Antenatal multiple micronutrient supplementation: benefits beyond iron-folic acid alone

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Multiple micronutrient deficiencies remain a major public health concern in low-income and middle-income countries (LMIC). Infants, young children, and women of reproductive age are especially vulnerable. Pregnancy places an additional burden on women's micronutrient status, as nutrient needs increase to meet the demands of both the mother and the developing fetus.[1] Maternal micronutrient malnutrition during pregnancy can permanently affect physiological development of the fetus, which can increase the risk of morbidity, mortality, poor growth, and neurocognitive development later in life.[2]

A 2017 Cochrane review by Haider and Bhutta[3] concluded that, in comparison with iron with and without folic acid, daily multiple micronutrient supplementation during pregnancy reduced the risk for low birthweight and small-for-gestational-age births in LMICs.[3] However, despite an increasing body of evidence demonstrating beneficial effects of antenatal multiple micronutrient supplements, the updated 2016 WHO guidelines[4] on antenatal care continue to recommend iron-folic acid supplementation "for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight, and preterm birth".[4] Antenatal multiple micronutrient supplementation, by contrast, is "not recommended to improve maternal and perinatal outcomes" on the basis that "there is also some evidence of risk, and some important gaps in the evidence".[4] A 2016 systematic review and meta-analysis[5] found no evidence for long-term health benefits of antenatal multiple micronutrient supplementation compared with iron-folic acid supplementation.[5]

The ongoing debate on the benefits and risks of multiple micronutrient supplements during pregnancy motivated the individual-patient data meta-analysis by Emily Smith and colleagues in the *Lancet Global Health*.[6] The authors aimed to identify factors that modify the effects of multiple micronutrient supplementation (minimum of eight micronutrients in addition to iron-folic acid), compared with iron-folic acid supplementation alone, on stillbirth incidence, birth outcomes, and infant mortality. Data for 112 953 pregnant women from 17 randomised trials done in 14 LMICs were included.

The study confirmed the previously reported effects of multiple micronutrient supplementation on reducing the risk of low birthweight, preterm birth, and being born small for gestational age. The main contribution of this study, however, is the identification of several subgroups of mothers that might experience greater benefits from antenatal multiple micronutrient supplementation than from iron-folic acid supplementation alone. In anaemic women, multiple micronutrient supplementation resulted in greater reductions in risk of low birthweight (–19%), small-for-gestational-age births (–8%), and infant mortality at 6 months of age (–29%) than in non-anaemic women. In underweight women (BMI <18·5 kg/m^2), multiple micronutrient supplementation reduced the risk of preterm birth by 16%. Furthermore, initiation of multiple micronutrient supplementation before 20 weeks' gestation decreased the risk of preterm birth (–11%) and high adherence to regimen (≥95%) decreased the risk of infant mortality (–15%).

Interestingly, female infants born to mothers who received antenatal multiple micronutrient supplementation had an approximately 15% reduction in mortality risk during the first year of life. This survival benefit was not significant in male infants. As indicated by the authors, the sex-specificity of effects needs to be confirmed and potential underlying biological mechanisms elucidated in future studies.

None of the subgroups experienced an increased risk of stillbirth or mortality during the first year of life. Thus, the current study does not confirm the increased risk of mortality that has been reported previously.[4] The authors pointed out that some trials provided lower iron doses in the multiple micronutrient supplementation (≤30 mg elemental iron) than in the iron-folic acid (60 mg elemental iron) groups. The authors therefore did a sensitivity analysis, which revealed no significant harmful effects overall or in any subgroups among trials that used the same dose of iron in the multiple micronutrient supplementation and the iron-folic acid groups. By contrast, in trials that used a lower iron dose in the multiple micronutrient supplementation group, the risk of stillbirth and mortality was greater

in some subgroups. The researchers thus recommend that "programmes considering implementation of multiple micronutrient supplementation should use a formulation with an iron dose similar to what they currently use".[6]

The results of this meta-analysis[6] are important, as they guide researchers and policy makers on subgroups to be targeted by multiple micronutrient supplementation and other potential nutrient intervention strategies. The study provides further evidence on the additional benefits of multiple micronutrient supplementation (including iron-folic acid) above iron-folic acid alone in women entering pregnancy with poor nutritional status. The authors thus stated that "this new evidence suggests that WHO should consider re-evaluating the balance of benefits and harms of universal multiple micronutrient supplementation in their antenatal care recommendations".[6]

However, concerns have been raised about the safety and efficacy of routine antenatal iron supplementation, particularly in areas with a high infectious burden and in women entering pregnancy with high haemoglobin concentrations.[7] A growing body of research in infants and children shows that unabsorbed iron from supplements can result in dysbiosis of the gut microbiome associated with gut inflammation and a potentially increased risk for morbidity.[8] Information is missing on the effect of antenatal oral iron supplementation on the gut microbiome of the mother and the neonate. The risks of antenatal multiple micronutrient supplementation investigated in the current study[6] are limited to stillbirth, birth outcomes, and infant mortality as compared with iron-folic acid alone. Thus, potential risks attributed to multiple micronutrient supplementation beyond these outcomes cannot be dismissed. Future trials testing the efficacy of antenatal nutrient supplementation should therefore perform a more thorough investigation of potential risks, by not only assessing maternal and offspring morbidity but also measuring novel and traditional biomarkers of health and disease.[9] Trials should also include outcomes of long-term health, such as measures of motor, cognitive, and socio-emotional development and cardiometabolic health. These data will be necessary to make an evidence-informed decision on whether benefits outweigh risks of iron-folic acid supplementation, multiple micronutrient supplementation, or alternative nutrient interventions (ie, lipid-based nutrient supplements) during pregnancy.

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I declare no competing interests.

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