Precision in prescription: multiple micronutrient supplements in pregnancy

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The programmatic possibility of introducing multiple micronutrient supplements (MMS), which include iron and folic acid, for routine antenatal care in low-income and middle-income countries (LMIC) has been enthusiastically welcomed by many, but it is equally opposed by others. This is reflected in the language of the WHO recommendation,[1] which states that more rigorous research is required, specifically, using early ultrasound to date pregnancies accurately and to rigorously evaluate outcomes and the follow-up of infants into childhood. Additionally, where programmes of MMS are being considered, implementation research is required to establish the effect of switching from iron and folic acid supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity, and cost-effectiveness.

In *The Lancet Global Health*, Ellen Caniglia and colleagues[2] report an admirable programmatic evaluation at scale, of the effectiveness of MMS against iron-folic acid supplementation (IFAS), iron-only, and folic acid-only supplementation, in Botswana. Pregnant women initiating IFAS had lower risks of most adverse birth outcomes compared with those who initiated iron-only or folic acid-only supplementation. However, those initiating MMS had a lower risk of preterm delivery and low birth weight, compared with women who initiated IFAS. This finding needs careful scrutiny to inform the ongoing debate.

First, limitations imposed by the study design, particularly the potential for allocation bias and stock-out induced switching between intervention groups, reduce the quality of evidence. Second, ultrasound-based gestational dating was not available, nor were preterm outcomes specified as spontaneous or induced; these are crucial shortcomings, although admittedly difficult to overcome in programmatic evaluations in LMICs. Third, the small contrasts in birth weight (1·2 g [95% CI −9·7 to 12·1]) and gestation (0·8 days [95% CI 0·5–1·1]) between the IFAS and MMS groups seem incompatible with the observed risk differences in low birth weight (−0·99% [95% CI −1·59 to −0·38]; risk ratio reductions 10·48%) and prematurity (−1·06% [−1·69 to −0·42]; risk ratio reductions 11·63%). Notwithstanding this, the policy relevance of these marginal benefits without simultaneous survival advantages, is uncertain. Finally, using subgroup analyses, the authors emphasise the greater benefit of MMS in women who were HIV positive and those who were older than 35 years.[2] By contrast, there is no convincing evidence of benefit for preterm births in women who were younger (<20 years), anaemic (haemoglobin <11 g/dL), primiparous, primary school educated, non-salaried, and had care initiation in first trimester, and those who had low weight (<50 kg). For low birthweight, the findings were similar, except for parity, education, and salary, which are the groups of pregnant women who are most in need for improving birth outcomes, especially in the LMIC context. These subgroup analyses were also discordant from a meta-analysis of MMS benefits in 17 trials in 112 953 participants from LMICs, in which MMS was associated with greater benefits in undernourished and anaemic pregnant women.[3] Thus, concerns about the purported benefits of MMS in a programmatic mode become important. A detailed analysis of the implementation challenges would also prove invaluable for global policy.

Different MMS formulations have been studied, most commonly the UN International Multiple Micronutrient Antenatal Preparation (UNIMMAP).[1] However, because nutrient intake deficiencies will vary by local nutrient intakes and the nutrient requirement metric used, a universal MMS composition is problematic. The currently recommended use of the lower metric of the average requirement rather than the inflated recommended daily allowance[4] for populations is also relevant. A careful mapping of nutrient deficiencies is required, including evaluations of whether they are small and manageable by reasonable diet diversification, and whether they are heterogenous, even within countries. If so, the wisdom of a fixed (high) dose global MMS is questionable, and some alternate thinking and precision is called for. A relevant question might be: is the goal pharmacological intervention or physiological repletion?

Adding large amounts of supplementary nutrients into the daily nutriture has its own risks, which can be

magnified with overzealous layering of interventions for the same micronutrient, including mandatory fortification.[5] For example, evidence suggests the risk of gestational diabetes with IFAS (increased oxidative stress with iron, unmetabolised folic acid, and a possible imbalance with vitamin B_{12})[6–8] with life-long consequences for the progeny. Higher antenatal serum copper concentrations are associated with increased risk for spontaneous preterm birth,[9] possibly due to induced dyslipidaemia. In context, the copper content (2 mg) in the UNIMMAP formulation is quite high compared with its average requirement (0·8 mg), as are many of the other micronutrients. Improved dietary diversification will not offer these risks, and the programmatic inclusion of MMS in antenatal care needs more research. In particular, the presumption of no harm needs testing from the perspective of subclinical metabolic risk. It is time that LMICs moved towards precision in nutrition prescription, based on accurate deficiency biomarkers.

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