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Commentary

Altered cord blood lipid profile, insulin resistance & growth restriction during the perinatal period & its potential role in the risk of developing cardiovascular disease later in life

The epidemiological studies carried out by Barker *et al*[1] in the late 1980s found that those who were born with low birth weights were at an increased risk for death from cardiovascular diseases. Based on this observation, they proposed the famous hypothesis concerning the foetal origin of adult diseases. In this theory, they have postulated that impaired foetal growth may have predisposed the surviving infants with low birth weights to heart disease in adult life. Since the initial observations by Barker *et al*, many animal studies and human epidemiological studies have shown an association between intrauterine growth retardation/ small for gestational age (SGA) and hypertension, coronary heart disease, insulin resistance, and other metabolic diseases in adult life[2-4].

The theory of a foetal origin for adult chronic diseases is of importance in South Asian countries, such as India, where cardiovascular diseases and diabetes are on the rise, and a large proportion of SGA infants are born due to maternal malnutrition[5]. The occurrence of heart disease is found to be 14 per cent higher in men and women who are born with birth weights <2.5 kg compared to those born with higher birth weights[3]. Evidence of early cardiovascular and metabolic diseases can be seen in the form of deranged lipid profiles and elevated insulin levels. The SAGA-ACT study[5] in this issue was designed to compare the cord blood lipid profile and serum insulin levels of SGA newborns with those of appropriate for gestational age (AGA) newborns. The authors enrolled a sample of healthy newborns, whose mothers were without major pregnancy complications, and who were born during a two month period at a tertiary care hospital in southern India. The enrolled infants were stratified based on birth weight, being either SGA or AGA. Cord blood lipid profile and serum insulin levels were measured in each newborn enrolled in the study. In addition, the total cholesterol/high-density lipoprotein (HDL) cholesterol ratio was also calculated for each newborn. A total of 103 infants were enrolled in the study, 51 of whom were considered SGA and 52 were AGA. Despite the relatively small sample size, the results showed significantly higher levels of mean total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol levels in SGA infants compared with those of the AGA infants. Mean very-LDL (VLDL) and total cholesterol/HDL levels were found to be lower in the SGA group. No significant difference in the mean insulin levels was observed between the two groups of infants. Furthermore, advanced maternal age and anaemia were found to have minimal, but not significant effects on the cord blood lipid profile difference between the two groups.

The results of this study are in line with those of several other studies, which have shown an association between low birth weight and an atherogenic lipid profile. A study of 296 neonates by Wang *et al*[6] reported higher levels of triglycerides, total cholesterol, and LDL cholesterol in SGA as compared with AGA neonates. Rodie *et al*[7] also reported similar outcomes where foetal lipids and triglyceride levels were found to be elevated in foetal cord blood from growth-restricted foetuses as compared with those of AGA foetuses. Although there are some studies such as that of Elizabeth *et al*[8] that report lower triglyceride and cholesterol levels in SGA infants compared with AGA infants, most studies support the findings of the SAGA-ACT study, and thus the concept of foetal origins of cardiac and metabolic diseases.

The current SAGA-ACT study[5] has an advantage over similar studies in that the lipid and insulin levels

were collected from the cord blood, which helps to avoid potential influences from postnatal factors. Since insulin plays a critical role in foetal growth and development, it has been suggested that disorders of glucose and insulin metabolism play an important role in the development of cardiovascular disease and type 2 diabetes in adult life. Although this study did not find any difference in insulin levels between the two groups, many studies, including a cross-sectional study by Wang *et al*[6], found increase in insulin resistance among SGA neonates. One explanation for this finding may be that while the metabolic derangements seen in SGA infants could have occurred much earlier in foetal life, their manifestations might not be present immediately in postnatal life. Furthermore, measuring simultaneous glucose and insulin levels with a glucose/insulin ratio could better help elucidate insulin resistance in this population. Previous studies suggest that the activity of lecithin–cholesterol acyltransferase (LCAT) plays an important role in the regulation of lipid metabolism. The activity of LCAT is reduced in premature infants and is linked to cholesterol and phospholipid levels in premature cord blood[9,10]. The investigation of LCAT activity and any association with elevated cholesterol levels in the cord blood of the SGA newborn infants in the SAGA-ACT study would have strengthened its conclusions.

The biological basis for the theory of the foetal origin of adult diseases is not completely understood. *In utero* foetal growth depends on many factors including maternal diet, the ability of the placenta to deliver nutrients to the foetus, foetal and placental hormones, and foetal genetic makeup. Disruption of the supply of nutrients to the foetus can alter its growth potential, which can have long-term anatomical and physiological consequences. The foetus maintains glucose homeostasis during these periods of malnutrition by developing insulin resistance in peripheral organs, a consequence of which is that there is increased production of insulin (hyperinsulinaemia) by pancreatic β-cells. Hyperinsulinaemia is known to enhance hepatic VLDL synthesis[11], which may contribute to increased levels of plasma triglycerides and LDL-cholesterol. Thus, these SGA infants develop a propensity to store fat, a calorically dense nutrient. Adipose tissues are known to regulate key metabolic systems of the body including insulin sensitivity; thus, it is conceivable that foetal modification of adipose tissues may lead to an increased risk for insulin resistance and metabolic complications. It has also been suggested that maternal levels of antioxidants such as vitamins E and C are linked to newborn birth weight[12,13]. Deficiencies of many of these micronutrients as a result of poor maternal diet and prenatal care can lead to oxidative stress and vascular inflammation[12]. This may play a role in the development of foetal complications during pregnancies. These risk factors can lead to atherosclerotic changes in the cardiovascular system. Assessment of cardiovascular risk through measurement of carotid and abdominal aorta intima-media thickness and other anatomical changes in foetuses and newborns could have helped validate the association between impaired foetal growth and the origin of adult diseases[14].

Although several studies including the SAGA-ACT study[5] support the hypothesis of a foetal origin for adult diseases, there are several postnatal factors including the velocity of catch-up growth, lifestyle, diet, and smoking that can modulate the risk of developing cardiovascular and metabolic diseases throughout the life of an individual. SGA infants with relatively fast catch-up growth rates have been found to have increased evidence of adiposity and unfavourable lipid profiles as compared with infants unable to catch-up growth[15]. The SAGA-ACT study is limited by its lack of long-term follow up of these growth-restricted infants. A long-term prospective study needs to be done to understand the continuous effects of abnormal lipid profiles, insulin resistance, and the effects of catch-up growth in growth-restricted infants. The possibility of a foetal origin for adult diseases is an important topic, both in developing countries, where maternal and foetal health can be compromised, and in developed countries, where obesity and type 2 diabetes are on the rise[16]. To better understand this phenomenon, studies such as the SAGA-ACT study need to incorporate long-term follow up along with methods to understand the roles of epigenetics and postnatal factors in the development of cardiovascular diseases and type 2 diabetes in growth-restricted individuals. This can help obstetricians and paediatricians to provide better health care to pregnant women and their growth-restricted neonates.

There is a saying that "You are what you eat". The literature concerning the possible foetal origin of adult diseases shows that this adage could be modified to say, "You and your children are what you eat". Having said that we strongly believe that all of these risk factors can be modified by changing lifestyles and developing healthy eating habits.

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