Commentary: Fetal origins of cardiovascular risk—nutritional and non-nutritional

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A paper in this issue of the IJE adds to the already long list of papers which show an association between small size at birth and cardiovascular risk in later life. Barker's idea of the 'fetal origins'[1] has survived and strengthened through the last decade, albeit undergoing a degree of metamorphosis to include contributions from childhood growth.[2]

The multicentre study[3] confirms the relationship of small size at birth with blood pressure in young children from three developing countries (China, Guatemala and Chile). There was no relationship of small birth size with blood pressure in Nigerian children, confirming some previous observations in African subjects. The body proportions at birth in these babies were different not only from those in the developed countries but also between themselves, implying different patterns of intrauterine growth. Unfortunately, the study did not include Indian babies which are the smallest in the world, have a characteristic body composition and will grow up to become part of the massive epidemic of diabetes and coronary heart disease (CHD) over the next few decades.[4] In the Swedish children (control group from a developed country) there was a weak relation of blood pressure with 'thinness' at birth (low ponderal index). Thus, *any* disturbance of growth *in utero*: either throughout gestation (children from developing countries) or in the later stages (Sweden), occurring in malnourished as well as well nourished mothers, is associated with elevated blood pressure in later life. Aetiological factors in these different situations are likely to be different.

There are difficulties in performing Barker-type studies in developing countries but gradually data are emerging. A study in Mysore (India), showed that people who were born small (weight, length and head circumference) had higher prevalence of CHD (history of 'angina' and Q waves on resting electrocardiogram).[5] These people were born to mothers who were 'underweight'. On the other hand people who developed diabetes were short and fat at birth, and were born to 'overweight' mothers.[6] The sampling strategy in this study was not ideal and the criteria for diagnosing CHD have not been validated in Indians. In Pune, we have shown that insulin resistance and other cardiovascular risk factors in childhood are related to low birthweight, especially if there is subsequent 'catch up'.[7] A study in Jamaican children[8] showed a relationship between small size at birth and blood pressure, glycated haemoglobin concentration and serum cholesterol concentration, though the findings were not always reproduced in other studies of African children. A recent study in China showed that small size at birth increased the risk of insulin resistance syndrome in later life;[9] low body mass index of the mother was an independent risk factor.

If maternal (under)nutrition is a major influence in fetal 'programming', it will have substantial public health implications, especially in the developing countries. The 'original' fetal origins concept relates to fetal *undernutrition* in an *undernourished* mother. Fetal overnutrition, for example in an infant of a diabetic mother also increases future risk of diabetes and cardiovascular disease, suggesting a U-shaped relationship between intrauterine growth and adult disease, first demonstrated in Pima Indians for diabetes.[10] Public health interventions will need to keep this in mind.

In animals, dietary protein restriction in pregnancy predictably leads to higher blood pressure[11] and reduced insulin secretion[12] in the offspring. Human data is however inconsistent and somewhat confusing. Maternal starvation during the Dutch Hunger winter increased cardiovascular risk in the offspring[13] but not during the siege of Leningrad.[14] A number of recent publications relating maternal intake of carbohydrates, proteins and fats to fetal growth failed to show a consistent relationship.[15,16] Most studies have reported only maternal macronutrient intake. In our recent study in six villages near Pune, frequency of maternal intake of foods rich in micronutrients (green leafy vegetables, fruit and milk) and circulating concentrations of micronutrients (folate and vitamin C) were strong determinants of neonatal size.[17] Intake of calories, proteins and carbohydrates was not related. In studies from Aberdeen, *higher* intake of carbohydrates, proteins and fats during pregnancy has been associated with hypertension and diabetes in the offspring.[18,19] These results point towards the complexity of the relationship between maternal nutrition and fetal programming. The effects of nutritional factors may vary depending on the position of the population in the epidemiological and nutritional transition. In addition, the genetic makeup of the population will modify the response to nutritional stimuli.

Findings to date suggest there could be a multitude of mechanisms by which intrauterine environment could influence adult disease. There is little information on factors like intrauterine infections in relation to future cardiovascular risk. Rare mutations which affect glucose and insulin metabolism, cause diabetes and also affect fetal growth have been reported (glucokinase,[20] insulin receptor[21]), as well as other more common predisposing genetic polymorphisms (INS-VNTR[22], mitochrondrial DNA[23,24] and angiotensin-converting enzyme[25]). We need to know more about gene-environment interaction (nutritional and non-nutritional) during the intrauterine period which may hold important answers to this novel mechanism of disease. Only then may we think about public health interventions for primordial prevention.

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