



Fetal Origin of Adult Disease

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Introduction

It is now widely accepted that the risks of a number of chronic diseases in adulthood such as insulin-dependent diabetes mellitus, hypertension and coronary heart disease may have their origins before birth. Professor David Barker and colleagues in Southampton have produced a large proportion of the data in this field over the last decade, although the relationship between early life events and adult disease had been raised many years earlier(1-2). Measurements made on babies at birth, including birth-weight, length, body proportions and placental weight, are strongly related to either later disease incidence (coronary heart disease mortality, non-insulin-dependent diabetes) or risk factors for those diseases (hypertension, glucose intolerance, hyperlipidemia) (1,3).

The 'Fetal Origin of Adult Disease (FOAD)' Hypothesis

Barker hypothesized that the associations between small size at birth or during infancy and later CVD reflect permanent effects of fetal undernutrition. The fetus is dependent on the nutrients from the mother and adapts to an inadequate nutrient supply in a number of ways: prioritization of brain growth at the expense of other tissues such as the abdominal viscera, reduced secretion of /sensitivity to the fetal growth hormones insulin and IGF-I, and up-regulation of the hypothalamo-pituitary-adrenal (HPA) axis. The FOAD hypothesis proposes that although occurring in response to a transient phenomenon (fetal under-nutrition) these adaptations become permanent or 'programmed' because they occur during critical periods of early development.

The hypothesis is supported by examples in experimental animals of permanent structural and

metabolic changes resulting from transient nutritional insults in utero. It is a well-established biological phenomenon and there are many well-known examples. Female rats given testosterone during the first 4 days fail to develop normal patterns of female sexual behavior (4). Thus a programming stimulus in fetal life. Underrubitions result in susceptibility to disease in later life, as reduced insulin sensitivity, low muscle mass, pancreatic beta cell mass and nephron numbers, altered arterial structure, and up-regulation of the HPA axis and sympathetic nervous system(5).

In rats, maternal protein restriction in pregnancy leads to higher blood pressure, impaired glucose tolerance, insulin resistance and altered hepatic architecture and function in the adult offspring.

There are a number of possible reasons why weight and height gain in childhood, on a background of fetal restriction, might be associated with disease. Low birth weight babies undergo compensatory post-natal growth, the rapidity of which may simply indicate the severity of the growth retardation. Alternatively rapid weight gain may be disadvantageous in itself, for example because of excess demand on tissues which are not capable of compensatory hyperplasia such as the pancreas , or through body composition(6).

The Fetal Origins Hypothesis

The role of Nutrition

Neonatal size is strongly related to maternal BMI, height, head circumference and even birth weight. This probably has both genetic and environmental components, but strongly suggests that the nutrition of a female throughout her life (during her own fetal life and childhood) as well as during pregnancy, influences the

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growth of her fetus. Nutritional effects on fetal growth are also shown by the drop in birth weight observed during famines (7). There is some evidence that improvement in the micronutrient quality of mothers' diets leads to an increase in fetal growth.

Among men and women born during the Dutch famine of 1944-45, late gestation exposure to famine was associated with glucose intolerance, insulin resistance, and a (small) increase in type 2 diabetes. Early gestation exposure was associated with higher LDL/HDL cholesterol concentrations and (in women) higher BMI and waist circumference. Three recent studies suggested that the balance of maternal protein and carbohydrate intakes during pregnancy is related to blood pressure in the offspring (8).

Low Birth Weight and Adult Cardiovascular Disease (CVD)

Following up this theory, by using 1911-1930 birth records for one English county (Hertfordshire), Barker showed that lower birth weight and weight at one year were associated with an increased risk of death from CHD and stroke (9,10). There was an approximate doubling of CVD mortality from the highest to the lowest extremes of birth weight, similar in men and women. It is restricted fetal growth rather than pre-term delivery which carries the risk of CVD. The effects are linear, graded across the whole range of birth weight and independent of adult socio-economic status.

CVD Risk Factors

Subsequent work has shown that lower birth weight and other measures of small size at birth are also associated with higher levels of some 'classical' CVD risk factors.

Insulin resistance syndrome, blood pressure, type 2 diabetes, insulin resistance, and combination of these are consistently related to low birth weight in a large number of studies in different populations(11,12).

Lipids and clotting factors: Although lipids show some associations with size at birth, these are weaker and less consistent.

Cardiovascular Function: Arterial intima media thickness and carotid stenosis, examined using ultrasound, are increased in lower birth weight men and

women and flow-mediated dilatation, a measure of endothelial function, is reduced in young adults and children of lower birth-weight (13-15).

Obesity: People who were heavier at birth tend to become 'fatter' adults as measured by body mass index. However, this may reflect increased lean mass rather than adiposity. There is no evidence that low birth weight leads to increased total body fat, but leptin concentrations were increased in low birth weight men and women in one study and central obesity has been linked to small size at birth. The sub scapular/triceps ratio is consistently higher in adults and children of lower birth weight (16-17).

Post -natal Growth and Adult Obesity

CVD and its risk factors are also linked to patterns of growth in infancy and childhood. In Hertfordshire, men with lower weight at the age of one year had increased CVD mortality and type 2 diabetes and also had higher fibrinogen and cholesterol concentration. This was confirmed in men born in Finland (18-20).

Unlike weight gain during infancy, accelerated childhood weight gain is associated with an increased risk of high blood pressure in young adults.

Fetal Growth and Type 2 Diabetes

Low birth weight is also associated with a high prevalence of the insulin resistance syndrome. Data from animals and recent human observations have suggested a mechanism in that adverse events in early life which lower birth weight, appears to permanently alter or 'programme' the secretion of stress hormones including cortisol. Together with obesity this leads to a high risk of the metabolic syndrome and the predisposition to cardiovascular disease.

Maternal Diabetes and Fetal Macrosomia

Recent data shows that diabetes in mothers, which results in fetal macrosomia, also has an increased risk of obesity and type 2 diabetes in their offsprings compared with offspring of non-diabetic mothers or women who become diabetic after pregnancy. The difference in risk holds true for siblings born before and after the onset of maternal diabetes and is not seen among offsprings of diabetic fathers. Gestational diabetes produces a U- shaped or J- shaped relationship between birth weight and adult type2 diabetes.(19)



Neurodegenerative Disease

There is preliminary evidence that a bacterial stimulus (endotoxin) can produce cytokines that impair the development of the mesencephalic dopaminergic systems during pregnancy leading to a possible increased risk for Parkinson's disease in later life. There is preliminary evidence that exposure to environmental neurotoxins during dopaminergic development enhances the susceptibility to accelerated dopaminergic cell death during aging. In utero exposure to polycyclic biophenols (PCGs) leads to altered thyroid function and subsequent learning disabilities later in life (21).

Immune System Programming

The development of immune system, including the development of the repertoire of reactive lymphocytes that will exist in postnatal life, begins prenatally. Alteration of the fetal immune environment might pre programme the highly sensitive fetal immune system for aberrant immune regulation, leading to loss of tolerance to self- antigens and resulting in an increased risk for autoimmune disease. These changes might manifest in adult life and perhaps only after a second exposure to related environmental chemicals. There is evidence in humans and experimental animals that prenatal exposure to immunosuppressive drugs can lead to a higher risk of autoimmune disease in the later life(21).

Birth Defects and Fetal Basis of Adults Disease

It is recognized that two to five percent of all live-born infants have a major birth defect. Approximately 40 percent of these defects are thought to be due to the effect (s) of an adverse exposure of genetically pre-disposed fetus to intrauterine environmental factors. Exposure to environmental agents during early development can result in death, structural malformation, and / or functional alteration of the embryo/ fetus. These toxicant induced pathogenic responses are most likely the result of altered gene expression associated with altered cell production and cell differentiation (21).

Cleft Palate

Cleft lip and palate is common disfiguring birth defect and results from miscues during fetal development of facial structures. This may be triggered in the fetus by the mother's exposure to the environmental toxins and

interactions.(22)

Cardiac Malformations

Cardiovascular malformations (CVM's) are the most common type of birth defect in the US, affecting almost 1% of live births. Causes include genetic, maternal disease, drugs such as phenytoin and cocaine, dietary factors such as folic acid deficiency, vitamin A excess and copper deficiency and certain environmental chemicals (e.g., paints, solvents and degreasers, pesticides, air pollutants, trichlorethylene, bis-diamine,dioxin) (22) .

Cancer

Childhood leukemia and brain cancer may have environmental components in their development due to pesticides. DES daughters have risk of cancers and abnormalities in reproductive tract.

Diabetes

Type 1 Diabetes Mellitus is a common and serious disease of the childhood. There is a 40-45% risk of inheriting this disease through high risk HLA alleles and is influenced by other factors like viruses, nutrition, toxic agents and socio- economic factors. Agricultural Health study from UK shows that the incidence is common in the areas with high nitrate levels in water.

Controversies for the FOAD Hypothesis; Clinical Importance

It has been argued that the increased risk of adult disease attributable to intra-uterine under nutrition is very small and the effects are most marked at the extremes of birth weight. In addition, effects of size at birth are conditioned by childhood growth and adult obesity and predict large differences in the risk of CHD, hypertension and diabetes (23).

Controversies for the FOAD Hypothesis; Genes 'Versus' Environment

The time trends in CVD and type 2 diabetes in western countries and in different socioeconomic groups during the 20th century, and the recent rise in developing countries, suggest a susceptibility to environmental changes, which could either have a genetic basis (thrifty genotype) or arise from fetal programming (thrifty phenotype). However these would make different predictions for the future. The former would predict



continuing high levels of disease unless people reduce their lifestyle risk factors and become less obese. The later would predict a downturn in disease as better nutrition of girls and mother leads to improved fetal nutrition.

The 'genes versus environment' debate is currently stimulating a great deal of hypothesis-testing research in this field. With increasing understanding of epigenetic effects and gene-environment interactions, it is no longer possible to think of disease as being either 'genetic' or environmental.

Relevance of FOAD to India and Developing Countries

The linear and graded trends in CVD mortality with birth weight suggest that majority of the world's population experience sub-optimal fetal growth being highest in developing countries. In India the mean full-term birth weight is 2.6-2.7kg, almost 1 kg lower than in Western Europe (24). A high proportion of infants and children in India are still undernourished, but with economic progress, childhood and adult obesity is an emerging problem, especially in cities (30). It is estimated that 20% of women and 16% of men in India will be overweight (BMI>25kg/m²) by the year 2020 (25).

Furthermore, there is evidence that any level of BMI, South Asian is & women have a higher fat mass, more centrally distributed fat, and a higher risk of Obesity associated disease than white caucasians (26).

According to the FOAD hypothesis, increasing child and adult obesity in combination with persistently poor fetal growth creates a high risk for adult CVD and diabetes more so because of undergoing rapid economic development and modernization. In India mortality from cardiovascular disease is expected to rise by about 60% and overtake deaths from infectious disease, by 2015-20 (27). The prevalence of type 2 diabetes has increased by 40% in Chennai, India between 1988 and 1994 (30). King has predicted (28) that the prevalence of type 2 diabetes will rise by 30% world wide, from 4.0% to 5.4% by 2025, and that the proportional rise will be greatest in developing countries (48%), especially China (68%) and India (59%). India will have more people with diabetes (57 million) than any other country, with the

greatest numbers in the 45-64 year age group with likelihood increase in type 2 diabetes in children.

There are many research projects under way in various parts of India i.e. Pune, Mysore, New Delhi, Vellore and some setup by ICMR to clarify the relative importance in Indian populations, of maternal size and body composition, and individuals own neo-natal size, childhood growth and adult body composition and life style to CVD risk.

Public Health Implications and Future Research

The FOAD hypothesis is attractive because it suggests that several common degenerative diseases could be prevented by improving maternal health and fetal development. Data from experimental animals provide powerful evidence that a mother's nutrition programs the metabolism of her offspring.

Future research (Epidemiological as well as Experimental) is in progress through out world to explore the relationships between prenatal, natal and post natal life and also on fetal retardation, its neuro- endocrine and metabolic effects; and the possible mechanism by which metabolism, body composition and growth may be permanently affected. Thus the public health implications of this concept are quiet this evident.

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