Editorials

Foetal Solutions to a Fatal Epidemic: The Relevance in India

Hypothesis

David Barker's suggestion that the seeds of adult diabetes and cardiovascular disease (CHD) are sown during 'lean periods' in foetal life is a novel thought in cardiovascular medicine.[1,2] In a series of studies in men and women born in the United Kingdom in the first half of this century, he showed that 'smallness' (especially 'thinness') at birth due to intrauterine growth retardation (IUGR) predicted adult diabetes, hypertension and CHD. He speculated that the metabolic and structural adaptations to reduced supply of nutrients during critical periods of foetal development increase cardiovascular risk in adult life. The increased risk of diabetes and CHD in small babies has been confirmed in different populations of the world. To an average clinician weaned on the 'thrifty genotype' explanation for the aetiology of type 2 diabetes, suggestion of a 'thrifty phenotype' was a bit daunting. Unlike the thrifty genes which were thought to have evolved over thousands of years (conveying a sense of helplessness about their existence and inevitability about their continuation), the 'foetal origins' owe to disturbances in the few days of gestation. Risk of maternal gestational hyperglycaemia for future diabetes and obesity in the offspring was demonstrated previously[3-5] but its application to the general population was not appreciated.

The Indian scene

Maternal nutrition in India is amongst the poorest in the world and Indian babies are amongst the smallest, a third are low birth-weight (LBW, i.e. <2500 g) mostly due to IUGR. An epidemic of type 2 diabetes and CHD has swept across India in the last few decades. In 1975, the nine-centre Indian Council of Medical Research study reported the prevalence of diabetes in adults (>15 years) to be 2.3% in urban and 1.5% in rural India.[6] Subsequent studies have reported considerably higher prevalence. In Chennai, the prevalence of diabetes in adults (>20 years) was 8.2% in urban and 2.4% in rural areas in 1988; in 1994 it increased to 11.6% in urban areas—a rise of 40%.[7] A similar rising trend of prevalence and an urban–rural gradient have been reported for CHD.[8] India is an ideal ground to test the relevance of the 'foetal origins' of adult diabetes and CHD.

The profile of type 2 diabetic (and CHD) patients in India differs in many ways from that of white Caucasian patients in the western world.[9] At diagnosis, Indians are a decade younger, considerably thinner (particularly in the limbs) but centrally more obese, more insulin-resistant and hyperinsulinaemic. Metabolic components of the 'insulin resistance syndrome', i.e. high circulating triglycerides and low HDL-cholesterol are prominent in Indians; thus increasing the risk of CHD. Premature death due to CHD is a particularly worrisome feature. If the 'thrifty phenotype' were to explain some of these peculiarities, it would have profound implications in the prevention of these disorders.

Studies in India

When Professor Barker met us in 1991 we were excited to hear his ideas though with

some reservations. In India birth records are poorly kept, tracing individuals is difficult and death register information is particularly inadequate. It seemed a tall order to be able to do relevant studies.

Our first study was on four hundred 4-year-old children born at K.E.M. Hospital, Pune where birth-weights are recorded in the labour room register. Circulating glucose and insulin concentrations 30 minutes after an oral glucose load were related inversely to birth-weight but directly to current weight and skin-fold thickness.[10] Fasting and 2-hour glucose and insulin concentrations, lipids and blood pressure were not related to birth-weight. Thus, poor intrauterine growth (and subsequent obesity) was associated with a resistance to 'early stages' of insulin-mediated glucose disposal, possibly in the muscle and adipose tissue. This is the earliest age at which the relationship of poor intrauterine growth with glucose and insulin metabolism is demonstrated. These children were again studied at 8 years of age and the relationship of birth-weight with the 30-minute glucose concentration persisted. These children will be followed up to study their glucose–insulin metabolism and cardiovascular risk.

Another study at the Holdsworth Memorial Hospital in Mysore traced over 500 individuals born at that hospital and living in the surrounding area. Small babies (weight, length and head circumference) born to 'light' mothers had an increased risk of non-fatal CHD (angina and q waves in a resting electrocardiogram).[11] Small birth-weight was also related to insulin resistance (only men). Diabetes was, however, increased in short babies who were heavier and born to 'heavy' mothers with large pelvic measurements.[12] Short and heavy phenotype at birth was associated with deficient insulin response to glucose in adult life.

Relating the available data to the Indian epidemic

The association of LBW with insulin resistance (hyperinsulinaemia) in both the above studies is consistent with past findings. Being insulin-resistant from an early age could predispose to a spectrum of disorders grouped under the 'insulin resistance syndrome' (diabetes, lipid abnormalities, hypertension and CHD).[13] β-cell dysfunction due to whatever cause (genetic or environmental) in insulin-resistant subjects could precipitate diabetes at a relatively early age. Elevated risk of diabetes in short and heavy babies in Mysore is contrary to the 'thrifty phenotype' hypothesis which would have expected thin babies of malnourished mothers to get diabetes. The authors' speculation that 'heavy' mothers had gestational glucose intolerance ignores the fact that glucose intolerance was rare in India at the time these people were born. On the other hand, the increased prevalence of non-fatal CHD in short and thin babies born to light mothers in Mysore is consistent with previous reports in the West and merits further study in a prospective design.

A relevant question would be the numerical contribution of small babies to the 'epidemic' in a community. This is reported to be small for diabetes in Pima Indians[14] and for non-fatal CHD in the Nurses Health Study[15] but could be substantially more in the developing countries because of the high prevalence of LBW. The major concern in India is, however, that premature deaths due to undiagnosed diabetes and CHD will be missed in retrospective studies. In the recently reported Finnish study where lifetime information is available on all individuals, cardiovascular deaths were increased in thin babies born to short and fat mothers but reduced in thin babies born to thin mothers.[16] Such differential survival could influence prevalence figures of non-fatal CHD. We need to be cautious in interpreting cross-sectional data where information on deaths in the cohort is not available. If not, we could be misled in planning preventive programmes.

The urban–rural gradient and the rapid rise in the prevalence of diabetes and CHD in India over the last few decades is difficult to explain by the 'foetal origins' hypothesis alone. Birth-weights are lower in the villages where diabetes and CHD are uncommon, in urban babies with relatively higher birth-weights diabetes and CHD are fast increasing. It is clear that postnatal influences make a substantial contribution to the occurrence of diabetes and CHD. High cardiovascular risk in overseas Indian migrants highlights the significance of adult lifestyle.[17] A combination of poor

intrauterine environment (reflected in growth retardation at birth) and subsequent lifestyle of relative affluence (reflected in 'relative' obesity) seems to pose the highest risk for developing diabetes and CHD. Postnatal risk factors seem to be more detrimental in small babies adapted to a life of scarcity *in utero*. This is the basis for the *adaptation–dysadaptation hypothesis*.[18] A recent report supports this contention where adult obesity exaggerated glucose–insulin abnormalities in babies exposed to famine *in utero*.[19] It would appear that being small at birth may not be enough to get diabetes and CHD in adult life, being big as an adult is equally important.

Prospective studies could answer some of the controversies. In collaboration with Professor Barker we have studied prospectively, in 6 villages near Pune, the relationship of maternal nutrition before and during pregnancy with the pattern of babies' growth *in utero* and the phenotype at birth. These babies will be followed up to study cardiovascular risk factors and disease pattern in later life. Over the years, we hope to provide answers to some of the vexing questions related to the foetal origins of cadiovascular risk.

To conclude, the 'foetal origins' hypothesis of diabetes and cardiovascular risk is the most exciting development in cardiovascular medicine in recent years. This could be relevant to India, though important questions remain. The nutritional transition in urban India has contributed to the growing epidemic of diabetes and CHD in a population which suffered foetal malnutrition. Urbanization is associated with infections, atmospheric pollution and psychosocial stress which could have an important role to play in these epidemics. Preventive strategies may need to target the health of young women and mothers in addition to controlling the risk factors associated with urbanization.

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