Influence of Maternal Vitamin B$_{12}$ and Folate on Growth and Insulin Resistance in the Offspring

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The current diabetes epidemic is recognized as one of the most challenging health problems ever. The epidemiology is changing rapidly, the young and the poor are increasingly affected, and the low- and middle-income countries are facing the greatest burden. India exhibits the classic dual burden: it is the ‘second capital’ of diabetes of the world and at the same time a country with the largest number of low-birthweight babies and undernourished children. This paradox was partly solved when Hales and Barker [1] proposed that intrauterine undernutrition and growth restriction might predispose to later diabetes by ‘fetal programming’. The idea of ‘epigenetic’ regulation of the phenotype challenged the dogma of exclusively genetic susceptibility to diabetes.

Initial research had shown an association of size at birth with future risk of diabetes; the role of nutrition was indirect and implied. Research in Pune focused attention on the influence of maternal micronutrient nutrition on fetal growth, body composition and future risk of diabetes. The Pune Maternal Nutrition Study was set up to investigate the influence of maternal nutrition on fetal growth and future risk of diabetes and cardiovascular disease. Mothers in this study were 42 kg, 1.52 m with a BMI of 18.1. Their babies were 2.7 kg and thin (ponderal index 24.1 kg/cm$^3$) [2]. This community survived mostly by subsistence farming, and the diet was predominantly vegetarian. The mothers consumed approximately 1,800 cal and 45 g protein per day; over 70% of calories came from carbohydrates. Reflecting their vegetarian habits, only an occasional mother had low circulating folate concentration, but almost two thirds had low vitamin B$_{12}$ concentrations. A third had high homocysteine concentration, but 90% had high methylmalonic acid concentration, indicative of tissue vitamin B$_{12}$ deficiency [3]. Higher maternal homocysteine concentration predicted smaller neonatal size because of both shorter gestation and growth restriction [4]. Follow-up of these offspring revealed that higher
Folate in pregnancy predicted higher adiposity in the children at 6 years of age. Independent of the folate effect on adiposity, low maternal vitamin B12 status coupled with high folate increased the risk of insulin resistance in the child (fig. 1) [3]. Maternal vitamin B12 status in pregnancy was also associated with neurocognitive development of the child. In the Parthenon study in Mysore, we found that maternal vitamin B12 deficiency was associated with increased risk of gestational diabetes and permanent diabetes, especially when folate status was high [5]. Finally, in a large study in four Indian centers, we found that low maternal holotranscobalamin concentrations were associated with the risk of neural tube defects [6].

Vitamin B12 and folate are major dietary methyl donors, and our results suggest an important role for maternal one-carbon metabolism in offspring growth, development and programming of non-communicable disease risk. These ideas are supported by animal studies. In preliminary studies, we have demonstrated an association between maternal genotypes influencing homocysteine (MTHFR C677T), vitamin B12 [FUT2 rs601338 (c.461G→A)] and holotranscobalamin [TCN2 rs1801198 (c.776C→G)] levels and fetal growth and insulin resistance, thus supporting causality in our epidemiological observations.

Fig. 1. Pune Maternal Nutrition Study: insulin resistance (HOMA-R) in children at 6 years in relation to maternal plasma vitamin B12 (at 18 weeks) and erythrocyte folate (at 28 weeks) concentrations. Maternal folate concentrations in pregnancy directly predict insulin resistance in the child. The most insulin-resistant children were born to mothers who had the lowest vitamin B12 and highest folate concentrations [3].
Hyperhomocysteinemia and vitamin B$_{12}$ deficiency are common in Indians living in India and abroad [7]. They are partly related to vegetarian dietary habits, but probably also to other unknown factors. There is a unique opportunity to influence the escalating epidemic of non-communicable diseases by influencing adolescent nutrition.

References