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Consequences of poor maternal micronutrition before and during early pregnancy

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Summary

In developing countries, micronutrient deficiencies are common and associated with poor pregnancy outcomes, which may in turn have longer-term effects on human health. The peri-conceptional period represents a particularly sensitive window of feto-placental development, during which sub-optimal maternal micronutrition may have far-reaching consequences. The effects of targeted interventions during this period have been little studied in humans.

Keywords

micronutrient; vitamin; pregnancy; fetus; peri-conceptional; pre-conceptional

With growing understanding of the roles of vitamins and minerals in physiological processes, micronutrient status is no longer interpreted merely as the presence or absence of the classical deficiency diseases. In poor populations, low micronutrient intakes are common, frequently cause sub-optimal status across the whole range of micronutrients, and interact with infections and other pathologies. In pregnant women, inadequate micronutrition is associated with poor outcomes for both the mother (anaemia and pre-eclampsia) and the baby (fetal growth restriction, pre-term delivery, and low neonatal micronutrient stores), for whom there may be long-term health impairment. There has therefore been considerable interest in balanced multiple micronutrient supplementation for pregnant mothers.

A recent systematic review of nine randomised controlled trials during pregnancy concluded that multiple micronutrient supplements produced only modest increases in maternal haemoglobin and birthweight, and offered no advantages over conventional antenatal iron and folate supplements (Haider and Bhutta, 2006). Birth-weight was the main outcome measure, and examination of functional outcomes was limited. Another systematic review, covering more recent trials, and providing data on infant mortality as well as maternal and neonatal outcomes, is expected later this year from the UN Standing Committee on Nutrition.

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Peri-conceptional interventions were specifically excluded from these reviews, and most trials started supplementation in the second trimester of pregnancy. The nutrient demands of the pre-implantation embryo and first trimester fetus are small, but likely to be highly specific. Before placentation occurs, a sufficient range and quantity of nutrients must be present in the embryo's immediate environment. The importance of peri-conceptional micronutrition has been convincingly demonstrated by the reduction in neural tube defects and other congenital malformations in trials of pre-conceptional folate supplementation. These trials did not examine other outcomes, however, and the potential of other micronutrient interventions to improve pregnancy and later outcomes remains under-explored.

In experimental animals, general peri-conceptional under-nutrition alters the fetal growth trajectory, induces early activation of the fetal hypothalamo-pituitary-adrenal axis and pre-term birth, and causes long-term changes in the offspring, such as hypertension (Bloomfield et al., 2005). A recent study from the USA, focusing specifically on micronutrients, recruited women at a mean (SD) gestational age of 10 (4) weeks (Catov et al., 2007). After adjustment for important confounding factors, peri-conceptional multivitamin use was associated with a lower risk of pre-eclampsia (OR = 0.55, 95% CI 0.32, 0.95), very preterm birth (<34 weeks; OR = 0.29, 95% CI 0.13, 0.64) and severe fetal growth restriction (birthweight for gestational age <5th percentile; OR = 0.64, 95% CI 0.40, 1.03).

There are several mechanisms by which inadequate peri-conceptional micronutrition may influence fetal development. Implantation, differentiation of the embryo into placenta and fetus, and placental growth are characterised by strictly regulated oxidative stress and inflammation, vascular remodelling and rapid cell turnover. Inadequate micronutrition could compromise any of these processes, leading to placental dysfunction, fetal growth restriction and premature delivery. Several micronutrients, especially those involved in 1-carbon metabolism (such as folic acid and vitamin B12) act as co-factors or molecular donors for epigenetic processes such as DNA methylation, which modulate gene expression, and therefore cellular proliferation and apoptosis, in early pregnancy. Genome-wide demethylation occurs just after fertilisation, followed by re-methylation at different stages of embryonic development (Godfrey et al., 2007). Epigenetic changes induced at this time may become permanent and heritable, determining outcomes in later life and in the next generation. Interestingly, a recent meta-analysis of seven case-control studies, suggested a significant reduction in childhood cancer risk with periconceptional micronutrient supplementation (Goh et al., 2007).

There is more work to be done on the short- and long-term effects of peri-conceptional micronutrient status. Although birthweight is a useful predictor of health outcomes during infancy and later life, it is a crude summary of the subtle structural and metabolic effects of adverse intra-uterine conditions during critical periods of fetogenesis. It is important that trials are designed to examine functional outcomes in the mother and baby, going beyond haemoglobin and birthweight. It cannot be assumed that non-selective micronutrient supplementation of pre-pregnant women, even in poor populations, would necessarily be beneficial across all parameters. For example, one could speculate that where chronic micronutrient deficiency is endemic, early prenatal supplementation may programme inappropriate fetal physiological responses which mal-adapt offspring to a poor postnatal micronutrient milieu. Studies should therefore ideally extend follow-up into infancy, childhood and beyond. Pre-and peri-conceptional studies are not easy to do in humans, but the limited data we have on the effects of nutrition during this crucial period of development, suggests that such studies are an essential step towards optimising public health.

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