency</td>
<td>0.0 (5)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Vitamin A deficiency</td>
<td>0.0 (17)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>0.3 (153)</td>
<td>0.4 (55)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate total numbers in thousands.

¹ Includes children.

² For numbers only – age range for females is 15–59 years.

### Significance

The significance of this likely relatively large burden (in numbers if not percentages of total) due to multiple micronutrient deficiencies is that it is heavily weighted against women and especially those in low-income countries. In resource-poor settings where diagnosis and treatment may be difficult to access, solutions are likely to need a large public health component approach [6]. Because LBW is associated with higher infant mortality rates, stunting and impaired intellectual

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development, there is a need to shift, at a population level, the whole birthweight curve towards adequate weight in low and middle-income countries [6]. The risks in doing this are likely to have been overemphasized, but it still means that health service improvements and sufficient monitoring and evaluation need to be strengthened, along with maternal antenatal nutritional interventions [17].

**Multimicronutrient Supplementation**

Over the last decade, there have been studies in at least 12 countries testing the impact of antenatal micronutrient supplementation [6], and at least four meta-analyses [12, 14, 15, 18]. However, the many confounding factors, different epidemiological environments and diverse methodological approaches mean that it remains difficult to have a consistent body of evidence in order to come to conclusions and make concrete recommendations, although there are some clear directions emerging. While most of the studies and meta-analyses have appropriately guarded conclusions, it has been noted that in public health, action can rarely wait for perfect knowledge [6]. The prevalence of HIV in communities and mothers has provoked a lot of the multiple micronutrient research, using composition of supplements ranging from single micronutrients, iron-folic acid supplements (IFAs) and multiple vitamins and minerals of varying composition and multiples of RNIs/RDAs. Women's stature probably leads to different study results – from the slight, undernourished women of rural Nepal, to the somewhat better nourished women of China, or the underweight but taller women of parts of Africa and so on [6]. Further confusing issues are the measured outcomes e.g. miscarriage rates, fetal deaths, neonatal deaths, size at birth, micronutrient status of the newborn, development of the young child and so on.

**Maternal Impact**

Clinically speaking, iron deficiency and anemia in pregnancy are associated with higher maternal mortality and morbidity, premature delivery, LBW, and iron-deficiency and anemia in infants [19]. Supplementation with iron and folic acid during the antenatal period has long been WHO policy and the policy of most countries. Surprisingly few of the antenatal supplementation studies have looked at the micronutrient status of mothers themselves, but where it has been examined for, there has generally been an improvement in the levels of other micronutrients as well, although not always. Long-term intermittent multiple micronutrient supplementation enhanced hemoglobin and micronutrient status more than IFA in Bangladeshi adolescent girls with nutritional anemia [9]. In the SUMMIT study, there was also a 33% decrease in the number of anemic mothers [20]. One meta-analysis that was done of ten randomized controlled efficacy and effectiveness trials covering 12 countries showed, among other things, supplementation can improve outcomes beyond anemia, including deficiencies.
of other micronutrients and birthweight and that the multiple micronutrients worked as well, if not better, than IFA in terms of reducing anemia [6]. Multiple micronutrient supplementation increased hemoglobin synthesis to the same extent as supplementation with iron or iron-folic acid supplements, although they often contained lower amounts of iron (30 mg as opposed to 60 mg) [4]. Nevertheless, a high prevalence of various micronutrient deficiencies persisted in those receiving the multiple micronutrient supplements [4].

Supplementation with multivitamins has also been shown to reduce morbidity and mortality in non-pregnant HIV-infected women [21]. Another finding in many of the studies was that adolescent girls and women in real-life situations can have very adequate compliance/adherence rates when there are adequate supplies and some support [4, 6, 9, 17].

Neonatal Impact
In an early study in low-income urban US women, supplement use was associated with an approximately twofold reduction in risk of preterm delivery and in overall risk of LBW [22]. However, a Cochrane review in 2005 found that taking vitamin supplements prior to pregnancy or in early pregnancy did not prevent women from experiencing miscarriage or stillbirth, but they were less likely to develop pre-eclampsia, but also more likely to have a multiple pregnancy [23]. In a study of 4,752 US women (of whom 95% self-reported vitamin supplement use in early pregnancy), it was found that any use of vitamins during pregnancy was associated with decreased odds of miscarriage in comparison with no exposure [24]. On the other hand, Alwan et al. [25] in a prospective birth cohort study of UK women in Leeds found that regular multimicronutrient supplement use during pregnancy in a developed country setting, while not associated with size at birth was associated with reduced preterm birth if taken daily in the third trimester. In the context of HIV, a placebo-controlled trial in Tanzania showed that HIV-infected pregnant women who took multivitamins of multiples of RDAs gave birth to fewer low-weight and preterm infants [21]. Interestingly, a recent paper demonstrated that multivitamins at multiple and single doses of the RDA had similar effects on the risk of LBW [21]. An Indian study found that early neonatal morbidity was decreased by 58% [26].

Using three sets of DHS data, an Australian group found that IFA during pregnancy in Indonesia significantly reduced the risk of early neonatal death [27]. In a double-blind cluster-randomized trial in Lombok, where Indonesian women were given multimicronutrient supplements by midwives to be taken daily, their infants had an 18% reduction in early infant mortality compared with those of women given IFAs, and infants of those mothers who were undernourished or anemic at enrollment had a reduction in early infant mortality of 25 and 38%, respectively [20].

However, some important questions remain. Findings from two separate, and different, studies in Nepal showed an increase, not statistically
significant, in the risk of early neonatal mortality associated with the use of multiple micronutrient supplements compared with IFA and vitamin A, but which was significant when the studies were combined [28, 29]. The findings of an increased neonatal mortality have not been supported by at least three of the systematic reviews, as well as by data from other studies in different populations [2, 6, 12]. The meta-analysis of Ronsmans et al. [15] concluded that there was no overall difference in deaths, although when the SUMMIT results were excluded from the analysis because of significant heterogeneity (p < 0.10), there was a statistically higher odds ratio of early neonatal mortality [6]. Nevertheless, overall the meta-analysis reported by the United Nations System Standing Committee on Nutrition (SCN) found no statistically significant differences between infants of mothers supplemented with IFC and those supplemented with multimicronutrients, and noted that increased birthweight has consistently been found to be associated with reduced risk of dying in infancy in other situations [6]. A recent review by Bhutta’s group concluded that there was no significant increase in the risk of neonatal mortality where skilled birth care is available and the majority of births take place in facilities [2], a not common situation in many populations with the greatest prevalence of multiple micronutrient deficiencies.

**Effects on Birthweight**

The meta-analysis reported on by the SCN and others observed a mean increase in birthweight of 22 g (4.9–75.5 across studies), and a reduction in the prevalence of LBW of about 10%, with a larger impact on birthweight in infants of heavier women [6, 14]. There was a positive shift in the entire birthweight distribution, with decreases in the numbers of LBW babies and SGA babies with no differences in birth length or head circumference [6]. It was noted that the small significant increase in mean birthweight among infants of supplemented mothers is of similar magnitude to that produced by food supplementation during pregnancy [6]. Haider and Bhutta in their meta-analysis for the Cochrane review, found a relative risk of 0.84 reduction in LBW compared with iron and folic acid [12]. There was a 14% reduction in LBW with a 33% decrease in anemic mothers in the large Lombok study [20].

Another meta-analysis and systematic review of 13 published trials that included HIV-positive women also found that prenatal multimicronutrient supplementation in resource-poor settings was associated with a significantly reduced risk of LBW by 17–19% and with an improved mean birthweight of 54 g when compared with IFAs [18]. They found no significant effect of the supplementation on the risk of preterm birth or SGA infants [18]. They concluded that: ‘With the possibility of reducing the incidence of low birth weight by 17%. . .providing pregnant women with multimicronutrient supplementation offers the highest possible return for the investment. . .and could avert 1.5 million births of LBW infants globally each year’ [18].
Increases in birthweight with antenatal multiple micronutrient supplementation have now also been found in studies reported since two of the meta-analyses were published but included in that of Shah and Ohlsson [18]. One was with well-nourished French women in a hospital setting where there was an increase in the average birthweight by 251 g as compared with a placebo [Hininger et al., cited in 6]. The other was an Indian study, also hospital-based, of thin women (BMI <18.5), and where the infants of the micronutrient-supplemented mothers group were heavier by a mean 98 g and measured 0.8 cm longer and 0.2 cm larger in mid-arm circumference compared with the placebo group [26]. Incidence of LBW declined from 43.1 to 16.2% with multimicronutrient supplementation (a 70% decrease).

Effects on Infant and Child Development of Maternal Micronutrient Supplementation

Besides the health and well-being of the mother herself, and successful immediate reproductive outcomes, the subsequent health and development of the infant and older child can be clearly affected by the intrauterine environment. Early iron deficiency is known to alter the neuroanatomy, biochemistry, and metabolism in the infant leading to changes in the neurophysiologic processes that support cognitive and motor development [5]. In a long-term study of Finns, there was a direct positive association between Hb levels of the pregnant women and the educational achievement of their children later in life (at 14 and 16 years of age) with also increased odds of having a higher level of education at the age of 31 years [30]. In a rural area of Nepal where iron deficiency is prevalent, aspects of intellectual functioning including working memory, inhibitory control and fine motor functioning among offspring were positively associated with prenatal IFA supplementation [5]. Positive functional and developmental milestones of the Nepalese children whose mothers were supplemented in pregnancy with multiple micronutrients showed small improvements in weight and a decrease in peripheral adiposity after 2 years [5]. Although in several of the studies in Nepal, the addition of other micronutrients or zinc attenuated or negated the impact of the IFA, this is the opposite to a study in China where multimicronutrient prenatal supplementation found modest improved changes in cognitive outcomes compared with IFA [31]. Similarly, in Bangladesh there were small but significant improvements in motor scores and activity ratings compared with mothers receiving iron/folic acid [32]. This was also found for psychomotor but not cognitive development indices of children born to multimicronutrient-supplemented HIV-positive Tanzanian mothers (compared to placebo) [33]. Reductions in subsequent stunting, e.g. in Vietnam, have also been reported [6, 17]. The public health significance of such findings is not yet known, but may be setting these children on a different developmental trajectory that mitigates the risk of chronic disease in adult life [6], a problem that is now greater
in low- and moderate-income countries, and in rural populations as well as urban ones [8, 16].

**Significance for Interventions**

Public health antenatal and obstetric interventions on a larger scale, as the above evidence seems to suggest, would also require monitoring for effectiveness, sustainability and impact. WHO already has recommendations regarding supplementation to improve iron stores in adolescent girls and women before they enter pregnancy in areas where anemia rates are greater than 40%, and more recently a position statement suggested intermittent IFA where the prevalence of anemia in women of reproductive age is greater than 20% [19]. It is also policy to provide HIV-infected pregnant women multiple micronutrients (of a single RDA), and multimicronutrients for pregnant and lactating women in emergency situations have been encouraged in a WHO/WFP/UNICEF statement. Nevertheless, cost-effectiveness has not been established, and neither has there been clear proof that there is an advantage over IFA, although it does seem likely that a lower dose of iron is effective in a multimicronutrient supplement.

There are some other positive aspects. Most of the research appears to be heading in largely the same direction, at least in terms of much improved antenatal maternal care, including supplementation where relatively high adherence rates have been shown to be achievable in field settings where it is emphasized [6, 9, 17]. There is increased policy and donor attention to maternal and early child nutrition and health, including through a wish to achieve the relevant MDGs by 2015. From a public health perspective, the maternal and child nutrition *Lancet* series concluded that effective micronutrient interventions for pregnant women should include supplementation with iron-folic acid, and noted that multiple micronutrients reduced the risk of LBW at term by 16% [34]. There is general agreement that supplementation programs should be part of a larger improvement in antenatal care programs including increased contact, improved nutrition, deworming and access to clinic care and delivery and so on. A very recent review by Haider et al. [35] concluded that there is good evidence ‘of a significant benefit of MMN supplementation during pregnancy on reducing SGA births as compared to iron-folate, with no significant increase in the risk of neonatal mortality in populations where skilled birth care is available and majority of births take place in facilities’. Nevertheless, some outstanding issues remain: the possible increased risk of neonatal mortality in some populations; the appropriate levels of the multiple vitamins and minerals in supplements [6], and issues of cost-effectiveness [13] as interventions are needed that are both efficacious and effective [1]. Nevertheless, taking all the studies together, and with experience in countries such as Indonesia,
Mexico, Vietnam and elsewhere, it is likely that effective distribution and promotion systems can be developed for different target groups and settings [36] ‘in the context of available services in health systems and [with] birth outcomes monitored’ [35].

Conclusions

There are substantial inequalities in maternal and newborn health, and in access to health care. In an ideal world, young women would be born with adequate birthweight, develop appropriately without stunting, and go into their first pregnancy no earlier than 18 years, and be adequately nourished. Their health, sanitation and social support should also be optimal, not least because it seems likely the significantly better survival and other results found in Lombok may well have been due to the attention paid to antenatal services and maternal care in general. In the absence of this happening, all evidence-based, simple and cost-effective measures must be adequately tried in low-resource settings. It has been frequently noted that antenatal supplement with multiple vitamins and minerals is the norm in many affluent countries and often for the affluent in poorer countries. More programmatic information will be coming from the limited number of countries using multiple micronutrient interventions to pregnant women, but these need to be closely monitored. WHO is currently using its new NUGAG process to develop guidance and then policy for recommendations.

Building on the commentaries written around the different meta-analyses, some conclusions might be drawn.

- Deficiencies in micronutrients affect many women of reproductive age, and are associated with adverse maternal and perinatal outcomes and have even longer-term impacts into adulthood
- Micronutrients likely to be important for maternal, infant and child outcomes include iron, vitamin B12, folate, vitamin D and selenium and probably zinc and maybe others (along with appropriate dietary energy intakes)
- In addition to multimicronutrient supplementation, optimal interventions to improve maternal nutrition need to address household food insecurity, reduce the burden of maternal infections such as HIV and malaria, and actively address gender and social disadvantage
- In the meantime, if proven effective and safe in representative health care systems, supplementation with multimicronutrients should replace supplementation with iron and folic acid in vulnerable populations as a way of breaking the intergenerational reality of LBW infants growing up disadvantaged and stunted to repeat the cycle.
References


