Chapter 11

THE LONG TERM EFFECTS OF EARLY POSTNATAL DIET ON ADULT HEALTH

S.E. OZANNE
Department of Clinical Biochemistry, University of Cambridge, Addenbrookes Hospital Cambridge, CB2 2QR, U.K. seo10@mole.bio.cam.ac.uk

1. INTRODUCTION

It has been recognised for over seventy years that the early environment in which a child grows could have long-term effects on its health.[1] This was suggested based on observations in England, Scotland and Sweden that death rates in specific age groups at any time depended more upon the date of birth of individuals than upon the year under consideration.[1] Further support came from a study by Forsdahl *et al* looking at geographical variations in current death rates from arteriosclerotic heart disease in Norway.[2] This showed that there was a significant positive correlation between these current death rates and geographical variations in past infant mortality rates. No such relationship was observed with current infant mortality rates[2]. It was subsequently shown that the geographical pattern of mortality from cardiovascular disease in England and Wales was related to maternal and neonatal mortality earlier in the century.[3] This was suggested to reflect a relationship between poor nutrition in fetal and early life, and cardiovascular disease.

A large number of epidemiological studies have subsequently demonstrated that there is a relationship between poor fetal and early growth and the development of adult diseases such as type 2 diabetes and the metabolic syndrome.[4] This relationship has been observed in a wide range of populations worldwide in different ethnic groups; thus the existence of the

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relationship is widely accepted.[5] However the mechanistic basis of this relationship and the relative role of genes and the environment and the interaction between the two remains the subject of much debate. Rare mutations have been identified in the glucokinase gene which have been associated with a low birthweight and the development of a rare monogenic form of diabetes, maturity onset diabetes of the young.[6] However extensive genome scans have failed to identify common diabetes susceptibility genes/polymorphisms. Recent studies have identified interesting gene-birth size interactions in the case of peroxisome proliferator receptor (PPAR)-gamma 2 gene polymorphisms.[7]

Some of the strongest evidence for the importance of the early environment in mediating the relationship between poor early growth and adult disease has come from the study of twins. A study of middle-aged twins in Denmark revealed that, in both monozygotic and dizygotic twin pairs who were discordant for type 2 diabetes, the diabetic twin had a significantly lower birthweight than the normoglycaemic co-twin.[8] Monozygotic twins are genetically identical, and therefore the difference in birthweight must be related to the fetal environment. A second study of twins in Italy who were significantly younger (mean age 32) than the cohort in Demark revealed similar findings.[9] These studies thus provide strong evidence for the importance of a non-genetic intrauterine factor in the development of type 2 diabetes in later life.

In light of the epidemiological observations it has been proposed that poor fetal nutrition leads to programming of metabolism in a manner beneficial to survival under conditions of poor postnatal nutrition.[10] This would give rise to a "Thrifty Phenotype" in which the organism was adapted to store carbohydrate. This metabolic programming was proposed to become detrimental if the fetus was born into conditions of either adequate or over nutrition, and obesity occurred. It may also increase the risk of the development of obesity. This has therefore drawn attention to the possibility that postnatal nutrition may be as important as antenatal nutrition in determining long-term health. More specifically the focus has been directed towards the role played by nutrition during the neonatal period.

2. EVIDENCE

2.1 Interactions between poor fetal growth and adult obesity

The apparent conflict between fetal nutritional experiences and adult obesity has been demonstrated by a number of human epidemiological studies. A study of 64-year old men in Hertfordshire U.K. demonstrated that the individuals with the worst glucose tolerance were those who were born small and who were currently obese.[11] Individuals with a high birthweight were relatively protected from the detrimental effects of obesity. Individuals who were born small but remained thin were also protected from diabetes. This would explain why in countries where there is chronic malnourishment, the prevalence of the metabolic syndrome is very low. Studies of individuals who were *in utero* during the famine known as the Dutch Hunger Winter have also shown that for any current body mass index, glucose tolerance was worse in those individuals exposed to the famine *in utero* compared to those born the year before the famine.[12] This meant that frank diabetes was generally only present at age 50 in those individuals who were malnourished *in utero* and were currently obese. The detrimental effects of poor early nutrition and adult obesity have also been shown in animal models. For example early protein restriction and adult obesity (induced by the feeding of a cafeteria diet) have been shown to independently and additively cause an increase in systolic blood pressure in rats.[13]

2.2 Catch-up growth

The importance of rates of growth during early postnatal life has become apparent from a number of epidemiological studies. A study by Crowther *et al* on 7 year old South Africans revealed that those children born with low birthweights but who underweight rapid childhood weight gain had the worst glucose tolerance and were thus proposed to be most susceptible to development of type 2 diabetes in adulthood.[14] Further studies by the same group have related these differences to alterations in ß cell secretory activity.[15] Children who had low birthweights and low weights at age seven had the lowest ß cell secretory response. However the children who were born small but had high weights at age 7 years had the greatest ß cell response and were most insulin resistant (as assessed by HOMA) but had the poorest glucose tolerance. They also had the lowest percentage of mature insulin and the highest percentage of pro-insulin and partially processed

intermediates. It was concluded that poor fetal growth followed by higher postnatal growth results in low ß cell numbers and reduced whole body glucose uptake which leads to reduced efficiency in the processing of pro-insulin. Similar deleterious effects of poor early growth followed by rapid catch up growth have been observed in a cohort of Finnish men and women.[16] The incidence of type 2 diabetes was shown to increase with decreasing birthweight. It was also observed that individuals who developed diabetes had above average heights at age 7 and age 15. This again suggests that the increased risk of diabetes that is associated with small size at birth is further increased by high growth rates in childhood. A study of pre-term children who were aged 9-12 years has shown that glucose concentrations 30 minutes after a glucose load were negatively related to birthweight.[17] Fasting split pro-insulin concentrations were highest in children who showed the greatest increase in weight centile between birth and time of study. Rapid growth during early life has also been associated with increased risk of cardiovascular disease. A study in Finland showed that the highest death rate from coronary heart disease occurred in men who were thin at birth but whose weight caught up postnatally such that they had an average or above average body mass from the age of seven years.[18] It was concluded that death from coronary heart disease may be a consequence of poor prenatal nutrition followed by improved postnatal nutrition. Accelerated neonatal growth has also been associated with lower flow-mediated endothelium-dependent dilation in young adolescents.[19]

Studies in rodents have also demonstrated that differences in early growth rates can ultimately affect longevity. The offspring of rat dams fed a low (8 %) protein diet during pregnancy have around a 15 % reduction in birthweight compared to control offspring of dams fed a 20 % protein diet. If these animals are cross-fostered to normally fed dams at birth they undergo rapid catch-up growth during the lactation period. This catch-up growth observed in these recuperated animals has a detrimental effect on longevity, resulting in approximately a 25 % reduction in lifespan in male rats.[20] The major cause of death in male rats is reported to be renal failure. Consistent with this is the observation that the reduced longevity in the recuperated animals is associated with accelerated loss of kidney telomeric DNA.[21] In contrast control offspring suckled by low protein fed dams and which therefore grew slowly during the lactation period have a substantial increase in longevity. Similar findings have recently been observed in mice.[22] These studies in mice revealed an interesting interaction with the post-weaning diet. An obesity-inducing cafeteria-style diet reduced the longevity of both control and recuperated animals. In contrast the animals that were suckled by low protein fed dams and thus grew slowly during the lactation period were completely protected from the detrimental effect of the obesity-inducing diet

to reduce longevity. The mechanisms underlying these effects are not known however there is an urgent need to see if similar mechanisms operate in humans.

There is some recent evidence from a study of young teenage children who were born pre-term to suggest that relative under-nutrition early in life may have beneficial effects on insulin resistance.[23] It was shown that those children who had been randomised to receive a nutrient-enriched diet neonatally had higher fasting 32-33 split pro-insulin concentrations than those given a lower nutrient diet. Breast-milk feeding, which is associated with slower growth than formula-feeding has been shown to be associated with reduced C-reactive protein and LDL to HDL cholesterol ratio in 13-16 year old children who were born pre term and breast-milk fed compared to those who were formula fed.[24] This suggests that breast-feeding is protective against the risk of atherosclerosis. Weight gain from birth to two years has also been shown to be a predictor of overweight at age six.[25]

2.3 Programming of appetite

In addition to being key to the full expression of the Thrifty Phenotype, it is also possible that obesity itself is a manifestation of the Thrifty Phenotype. Several studies have linked low birthweight to changes in body composition in adulthood including increased central fat[26] and reduced lean mass.[27] There is some evidence that the timing of the nutritional insult may also have an impact on the future susceptibility to obesity. Studies of men who were exposed to the Dutch Hunger Winter in early life have revealed that those who were exposed to the famine during the first half of pregnancy were more obese at age 19. In contrast those who were exposed to the famine during the last trimester of pregnancy and in early postnatal life had reduced obesity.[28] This provides some of the earliest evidence from human studies that nutrition during the neonatal period can have long terms effects on future susceptibility to obesity. It pointed towards slow growth during the lactation period actually having a beneficial outcome.

The detrimental effects of poor antenatal growth are exaggerated by rapid postnatal weight gain. Rapid weight gain in infancy has been shown to be a risk factor for future obesity. Infants who were growth restricted *in utero* and underwent postnatal catch-up growth between birth and 2 years of age have been shown to be fatter and to have more central fat than other children.[29] The mechanisms underlying postnatal catch-up growth are not well defined. However such rapid growth may be the consequence of programmed changes in gene expression that were established *in utero*. This therefore makes the interpretation of the role of postnatal growth patterns and scope for intervention complicated. It has been shown in a rodent model

that maternal protein restriction is associated with increased expression of insulin receptors which could drive post natal weight gain.[30] It may also be a consequence of programmed changes in appetite. Thus epidemiological studies showing relationships between post-natal growth and obesity with the long-term risk of disease might simply reflect patterns of gene expression already established during fetal life.

Increased rates of postnatal weight gain have been associated with reduced satiety in small for gestational age (SGA) infants (as assessed by volume of milk consumed by bottle-fed infants).[31] Leptin is one of many potential candidates that could mediate these changes in appetite. It has been shown that cord blood leptin is inversely related to rates of growth during infancy and that SGA infants have lower leptin concentrations.[32] One possibility therefore is that low leptin levels in SGA infants lead to reduced satiety and rapid postnatal weight gain. There are also a number of studies that have also suggested that breast-feeding is protective against obesity risk in later childhood. [33] These effects are not confounded by socioeconomic status. [34] It is thought that the reduction in risk of obesity is related to properties of human milk than to factors associated with breast-feeding.[35] Bottle-fed infants are known to have higher total energy and protein intakes than breast-fed infants [36] so one possible explanation is that early breast-feeding may affect subsequent appetite regulation.

Studies in rodents have also revealed that early nutrition can have long-term consequences on appetite. Early studies with rats where nutrition during lactation was manipulated by altering litter size revealed that reduced nutrition during lactation resulted in a permanent reduction in appetite.[37] More recent studies of litter size manipulation have revealed that rats in small litters have increased plasma insulin levels increased weight gain.[38] The authors hypothesised that hyperinsulinism during brain differentiation (as caused by overfeeding in a small litter) was a pre-disposing factor for the development of obesity, diabetes and cardiovascular disease. Further studies have shown that rats from small litters have reduced responsiveness of their paraventricular neurons in the brain.[39] Severe energy restriction during pregnancy has also been shown to lead to hyperphagia in adult life.[40] These findings suggest that appetite can be programmed upwards or downwards depending on the timing of the insult and suggest that the early postnatal period may be a time window for targeted intervention. Recent studies in mice have also pointed towards both the fetal and postnatal period being critical time windows for appetite regulation. Mice who were growth restricted *in utero* by maternal protein restriction but were cross-fostered to normally fed dams at birth and underwent rapid postnatal catch-up growth were permanently heavier than control offspring.[41] This effect was exaggerated when the animals were weaned onto an obesity-inducing

cafeteria-style diet. In contrast control offspring who were suckled by low protein fed dams and therefore grew slowly during the lactation period were permanently smaller than controls despite being weaned onto standard laboratory chow fed *ad-libitum*. They also gained less weight when weaned onto a cafeteria-style diet suggesting that they were relatively protected from its normal obesity-inducing effects.

Further evidence for the importance of the lactation period has come from cross-fostering experiments with diabetic rats. Control offspring that were cross-fostered and suckled by rats that had diabetes developed changes in the orexigenic and anorexigenic circuits in the brain.[42] If these changes were permanent they could have lifelong changes in regulation of food intake. There is evidence to suggest that these findings may be relevant to humans. A study of two year-old children showed that those who had breast-milk from diabetic mothers had an increased risk of becoming overweight and developing impaired glucose tolerance.[43]

The identification of the lactation period as a critical period for determination of appetite has been further emphasised by recent studies of transgenic animals. These demonstrated that neural connection pathways from the arcuate nucleus of the hypothalamus were permanently disrupted in leptin deficient mice.[44] Leptin treatment in adulthood, although normalising body weight was unable to reverse the neuro-anatomical defect. However treatment during the perinatal period completely restored the density of innervation to that observed in wild-type mice.[44] It is known that the timing of opportunity for rescue coincides with surge of leptin in control animals. This therefore provides a potential mechanism by which manipulation of food intake during a critical time period can have effects on adult appetite.

3. CONCLUSIONS

There is now overwhelming evidence to suggest that experiences during both the fetal and neonatal period can have long terms effects on health. Poor fetal growth followed by rapid postnatal catch-up growth appears to be particularly detrimental. The interpretation of the relationship between the two is complex. Therefore the designation of suitable intervention strategies is not straightforward and requires further research effort.

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