Prenatal micronutrient supplementation: Are we there yet?

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∞∞ See related research paper by Shah and colleagues, page E99

Maternal undernutrition is one of most neglected aspects of nutrition in public health globally. Although relatively few indicators are systematically tracked or reported, a recent review of the global burden of maternal undernutrition concluded, despite limited information, that some 10%–19% of women of reproductive age were seriously undernourished. With a body mass index (BMI) of less than 18.5, these women were at increased risk of delivering low-birth-weight infants.[1] A significant proportion of women of reproductive age also have deficient levels of micronutrients.[2] In the developed world, deficiencies in micronutrients may be associated with low maternal age, poverty and poor diets or food faddism. In much of the developing world, such deficiencies are also compounded by high fertility rates, repeated pregnancies and short intervals between pregnancies.

Key points

- Deficiencies in micronutrients affect many women of reproductive age and are associated with adverse maternal and perinatal outcomes.
- Micronutrients that may be important for maternal, infant and child outcomes include iron, vitamin B_{12}, folic acid, vitamin D and selenium.
- In addition to multimicronutrient supplementation, optimal interventions to improve maternal nutrition need to address household food insecurity and reduce the burden of maternal infections such as HIV infection and malaria.
- If proven effective and safe in representative health care systems, supplementation with multimicronutrients should replace supplementation with iron and folic acid in susceptible populations.

Information on the range and scale of micronutrient deficiencies among women of reproductive age is limited. Although iron-deficiency anemia is recognized as an important risk factor for maternal and perinatal mortality globally,[3] the contribution of other micronutrient deficiencies to adverse outcomes of pregnancy is less clear. However, emerging evidence suggests that micronutrients such as vitamin B_{12} and folic acid,[4] vitamin D[5] and selenium[6] may also be important for maternal, infant and child outcomes. It is thus logical to assume that, in poor populations with a high burden of disease, women of reproductive age may be malnourished, and have a low BMI, short stature and frequently subclinical deficiencies in multiple micronutrients.

In this issue of *CMAJ* (page 1200), Shah and Ohlsson,[7] representing the Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births, present the findings from their systematic review of the effect of supplementation with multiple micronutrients on pregnancy outcomes, including birth weight and the prevalence of low-birth-weight infants and preterm births. From their meta-analysis of 13 published trials, they conclude that supplementation with multiple micronutrients, compared with iron and folate supplements only, was associated with a 17%–19% reduction in the risk of low birth weight; they also found an increase in the mean birth weight of 54 g (95% confidence interval 36 g–72 g).

Limitations of their review should be considered before accepting these conclusions as definitive evidence of impact. Several recent studies included in the meta-analysis were cluster-randomized trials, and at least one was an effectiveness trial. Arguably, Shah and Ohlsson should have adjusted the meta-analysis for the possible design effect of these cluster-randomized trials.[8] They also did not perform a disaggregated analysis by maternal nutritional status or stature, which could indicate whether the reported outcomes and benefits were consistent across all categories.

Shah and Ohlsson do not report outcomes beyond nutritional status at birth. The benefits of interventions to improve maternal nutrition, especially micronutrient supplementation, may well accrue well after the newborn period. Indeed, benefits on improved survival[9] and growth in infancy and childhood[10] have been reported. More critically, the authors report a limited repertoire of outcomes, omitting perinatal and neonatal mortality and important morbidity outcomes. Such outcomes are relevant given the considerable controversy surrounding a reported increased risk of neonatal mortality following supplementation with multiple micronutrients during pregnancy.[11] If increased body size, especially head size, may be a consequence of such supplementation, then provision of adequate skilled care and referral services in childbirth are important prerequisites before the large-scale provision of multiple micronutrients to replace iron and folate supplements in malnourished populations can be recommended.

Notwithstanding the above considerations, appropriate strategies for the prevention and management of maternal undernutrition and micronutrient deficiencies in developing countries are a priority. However, these strategies may require multiple interventions. Evidence-based interventions that can

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improve maternal nutritional status and fetal growth include fortified food supplements or conditional cash transfers to address household food insecurity, micronutrient interventions that address iron-deficiency anemia and other deficiencies, and measures to reduce the burden of maternal infections such as HIV infection, malaria and helminthiasis.[12] In a recent evaluation of the benefits of administering multivitamins and deworming among pregnant women with severe anemia, an enhanced regimen with mebendazole therapy and multivitamin supplementation was found to have a modest benefit over the standard treatment of daily supplementation with iron and folic acid only.[13] Thus, optimal maternal nutrition should be achieved through multiple interventions supported and promoted by different delivery strategies, rather than micronutrient supplementation alone.

At the Copenhagen Consensus 2008, micronutrient supplementation and fortification were identified as among the most cost-effective interventions to address infant and child undernutrition globally, with benefit–cost ratios of 9.5–17.3 (estimated annual gains of $3.7 billion for net investments of $346.4 million).[14] However, other than iron fortification, the group identified no strategies for addressing the size of the problem among women of reproductive age.

Additional strategies clearly need to find their way into public health programs. Given the success of 2 recent large-scale projects for multimicronutrient supplementation in Indonesia[9] and China,[15] further system-wide projects need to be undertaken, with careful surveillance of perinatal mortality. If proven effective and safe in representative health care systems, multimicronutrient supplementation should replace iron–folic acid supplementation in susceptible populations.

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