Commentary: Can improving a mother’s diet improve her children’s cardiovascular health?

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Nearly 20 years ago David Barker and colleagues showed a surprising association between low birth-weight and an increased risk of adult hypertension, type 2 diabetes and death from cardiovascular disease. They put forward the controversial hypothesis that exposure to undernutrition in fetal life or infancy increases an individual’s vulnerability to these disorders. Undernutrition, it was suggested, forced the rapidly growing fetus/infant to make physiological adaptations that enabled short-term survival but ‘programmed’ permanent structural and metabolic changes that caused later disease. Implicit in the hypothesis is that since the mother’s nutritional status influences the quality and quantity of nutrients reaching the fetus, improving maternal diets could prevent common chronic diseases in future generations. If true, this could be particularly important for developing countries, where maternal undernutrition is widespread and where diabetes and cardiovascular disease are becoming major problems.

Animal experiments have provided ‘proof of principle’ that maternal undernutrition can produce these outcomes in the offspring, and that the effects can be prevented by nutritional interventions. For example in rats, maternal protein restriction during pregnancy leads to elevated blood pressure in the offspring, and this is prevented by supplementing the mother’s low-protein diet with folic acid. Animal studies have demonstrated mechanisms that could mediate adverse outcomes, including effects of maternal undernutrition on offspring organ structure, endocrine pathways and epigenetic characteristics. In contrast, until recently, debate about the importance of maternal nutrition for human health has relied mainly on observational data. Blood pressure has been measured in people whose mothers’ nutritional status or diet was recorded, or whose mothers were exposed to famine during pregnancy. The findings are inconsistent and confusing. While some studies showed higher blood pressure in offspring of women who were thinner, or famine-exposed, or had diets low in protein relative to energy, others showed no associations.

We are now beginning to see the hypothesis tested in intervention studies, by following up the children of undernourished women who took part in nutrition supplementation trials in pregnancy. In this issue, Hawkesworth et al. report a study of blood pressure in Gambian adolescents whose mothers received high-energy biscuits, providing up to 4250 kJ of energy, 22 g of protein and micronutrients daily from 20 weeks gestation, in a cluster randomized trial. Control women received the same supplement during lactation (from 20 weeks post-partum). The intervention certainly influenced fetal nutrition, increasing birthweight by 136 g, reducing the incidence of low birthweight by 40%, and halving perinatal mortality. However, in a rigorously carried out follow-up study, with high participation rates, the investigators found no difference in blood pressure between children of women in the intervention and control groups. The
authors also report that there were no differences in body composition, to be published separately.

These findings are consistent with two other recent reports,6,7 and different from a third. A follow-up study of adults born during the Institute of Nutrition of Central America and Panama trial in Guatemala, in which villages were randomized to receive Atole (a high-energy, high-protein drink) or Fresco (lower energy, no protein) found higher HDL cholesterol and lower triglyceride concentrations in those whose mothers had Atole, but no differences from the Fresco group in blood pressure or fasting glucose concentrations.6 Among adolescents in India, whose pregnant mothers received food-based energy and protein supplements as part of a package of public health interventions, insulin resistance and arterial stiffness were reduced compared with controls, but there was no difference in blood pressure.7 Like the Gambia study, the intervention in both these trials was predominantly ‘balanced’ energy and protein. Unlike the Gambia study, supplements went to children as well as pregnant women, and thus participants in the intervention group were exposed to supplementation in early childhood, as well as in utero. In the third study, systolic blood pressure was lower (−2.5 mmHg, 95% CI −4.55, −0.47) in 2-year-old Nepali children whose mothers received multiple micronutrients in pregnancy rather than standard iron/folate tablets.8 Among these studies, all of similar sample size, the Gambia intervention had the greatest impact on birthweight in the original trial. Hawkesworth et al.3 suggest several possible reasons for their negative results, apart from the obvious one, that maternal diet may have no effect on offspring blood pressure in humans. The control group were exposed to supplementation in infancy (via their lactating mothers), which may also have reduced their blood pressure. The age of the children when studied may not have been ideal; the normal tracking of blood pressure through childhood is lost during adolescence because children differ in their pubertal maturation rates, and the association between blood pressure and birthweight is weakest at this age. Nutrients other than those contained in the high-energy biscuits may be required to alter blood pressure; this is perhaps supported by the Nepal study results. Supplementation may have started too late; improved nutrition may be needed in the first trimester of pregnancy, or before conception, or even in the preceding generation (in grandmothers) to influence blood pressure.9 Finally, effects may be complicated by interactions with post-natal nutrition. In their study, higher blood pressure was observed among leaner adolescents in the intervention group. This, they suggest, could indicate harmful effects of mismatch between pre-natal nutrition (enhanced by the intervention) and poor post-natal nutrition.

There are many good reasons for improving the diets of undernourished mothers. The Gambia supplement produced an impressive reduction in perinatal mortality, and in Guatemala, early-life exposure to Atole improved childhood growth and adult economic productivity.10 Clearly, at present, there is inadequate evidence that such interventions improve cardiovascular health in the offspring. The findings from these four trials suggest that there may be beneficial effects on some cardiovascular risk factors, that these are complex, differing according to the population, the intervention and the post-natal environment, and that there may sometimes be harmful effects. Given the need for much deeper understanding, it is to be hoped that the investigators will follow-up their subjects further to determine the full extent of any effects, and that other trials of enhanced materno–fetal nutrition will add data to the currently meagre evidence-base on this important issue.

References
1 Hales CN, Barker DJP. Type 2 (non-insulin dependent) diabetes mellitus; the thrifty phenotype hypothesis. Diabetologia 1992; 35: 595–601.