Maternal malnutrition and the long-term health of populations: A new paradigm in health care

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Until recently, a successful pregnancy was equated with the delivery of a live baby, together with an additional minor concern about the baby's weight. There was little appreciation that the health of the baby in utero is intricately linked to its overall childhood and adult health. David Barker and colleagues changed this paradigm when they demonstrated that maternal nutrition influences the future risk of noncommunicable diseases (NCDs) in the baby (*1*). There is increasing understanding that these influences may span more than a single generation, and that non Mendelian, modifiable epigenetic mechanisms contribute to the heritability. Against this background, we are investigating the influence of maternal nutrition on fetal growth and its risk for future NCDs like diabetes, hypertension, and cardiovascular disease (CVD).

Around the globe, a major concern is maternal undernutrition and its effects on pregnancy outcomes and neonatal health. In the last three decades, an estimated 15% of reproductive age women (20 to 49 years) have been reported to be chronically undernourished (BMI <18.5 kg/m^2), with the highest proportion in Asian countries (~18%) (*2*). Survey data from India found that 36% of women aged 15 to 49 years had a BMI <18.5 kg/m^2 (*3*). The aggregate effect of maternal undernutrition (through fetal growth restriction, stunting, wasting, specific nutritional deficiencies, and suboptimal breastfeeding) contributed to an estimated 3.1 million child deaths in 2011, accounting for 45% of all child deaths (*2*).

The nutritional double burden

In many parts of the world, concerns about maternal undernutrition have now been replaced with concerns about overnutrition. In the developed world (United States and Europe), as many as three-quarters of mothers are reported to be overweight or obese (BMI >25 kg/m^2) (*2*). Excess maternal weight can adversely affect outcomes during pregnancy (increased incidence of diabetes and hypertensive disorders), delivery (hemorrhage, caesarean delivery, macrosomia, birth trauma, and infections), and postpartum (higher weight retention and failure of lactation). In the low and middle income countries (LMICs) undergoing nutritional transition, the proportion of overweight and obese pregnant mothers is increasing (*2*), due to urbanization, increasing age at the time of conception, and other lifestyle factors (*4*). Both undernutrition and overnutrition in the mother are transmitted to the child, setting up a cycle of intergenerational malnutrition, which disproportionately affects female children.

A rapidly changing epidemiology due to demographic and nutritional transitions produces a double burden of undernourishment in early life with relative overnutrition and NCD in later life. This creates additional challenges for health care providers and policymakers trying to manage the health of the population. It is notable that those parts of the world contributing the largest proportion to the burden of undernutrition in early life (LMICs), also suffer from NCD epidemics such as type 2 diabetes, hypertension, and CVD (Figure 1) (*5*).

Nutrition and disease

The idea that undernutrition in utero might influence future risk of NCDs was first documented in studies of Dutch men and women who were fetuses during the so-called hunger winter of World War 2 (*6*). Rationing during this time reduced food intake to about 600 calories per day per person. Follow up studies showed that male offspring who experienced hunger during the first two trimesters of pregnancy were at increased risk of obesity later in life, compared to those born outside of the hunger winter. On the other hand those undernourished in the third trimester were less likely to be obese. It was postulated that the increased obesity in the former group was due to resetting of the hypothalamic appetite centers, while in the latter group, reduced number of adipose cells decreased obesity. Subsequent studies have provided further evidence of the increased risk of diabetes, hypertension, and other NCDs in those who faced the hunger winter in utero (*7*). A recent study in China demonstrated an increased risk of diabetes in those who faced a famine in early life (*8*). It is interesting to speculate how famines and other natural calamities in different parts of the world in the last few hundred years could have sown the seeds of the modern day epidemics of NCDs.

David Barker and colleagues considered fetal growth and birth size as surrogates of fetal and maternal nutrition. They demonstrated an association between smaller size at birth and increased risk of diabetes, hypertension, and CVD (*1*). Smaller size was not due to premature delivery, but rather due to fetal growth restriction, which was ascribed to maternal undernutrition.

Fetuses appear to be highly sensitive to environmental changes that impact in utero conditions, particularly during critical stages of organ development. The in utero environment is influenced by the mother's size, food and nutrient intake, metabolism, endocrine balance, stress, exposure to pollutants, and many other factors. In early

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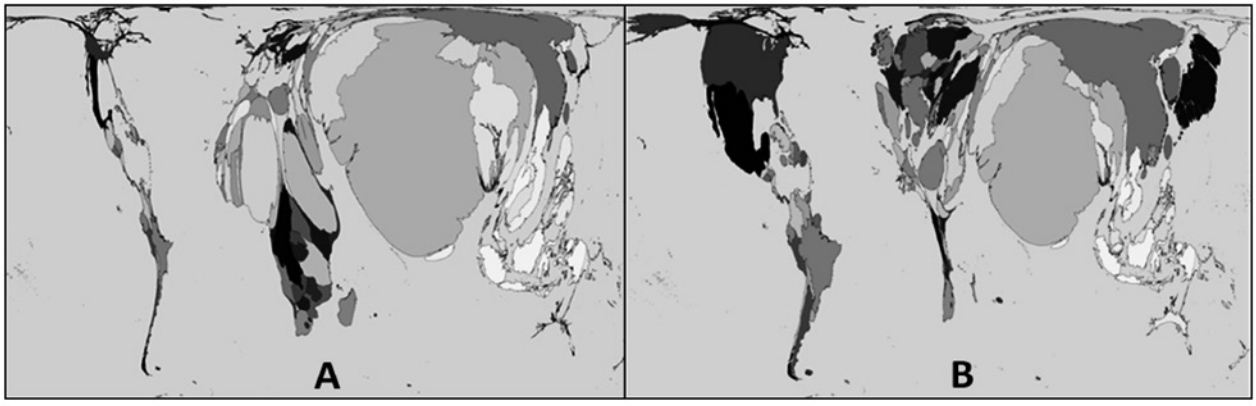

FIGURE 1. Cartograms showing the global burden of (**A**) malnutrition in early life, and (**B**) diabetes, represented proportionally as the country size. As the maps indicate, India assumes a prominent position in both of these problems (*5*).

pregnancy the mother communicates with and nourishes the embryo directly through the contents of the uterine cavity and subsequently through the placental circulation. A blueprint for fetal growth and development is established early in pregnancy making periconceptional maternal nutrition of special importance. Pregnancy with a female child presents an even more interesting situation, since the uterine environment impacts the mother, the fetus, and the fetus' developing oocytes; essentially three generations in a single pregnancy! Improving the intrauterine environment can therefore potentially improve the health of multiple generations. This makes a compelling case for the health practitioners and policymakers to target the health and nutrition of tomorrow's mothers for the future health of the planet.

Since the original description of a low birth weight phenotype, further work has been done on the association between neonate dimensions and future outcomes like obesity and diabetes, including use of the fetal ponderal index (kg/m^3), fetal body composition, placental size and shape, and metabolic, endocrine, and epigenetic markers in the cord blood (*9, 10*). In the past, fetal growth disturbances were considered exclusive determinants of future health. However, gestational length is now also considered important, and early embryonic nutrition is known to influence both fetal growth and length of gestation (*11*).

Nutrition and fetal programming

The concept of nutritional fetal programming contributed to a paradigm shift in the field of nutrition, with a focus on intergenerational health and its molecular mechanisms, seen from a systems biology perspective. An exciting discovery was the demonstration that nutrients influence gene function by interacting with nuclear receptors and also through epigenetic mechanisms (*12*), both of which modulate gene expression. The resulting impact on multiple cellular processes, particularly during critical times in fetal development, could influence the structure and function of organs and systems, contributing to long term effects on health and disease susceptibility (programming) (*13*). Although the pregnancy and infancy periods are important (the "first 1,000 days") (*14*), it is increasingly believed that the periconceptional period may be the most important (*15*).

Animal models of fetal programming frequently investigate the effect of maternal protein deficiency (*16*), but human data is sparse. A protein deficit leads to a shortage of amino acids, the building blocks of proteins, and can also disturb 1-carbon metabolism and DNA methylation, resulting in widespread downstream effects. Protein supplementation during pregnancy showed variable effects on fetal growth (*17*), indicating the need for further research. No specific role has been ascribed to carbohydrates and fats as macronutrients in fetal programming, but both are a major energy source and contribute to macrosomia in a diabetic pregnancy.

Micronutrients have emerged as important contributors to fetal programming. Methyl donors (folate, methionine, choline, and betaine, and co-factors vitamin B_{12} and B_6) are of special interest because of their potential to influence DNA methylation (*18*). Both maternal folate (a B vitamin) and vitamin B_{12} concentrations are associated with fetal growth (*19, 20*); higher folate is also associated with offspring adiposity and insulin resistance (*21, 22*), especially if vitamin B_{12} is low (*22*). This suggests a need for balanced nutrition. These two vitamins also influence offspring neurodevelopment. Higher maternal homocysteine concentration (caused by vitamin B_{12} and folate deficiency) is associated with fetal growth restriction. A maternal methylenetetrahydrofolate reductase (MTHFR) gene polymporphism that raises homocysteine concentrations also predicts fetal growth restriction, suggesting a causal role of

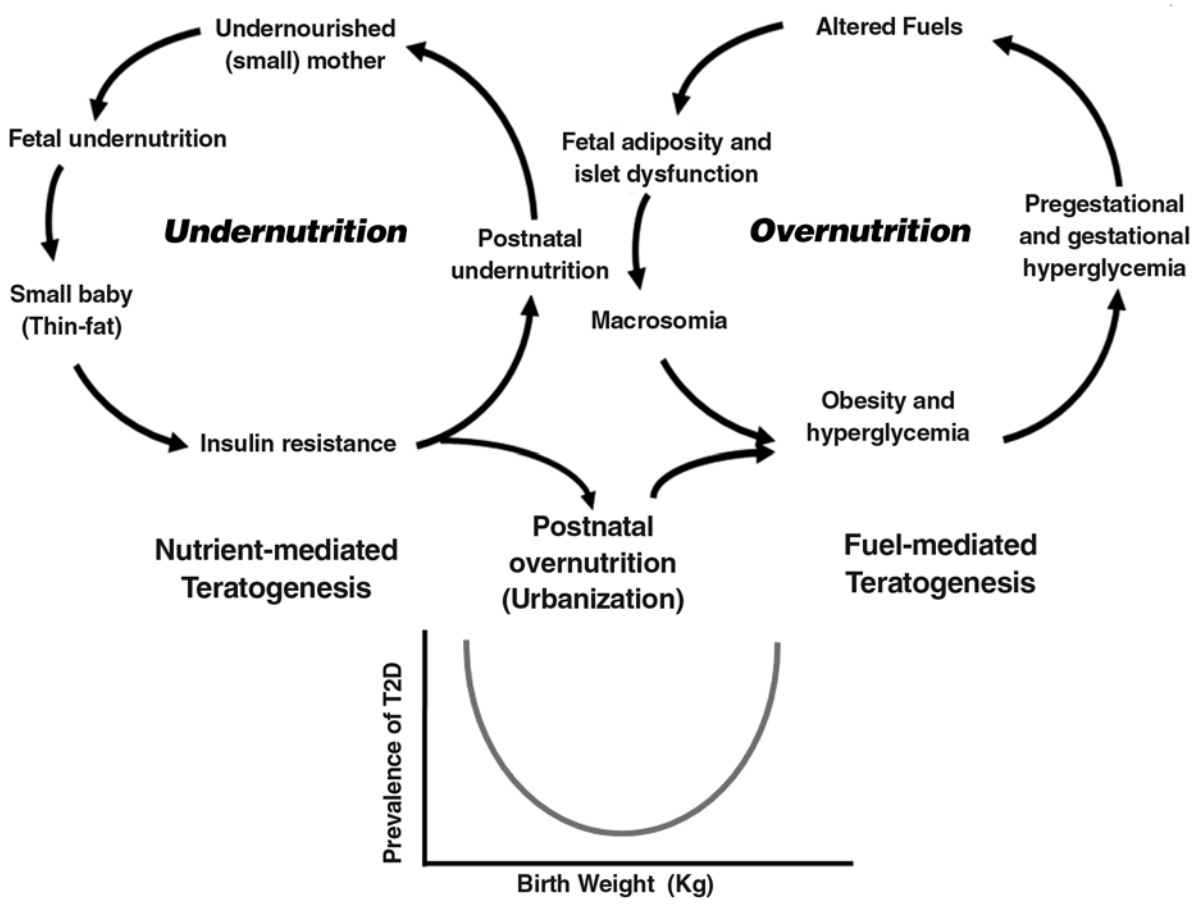

FIGURE 2. In undernourished populations, fetal undernutrition results in "thin-fat" babies who are insulin resistant. If postnatal nutrition is also low, they continue with the phenotype, and females can transmit this phenotype intergenerationally. If there is postnatal overnutrition, it can result in obesity and hyperglycemia, which can cause pregestational and gestational diabetes, promoting fetal macrosomia, and setting up an intergenerational cycle of obesity and hyperglycemia. In rapidly developing countries such as India, the two cycles operate simultaneously. This construct provides an explanation for the U-shaped association between birth weight and type 2 diabetes (T2D) (bottom graph) (adapted from *27*).

homocysteine (*23*). Studies in The Gambia demonstrated a seasonal pattern in methyl donor availability in the maternal bloodstream, which was reflected in different levels of DNA methylation in the cord blood (*24*). Similarly folic acid supplementation trials in pregnancy also influenced cord blood methylation (*25*). These human findings suggest a possible role for methyl donors in epigenetic fetal programming and later occurrence of NCDs. Animal models support such a role (*26*), but there is an urgent need for more human studies. Other micronutrients of interest in fetal programming include vitamin D, vitamin A, calcium, zinc, and omega-3 fatty acids.

We have proposed a "dual teratogenesis" construct to explain the U-shaped association between birth weight and diabetes (Figure 2) (*27*). Maternal-fetal undernutrition produces thin (poor lean mass) children with high adipose percentage and insulin resistance ("nutrient-mediated teratogenesis"). If these children continue to live in a deprived situation, they propagate this phenotype without overt diabetes. However, if they face overnutrition in postnatal life (urban migration), they are likely to develop obesity and hyperglycemia at a young age, and gestational diabetes in girls that propagates the obesity and diabetes phenotype ("fuel-mediated teratogenesis") (*28*). Rapidly transitioning countries like India seem to have both forms running simultaneously, feeding into an explosive epidemic of NCDs.

Vitamin B_{12} deficiency seems to be associated with both forms of teratogenesis in India (*21, 29, 30*).

Conclusions

It is high time that policymakers became more aware of the importance of maternal nutrition in improving the long-term health of populations. Hippocrates wrote "Let food be thy medicine and medicine be thy food." Modern science has extended this to intergenerational health. Ancient Indian physicians (Charak, Sushrut, and Vagbhat) understood that the transfer of nourishing maternal fluid to the fetus is important to attain proper body length, size, and health, and even provided dietary guidelines for both men and women planning to conceive. We would do well to develop similar evidence-based guidelines to improve fetal programming.

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