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Early Nutrition and Adult Health: How Strong are the Links?

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INTRODUCTION

The possibility that the nutrition in utero, in infancy and early in childhood can have a significant influence on health in later life was first proposed over 65 years ago (Kermack *et al*., 1934). Now that we know the long-term effects of single nutrient deficiencies, for example those of iodine and of folic acid. on the fetus and on the young child, such an association is unsurprising. Furthermore, when one considers the wide range of potentially toxic exogenous materials to which the fetus and infant are exposed via the diet, we are equally alert to other long-term effects. These hazards include specific, possibly non-nutrient, plant components such as phytosterols, residues of veterinary products (hormones and antibiotics), allergenic molecules, pollution arising from the use of fertilizers and pesticides or from the environmental release of dioxins and polychlorinated biphenols and radionucleides, and chemicals (e.g. phthalates) used in packaging materials. The outcomes of such exposure have been proposed to be the development of ambiguous genitalia, impaired sexual development and reduced fertility, reduced sperm counts, increased risk of cancer, impaired thyroid function and altered immunity. These hazards and the associated risks have been subjected to systematic characterization and assessment, and risk management has invariably resulted in the restrictions being imposed on the use and environmental release of such compounds. (Aggett & Kuiper, in press)

Recently interest in the possibility that quantitative and qualitative supply of essential components of the diet might influence health in later life was revived by Professor David Barker and his group at the MRC Epidemiology Unit at the University of Southampton, United Kingdom. Essentially, the group set out to investigate whether or not the observed variance and inconsistencies observed in the association of accepted risk indicators, such as obesity, lifestyle, smoking, alcohol consumption, saturated fat intake etc., with diseases such as coronary heart disease, hypertension, and other conditions which cause premature death, could be explained by a background propensity for these conditions which had been predetermined by intrauterine and early childhood experiences, particularly those related to nutrition. (Barker, 1993; 1994; 1995).

It was proposed that the long term function and responsiveness of developing tissues and organs could be programmed by the nature of the nutrient exposure and metabolic demands imposed on them at critical points in their growth, maturation and development. Although these points have not been well identified, the fetus and infant progress through significant metabolic transformations, some of which might be crucial to metabolic and functional programming (Koletzko *et al*., 1998). For example, the fetus is exposed to a constant transplacental stream of nutrients. To some extent this supply is regulated by the placenta. which can also protect the fetus from toxic and metabolic insults through its detoxification and sequestration mechanisms. It is also worth noting that the fetal circulation preferentially directs the oxygen and nutrient

enriched blood returning from the placenta towards the cranium and that the portal circulation is relatively small thereby reflecting the relative low dependence of the fetus on hepatic and intestinal function. Alter delivery the supply of nutrients becomes periodic and is particularly rich in lipids. The portal circulation becomes established, and the neonate needs to depend on its own gluconeogenic pathways. With the introduction of complementary feeding, the nutrient supply becomes more carbohydrate predominant and the infant develops, for example, fatty acid synthetic mechanisms. The nutrient-gene interactions involved with metabolic maturation and its adaptation to changes in quantitative and qualitative nutrient supply are being elucidated in animal models. The processes in man are poorly understood, but the implications of such relationships between early intrauterine and postnatal nutrition on adult disease and premature death, if indeed they are strong, have considerable implications for public health policy.

Associations between Fetal Growth and Health in Later Life

Barker's group have shown in numerous papers many intriguing associations of neonatal, infant, and maternal anthropometry and related characteristics with increased prevalence of adult diseases such as coronary heart disease, hypertension, stroke, altered lipid metabolism, impaired glucose tolerance, insulin resistance, and diabetes mellitus. Some examples of these follow.

Low birth weight, usually below 5.5 pounds (approximately 2.5kg) has been associated with increased and higher birth weights with decreased prevalence of death from coronary heart and cardiovascular disease, increased systolic and diastolic blood pressure, impaired glucose tolerance and insulin resistance, elevated serum total and LDL cholesterol levels and plasma fibrinogen and factor VII concentrations, and, in women, higher prevalence of thyroid antibodies. Crown-heel length at birth has been inversely associated with blood pressure as has been head circumference. Larger abdominal girths at birth have been associated with lower serum fibrinogen, total and LDL cholesterol and apolipoprotein B concentrations.

Other similar associations have been reported from populations outside the UK. For example in south India low birth weight, short birth length and small head circumference were found to correlate with increased prevalence of coronary heart disease (margetts *et al*., 1991). In the Gambia, the blood pressure of 8 years old children was inversely related to maternal weight gain in the final trimester of pregnancy (Stein *et al*., 1996). A study from Finland found that the prevalence of subsequent coronary heart disease in men correlated inversely with maternal weight during their gestation (Forsen *et al*., 1997). In Jamaica correlations between birth weight and length and risk indicators for cardiovascular disease, such as circulating cholesterol levels, were found in childhood (Forrester *et al*., 1996). These associations imply a broader generality for the concepts of Barker's work, and they show that biochemical and physiological factors which might be representative of any predisposition created earlier can be detected in childhood. Additionally, one can probably have greater confidence in the quality of the neonatal and maternal data in the relatively short-term studies conducted on children.

Such epidemiological associations would seem to support the crucial relationship of early growth to the pathogeneses of later disease. Increasingly sophisticated analyses of the anthropometric data from the newborn have been undertaken. In part these were to explore why previously demonstrated relationships were not apparent in some subsequent studies, but these further

analyses of the infant anthropometric data were developed also to try to identify the period and timing of any intrauterine insult which might have impaired growth.

A concept of disproportionate and proportionate growth retardation was applied to the analysis of the anthropometric data. Early gestational insults were presumed to reduce linear growth, and mid-trimester events to result in disproportionate growth with small head circumference and impaired skeletal muscle development. This was associated with insulin resistance and increased rates of cardiovascular disease and hypertension in adulthood. Insults in the last trimester were associated with poor weight gain, thinness and reduced abdominal circumference. The latter being interpreted as indicating reduced liver size with consequent impairment of lipid metabolism and of fibrinogen and factor VII synthesis. Early gestational "nutritional deprivations" were also considered to induce greater growth of the placenta. Thus associations between these additional indices of impaired fetal growth such as placental weight to birth weight ratios, the ponderal index (weight/length^3) and cardiovascular disease prevalence; impaired glucose tolerance and obesity were shown.

The relationships and the interpretation of the data were becoming complicated and difficult to explain metabolically. The complexity of some of these relationships is illustrated by a study from Aberdeen (Campbell *et al*., 1996), which investigated the correlation between maternal diet during pregnancy with the blood pressure of the offspring forty years on. It was shown that, amongst women on daily carbohydrate intakes in the range of 100-600gm and on less than 50g of animal protein per day during pregnancy, higher carbohydrate intakes were associated with increased systolic blood pressure in their "children" (a 100g increase was associated with a 3mmHg increase in systolic blood pressure). On the other hand, if the daily intake of animal protein was more than 50g daily, there was an 11mmHg decrease in systolic blood pressure for every 100g increase in carbohydrate intake. In this study there was no association between maternal nutrient intake and birth weight with the exception that higher protein intakes during pregnancy were associated with lower birth weights. It is noteworthy that this is one of the few studies on this topic, if not the only one, to have good data on the dietary intakes of the mothers during their pregnancies.

Some investigators have investigated the effect of early growth retardation on skeletal muscle function (Taylor *et al*., 1995). Muscle metabolism in a cohort of women who had had a low ponderal index (less than 23 kg/m^3) at birth was compared with that in women whose birth ponderal index had exceeded 23kg/m^3. The first group was more easily fatigued (flexor digitorum superficialis) and in early exercise their muscle phosphocreatinine and adenosine diphosphate respectively fell and increased more rapidly. There are few such mechanistic studies in man, but these findings are in accord with findings in experimental models (Dauncey, 1996) and point to a plausible basis for some relationships that have been found in epidemiological studies.

The associations that have been demonstrated do not necessarily represent causal events. Although these epidemiological associations are being interpreted as evidence of programming in human beings, this cannot really be claimed. The data might support Barker's concept of a propensity against which other dietary and lifestyle factors operate. This is no more than he proposed: it was never implied, in this context, that one's fate could be wholly determined in

utero. Elements of metabolic programming would contribute to that propensity. Unfortunately, the etiological database is not strong yet, and there is a persisting concern that very few of the published papers provide any information to support the concept that the impaired fetal growth necessarily represents intrauterine malnutrition. This element of the hypothesis derives from studies in animal models.

Data from models suggest several mechanistic bases for any association between early nutrition and later health. (Kermack *et al*., 1934; Dauncey, 1996; Fowden *et al*., 1998; Gardner *et al*., 1998). These include the selection effect of nutritional insults or intrauterine deprivations reducing cell numbers in some tissues and organs (e.g., the pancreas), favoring a particular series of stem cells or clones even before implantation, altering the endocrine milieu and metabolic sensitivity via influences on the expression of endocrine receptors, and the regulation of the pituitary-hypothalamic endocrine axes involving somatotrophin and glucocorticoids, and altered insulin secretion.

Reservations about the claimed links between early diet and adult health

Some reservations have been expressed about the evidence that early nutrition might influence later health and disease (Kramer & Joseph, 1996; Joseph & Kramer, 1996; Grivetti *et al*., 1998). The review by Joseph and Kramer discusses the following points in much more detail and it is recommended to anyone who wishes to have an alternative perspective on this topic and the methodologies used to study it (Joseph & Kramer, 1996).

Understandably, there are reservations about the reliability of the historical data as well as the quality of information and measurements made by many observers. The paucity of information about the nutrition of the mothers in published studies has been mentioned. The need, in establishing associations, to derive additional parameters from anthropometric data, such as ponderal indices, placental birth weight ratios, head circumference to crown heel lengths are seen as questionable. Essentially this is because the assumptions about the differential effects of early and late insults on intrauterine growth retardation have not been well validated, and neither has abdominal girth as a proxy of liver size. It has been pointed out that the value of distinguishing disproportionate from proportionate growth retardation is compromised by the severity of that growth retardation. It is argued that if this were corrected for them any proportionality or lack thereof has little etiologic or predictive value. More recently, Cole et al have queried the applicability of the ponderal index as an indicator of thinness or intrauterine malnutrition because it does not adjust for changes in length and gestation.

Another inevitable question is as to whether or not the observed associations always represent the outcomes of intrauterine nutritional or metabolic insults. Relatively few studies actually provide information about maternal dietary intakes and their distribution throughout pregnancy. This point is accompanied by concerns that confounding factors might not have been measured. Although some groups have shown that some of the relationships occur independent of socio-economic factors or class, the additional issue is raised about the timing of these factors and the certainty with which they are known.

Another criticism is that of selection bias. In many of the retrospective studies, only small

cohorts were available for follow up. Thus, it is difficult to be certain of how representative the residual group is of the original cohort. Of equal importance is that not all studies have demonstrated the associations outlined above. For example, some have found no correlation between low birth weight and blood pressure (Seidman *et al*., 1991). Difficulties in understanding such relationships can be seen in a study in 8-11 year old children which found no relationship between ponderal index or length: head circumference ratio at birth and blood pressure in childhood. An inverse association between birth weight and blood pressure was shown but essentially only in girls; the relationship was weak in boys. It was felt that current body size was a more important determinant of blood pressure in these children than size at birth (Taylor *et al*., 1997). Similarly in another study glucose metabolism and circulating insulin concentrations were most closely related to contemporary weight than to birth weight (Whincup *et al*., 1997).

The concept that adult chronic diseases are to some extent predetermined by early intrauterine and infant nutritional experience is appealing and has generated a lot of epidemiological study. Many challenging associations have been found between neonatal and maternal anthropometric measurements (and derived ratios) and later metabolic phenomena and premature disease. The difficulties of acquiring and interpreting retrospective data have been highlighted, particularly in allowing for possible confounders. Few studies provide information on nutritional exposure, and there are now few prospective data to strengthen the evidence. Nonetheless, it remains a challenging concept. It seems unlikely that further epidemiological studies would advance this issue. What would be better would be investigations directed at understanding better the ontogeny of substrate metabolism and its control from which hypotheses relating to stem cell selection, selective cell death, and nutrient-gene interactions. On the basis of animal models and the importance in human studies of associations with placental size, it would seem important to target in this exercise cellular differentiation in the preimplantation embryo.

As regards the public health implications, clearly the understanding of such relationships would place nutritional intervention strategies during pregnancy and infancy on a firmer foundation and would enable the development of prospective studies and predictive markers. Nevertheless, it is important to note that at a pragmatic level most, if not all, of the nutritional policy implications arising from the current evidence would be met by following current nutritional guidelines.

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