Micronutrients and Child Growth: Current Evidence and Progress

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Abstract

Vitamins and minerals are essential for growth and metabolism. The World Health Organization (WHO) estimates that more than 2 billion people are deficient in key vitamins and minerals. Groups most vulnerable to these micronutrient deficiencies are pregnant and lactating women and young children, given their increased nutritional demands. Although direct causal information on the link of micronutrient deficiencies to maternal and fetal malnutrition and child growth is difficult to establish, indirect information related to risk factors and intervention studies does suggest a close relationship between key micronutrients in mothers and children with impaired growth. These include iron, zinc, and multiple micronutrients. Micronutrient deficiency is prevalent in both underweight and obese populations and is linked to pregnancy outcomes. Several strategies are in use globally to address micronutrient deficiencies in children with a focus on survival, but relatively few have addressed growth. These include supplementation as well as food fortification. This presentation will summarize the available global evidence of best practices and strategies, as well as discuss next steps in relation to the Sustainable Development Goals.

Introduction

Micronutrient deficiencies continue to be a major public health concern worldwide, with an estimated 2 billion people [1] not meeting their requirements in essential vitamins and minerals (Table 1) [2, 3]. Also referred to as hidden hunger, micronutrient deficiencies are a form of chronic malnutrition closely linked with impaired growth and development. Expectant mothers and children under
5 years are especially vulnerable given their increased nutritional needs. Maternal undernutrition increases the risk of fetal growth restriction and preterm birth, and thereby perpetuates an intergenerational cycle of malnutrition and poverty. Pregnancy and the first 1,000 days of life, from conception 2 years of age, are considered a sensitive window of opportunity for nutritional interventions to promote optimal growth and development – the benefits of which extend into adulthood.

Despite considerable reductions since 1990, 156 million or 23.2% of children under 5 were still affected by linear growth stunting in 2015, and 43% of children worldwide are at risk of not reaching their developmental potential due to poverty and stunting [4, 5]. This developmental deficit is estimated to result in about

| Table 1. Daily micronutrient requirements for school-age children and adolescents |
|---------------------------------|----------------|----------------|----------------|----------------|
| Micronutrients                  | Male | Female | Pregnancy | Lactation |
| Vitamin A, μg RAE               |      |        |           |            |
| 4–8 years                       | 400  | 400    | 750       | 1,200      |
| 9–13 years                      | 600  | 600    |           |            |
| 14–18 years                     | 900  | 700    | 750       |            |
| Vitamin D, IU                   |      |        |           |            |
| 4–8 years                       | 600  | 600    |           |            |
| 9–13 years                      | 600  | 600    |           |            |
| 14–18 years                     | 600  | 600    |           |            |
| Zinc, mg                        |      |        |           |            |
| 4–8 years                       | 5    | 5      | 12        | 13         |
| 9–13 years                      | 8    | 8      |           |            |
| 14–18 years                     | 11   | 9      | 12        | 13         |
| Iron, mg                        |      |        |           |            |
| 4–8 years                       | 10   | 10     |           |            |
| 9–13 years                      | 8    | 8      |           |            |
| 14–18 years                     | 11   | 15     | 27        | 10         |
| Iodine, μg                      |      |        |           |            |
| 4–8 years                       | 90   | 90     | 220       | 290        |
| 9–13 years                      | 120  | 120    |           |            |
| 14–18 years                     | 150  | 150    | 220       |            |
| Vitamin B12, μg                 |      |        |           |            |
| 4–8 years                       | 1.2  | 1.2    | 2.6       | 2.8        |
| 9–13 years                      | 1.8  | 1.8    |           |            |
| 14–18 years                     | 2.4  | 2.4    | 2.6       | 2.8        |
| Folate, μg                      |      |        |           |            |
| 4–8 years                       | 200  | 200    |           |            |
| 9–13 years                      | 300  | 300    |           |            |
| 14–18 years                     | 400  | 400    | 600       | 500        |

IU, international units; RAE, retinol activity equivalents.
a 25% annual reduction in income-earning potential in adulthood, illustrating the consequences of poor development on human capital [6]. Asia and Africa bear the greatest burden of malnutrition; in 2015, 56 and 37% of stunted children lived in Asia and Africa, respectively [4]. Stunting also disproportionately affects children living in the poorest population quintiles and those in rural and remote communities [1]. The urgent need to address malnutrition is reflected in the second Sustainable Development Goal, which sets global targets for eliminating hunger, improving nutritional status, and supporting food security [7].

This chapter discusses key micronutrient interventions to promote growth and development, and touches on widely implemented strategies for transferring micronutrient interventions to women and children.

**Definitions**

Key definitions relating to infant and child growth include:

- **Intrauterine growth restriction (IUGR):** the pathological inhibition of fetal growth; indicators of IUGR include small for gestational age (SGA) and low birth weight (LBW)
- **SGA:** birth weight <10th percentile of recommended gender-specific weight for gestational age of a reference population
- **LBW:** birth weight <2,500 g, irrespective of gestational age
- **Stunting:** moderate-severe – below −2 standard deviations from median height-for-age of a reference population
- **Wasting:** moderate-severe – below −2 standard deviations from median weight-for-height of a reference population

**Preconception and Prenatal Micronutrient Interventions**

In this section, we outline micronutrient interventions delivered during the preconception and prenatal period that promote child growth. Table 2 and Figure 1 summarize the effect sizes and risk factors associated with each micronutrient intervention, respectively.

**Maternal Folic Acid, Iron, and Multiple Micronutrient Supplementation**

The delivery of micronutrient interventions before conception and during pregnancy is crucial to supporting optimal trajectories for growth and development. Globally, an estimated 40% of women between 15 and 49 years have anemia [8]. Neural tube defects arise from folate deficiency during embryonic development,
and periconceptional folic acid supplementation for women of reproductive age has been shown to prevent these neural tube defects (relative risk, RR, 0.31, 95% confidence interval, CI, 0.17–0.58; 5 trials) when compared with no intervention, placebo, or other micronutrients [9]. Additionally, supplementation of folic acid during the prenatal period has been shown to increase birth weight (mean difference, MD 135.76, 95% CI 47.85–223.68; 5 trials) [10].
Expectant mothers are especially susceptible to anemia due to heightened caloric and micronutrient requirements during pregnancy. Iron-containing supplementation during pregnancy can effectively reduce the risk of both iron deficiency (RR 0.43, 95% CI 0.27–0.66; 7 trials) and anemia (RR 0.30, 95% CI 0.19–0.46; 14 trials) at term compared with the same supplements without iron or with placebo [11]. Iron supplementation is also associated with increased birth weight (MD 41.21, 95% CI 1.20–81.23) and can decrease the risk of LBW (RR 0.81, 95% CI 0.71–0.93) [12]. WHO currently recommends daily supplementation with a combination of 30–60 mg iron and 400 mg folic acid, or weekly supplementation with 120 mg iron and 2,800 mg folic acid [13]. However, there is evidence suggesting similar benefits (with fewer overall side effects) for intermittent iron supplementation in pregnancy for nonanemic mothers with proper access to quality antenatal care [14].

Micronutrient deficiencies often coexist, especially in pregnant women and resource-limited settings. Antenatal multiple micronutrient supplements (MMN) containing folic acid and iron have thus been proposed as a more feasible and effective replacement for iron-folic acid supplementation during pregnancy. WHO does not recommend routine MMN due to limited evidence; however, a recent meta-analysis of trials conducted in low- and middle-income countries (LMIC) suggests that MMN supplementation can reduce the risk of SGA birth (RR 0.92, 95% CI 0.86–0.98; 14 trials) and LBW (RR 0.88, 95% CI 0.85–0.91; 15 trials) compared with iron supplementation with or without folic
Acid [15]. A separate analysis of 1 trial from a high-income country did not yield significant results for these outcomes, suggesting that beneficial effects may be limited to populations with a high burden of MMN deficiencies [15]. Additional research is required to determine the optimal combination and dosage of micronutrients included in MMN supplements.

**Calcium Supplementation**

The gestational hypertensive disorders – preeclampsia and eclampsia – are leading causes of maternal morbidity and mortality globally [16]. High-dose calcium supplementation of at least 1 g/day has been found to reduce the risk of preeclampsia by 55% (RR 0.45, 95% CI 0.31–0.65; 13 trials), with an even greater effect observed among women with low calcium diets (RR 0.36, 95% CI 0.20–0.65; 8 trials) and women at high risk for preeclampsia (RR 0.22, 95% CI 0.12–0.42; 5 trials). There is also evidence for a significant reduction (RR 0.76, 95% CI 0.60–0.97; 11 trials) in the risk of preterm birth, an outcome commonly associated with hypertensive disorders [17]. Preterm birth complications are a leading cause of mortality in neonates and children <5 years of age, especially in resource-limited contexts [16]. Survivors are at higher risk of morbidity, including respiratory diseases and their sequelae, and poor neurological development. A separate meta-analysis examining the effect of calcium supplementation on improving pregnancy and infant outcomes outside of preventing or treating hypertension did not find a significant link with prevention of preterm birth. However, a small, yet statistically significant, increase in birth weight was found [18]. It should be noted that calcium can interfere with the absorption of other minerals, such as iron; hence, despite its observed benefits, issues remain regarding supplementation alongside other micronutrients during the antenatal period.

**Vitamin D Supplementation**

Vitamin D is produced by the body from sunlight exposure and can also be found naturally in oily fish, mushrooms, eggs, and liver. A low vitamin D status in pregnant and lactating women is widespread, even in regions with abundant sun exposure all year round [19]. Like calcium, vitamin D supplementation during pregnancy may lower the risk of preeclampsia (RR 0.52, 95% CI 0.25–1.05; 2 trials) [20]. Beneficial effects have also been seen on birth outcomes, with a reduced risk of both preterm birth (RR 0.36, 95% CI 0.14–0.93; 3 trials) and LBW (RR 0.40, 95% CI 0.24–0.67; 3 trials) [20]. When supplemented alongside calcium, vitamin D is associated with a lower risk of preeclampsia; however, it is also accompanied by an increased risk of preterm birth [20]. More research is needed before vitamin D supplementation can be recommended during pregnancy to improve maternal and infant outcomes.
Vitamin A
Globally, an estimated 190 million preschool children and 19.1 million pregnant women are deficient in vitamin A, defined as a serum retinol concentration of <0.70 μmol/L [21]. Vitamin A deficiency (VAD) is most prevalent in LMIC, with Africa and Southeast Asia bearing the greatest burden of VAD worldwide [22]. A meta-analysis of 5 trials from South Africa, Nepal, Indonesia, Tanzania, and the United Kingdom suggests that vitamin A supplementation during pregnancy may reduce maternal clinical infection by 55% (RR 0.45, 95% CI 0.20–0.99); however, this evidence is of low quality [23]. A significant effect on newborn outcomes following vitamin A supplementation during pregnancy has also not been shown [23].

Zinc Supplementation
Like calcium and vitamin D, zinc supplementation during pregnancy has been associated with a reduction in preterm birth (RR 0.86, 95% CI 0.76–0.97; 16 trials) [24]. This analysis primarily involved women from low-income settings, and Ota et al. [24] suggested it has relevance in areas with high rates of perinatal mortality. The authors concluded that this association could reflect a poor overall nutritional status of study participants, and that the benefits of zinc supplementation alone during pregnancy may thus be limited.

Lipid-Based Nutrient Supplementation
Micronutrients can be delivered to mothers within a calorie-rich vehicle that also contains small quantities of macronutrients. In addition to vitamins and minerals, lipid-based nutrient supplements (LNS) provide energy that is largely in the form of fats. In a recent trial from Ghana, LNS was shown to improve length-for-age at 18 months, as well as lower hemoglobin and iron status in pregnant women, compared with iron-folic acid alone [25, 26]. A trial in Bangladesh also found an effect of LNS on growth indicators. When given to pregnant women, LNS reduced the risk of both wasting and stunting in newborns, potentially through a reduction in IUGR [27]. LNS did not affect maternal anthropometric indicators in the overall sample of this trial; however, increased mid-upper arm circumference was observed among women aged at least 25 years and those with lower stature, and weight gain among multiparous women aged at least 25 years [28].

Marine Oil Supplementation
Supplementation with fatty acid-containing fish/marine oils or other prostaglandin precursors during pregnancy has been shown to increase the length of pregnancy by 2–3 days (weighted MD, WMD, 2.55, 95% CI 1.03–4.07; 3
trials), slightly increase birth weight (WMD 47.24, 95% CI 1.05–93.44; 3 trials), and birth length (WMD 0.48, 95% CI 0.13–0.83; 2 trials), and slightly reduce the number of babies born before 34 weeks of gestation (RR 0.69, 95% CI 0.49–0.99; 2 trials) [29]. Although promising, these findings are based solely on studies conducted in high-income countries. The review authors, Makrides et al. [29] conclude that there is insufficient evidence to support the routine use of such supplements during pregnancy to reduce the risk of pre-eclampsia and poor neonatal outcomes, such as preterm birth, low birth-weight, or SGA.

Infant and Child Micronutrient Interventions

In this section, we outline micronutrient interventions delivered during infancy and childhood that promote growth.

Multiple Micronutrient Supplementation
Micronutrient deficiencies, especially in LMIC, occur often concomitantly, highlighting the need for micronutrients to be packaged together for more feasible, comprehensive, and cost-effective supplementation. Home fortification of complementary foods, such as with MMN powder (MNP), has been a widely implemented strategy to address micronutrient deficiencies globally. Sachets of MNP contain ≥2 powdered vitamins and minerals that can be added to prepared foods. A recent randomized trial in Bangladesh found that full-term LBW infants who received MNP were significantly less likely to be stunted at 12 months of age (OR 0.35, 95% CI 0.15–0.84) [30]. Conversely, iron-containing MNP that can effectively treat iron deficiency anemia has shown no benefit on growth outcomes and may slightly increase the risk of diarrhea [31].

Vitamin A Supplementation
VAD is the leading nutritional cause of preventable night blindness in children. It also increases the risk of severe infections and, as a result, compromises childhood growth and development. In populations at risk for VAD, supplementation of vitamin A in children from 6 months to 5 years of age has been shown to reduce the incidence of both diarrhea (RR 0.85, 95% CI 0.82–0.87; 15 trials) and measles (RR 0.50, 95% CI 0.37–0.67; 6 trials) [32]. However, a meta-analysis examining the association between vitamin A supplementation and growth did not indicate a significant effect of supplementation on height, weight, and weight-for-height in children <5 years of age [33].
Zinc Supplementation
Zinc deficiency is associated with impaired growth and significantly contributes to childhood pneumonia- and diarrhea-related morbidity and mortality. High stunting prevalence is used as a proxy for zinc deficiency at population level. The applications for zinc are twofold – it is both a nutritional supplement and a treatment for persistent diarrhea. Zinc supplementation has been shown to have a small but significant effect on growth in children aged 6 months to 12 years, with an increase in height (standardized MD $-0.09$, $95\%$ CI $-0.13$ to $-0.06$; 59 trials) and weight (standardized MD $-0.10$, $95\%$ CI $-0.14$ to $-0.07$; 52 trials), and a reduction in the risk of all-cause diarrhea ($RR$ $0.87$, $95\%$ CI $0.85$ to $0.89$; 35 trials) [34]. Moreover, zinc supplementation has also been proposed to prevent pneumonia in infants and young children [35]. It has been shown to reduce the incidence of pneumonia in children aged 2–59 months by 13% ($RR$ $0.87$, $95\%$ CI $0.81$–$0.94$; 6 trials) and, for cases confirmed by chest examination or radiograph, by 21% ($RR$ $0.79$, $95\%$ CI $0.71$–$0.88$; 4 trials) [35].

Delivery Platforms to Address Micronutrient Deficiencies

Figure 2 indicates 5 widely implemented strategies for delivering micronutrient interventions to women and children:

- *Dietary Diversification.* Also referred to as “dietary modification.” This household strategy promotes optimizing the intake of micro- and macronu-
trients through consuming a greater variety of foods. It also involves enhancing the nutrient density and bioavailability of locally sourced foods. This increase in nutritional content can be achieved through food preparation techniques and inclusion of enhancers of micronutrient absorption in the diet.

- **Supplementation.** The ingestion of a product, containing one or more micronutrients, that is specifically intended to prevent or treat nutritional deficiencies.

- **Point-of-Use Fortification.** MNP are single-dose sachets containing ≥2 powdered vitamins and minerals that can be added to foods consumed at home, school, or any other point of use. LNS supplementation is another example of point-of-use fortification.

- **Mass Fortification.** Also referred to as “universal fortification.” The addition of micronutrients to staple foods or condiments regularly consumed by the population, such as sugar, salt, cooking oils, flour, and rice.

- **Biofortification.** The nutritional enhancement of food crops via biological means, such as selective breeding and genetic engineering.

**Way Forward**

The available evidence on the global distribution of micronutrient deficiencies suggests that they are present in many malnourished and at-risk populations in LMIC and they frequently coexist. They are also frequently associated with growth failure in children and fetal growth retardation in pregnancy, a recognized antecedent of stunting in early childhood. To address these deficiencies, we need concerted strategies that address the underlying causes of malnutrition and poor diet, which are frequently associated with poverty, food insecurity, low levels of awareness, and education. Factors contributing to poor nutrition may be exacerbated in special situations such as conflict and displacement. In populations with high rates of malnutrition associated with gender disparities, high fertility rates, and poor female empowerment, it is easy to understand why this can be a vicious cycle and often intergenerational. Hence, investments in addressing the determinants underlying malnutrition and micronutrient deficiencies are key.

Additional strategies to address micronutrient needs include fortification strategies for either staples or commonly used foods, especially complementary foods for children. While there is evidence for the benefits of single nutrient supplementation strategies, there is strong evidence that MMN supplements in pregnancy and early childhood could impact growth and potentially reduce stunting. The key strategies needed to scale up these interventions include social
safety nets to ensure that food insecurity is addressed and that access to such commodities is ensured. Addressing malnutrition is a key component of the Sustainable Development Goals, especially goal 2 for eliminating hunger in all its forms and within our grasp.

**Disclosure Statement**

The authors have no conflicts of interest to disclose.

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