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Resource allocation in utero and health in later life

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ABSTRACT

The way that a fetus obtains and allocates nutritional resources has profound consequences for its life-long health. Under the new developmental model for the origins of chronic disease, the causes to be identified are linked to normal variations in the processes of feto-placental development, that are associated with differences in the supply of nutrients to the baby. These differences programme the function of a few key systems that are linked to chronic disease, including the immune system, anti-oxidant defences, inflammation, and the number and quality of stem cells. There is not a separate cause for each different disease. Which chronic disease originates during development may depend more on timing than on qualitative differences in experience.

1. Introduction

The way that the human fetus obtains and allocates nutritional resources has profound consequences for its life-long health. Like all life forms humans are challenged during their development. There are insufficient resources to perfect every trait [1]. Resources are limited by the availability of nutrients in the mother's body, her ability to deliver them to the placenta and the effectiveness of the placenta in transporting nutrients from mother to baby. This paper reviews resource allocation in utero and how it programmes health and disease in later life.

There is now clear evidence that people who develop a range of chronic diseases in later life grew differently in utero to other people. They tended to grow slowly so that their birth weights were towards the lower end of the normal range [2,3]. Fig. 1, based on the original observations in Hertfordshire, UK, shows that the relation between birth weight and later coronary heart disease is graded, extending across the entire normal range of birth weight [4]. In that study mean birth weights were 7.8 pounds in men and 7.5 in women. There are similar graded associations with other disorders, including hypertension and type 2 diabetes. Associations between low birth weight and later disease have been extensively replicated [5–8]. Findings in the Helsinki Birth Cohort and in other studies have shown that, after birth, children who will later have coronary heart disease or type 2 diabetes tended to remain small for the first two years [3,9], but thereafter they gained weight and body mass index (weight/height^2) rapidly [9]. This pattern of growth is associated with large effects. For example, it has been estimated that if each individual in the Helsinki Birth Cohort had been in the highest third of birth weight and had decreased their standard deviation score for body mass index between ages 3 and 11 years, the incidence of type 2 diabetes would have been halved [10]. These findings have led to a new developmental model for chronic disease in which the diseases are thought to be initiated by normal variations in feto-placental development [11]. These variations are associated with differences in fetal nutrition, which permanently change the structure and function of the body, a phenomenon known as "programming" [11–13].

2. Fetal nutrition

Challenged by limited resources the baby allocates resources according to a hierarchy of priorities. Brain growth is at the top of this hierarchy and the development of organs such as the kidney and lungs, which do not function in the womb, are at the bottom. The development of low priority organs and systems is traded-off to protect more important ones. Consistent with this low birth weight is associated with chronic obstructive lung disease in later life [14].

Size at birth is the product of the fetus's trajectory of growth, which is set at an early stage in gestation, and the materno-placental capacity to supply sufficient nutrients to maintain this

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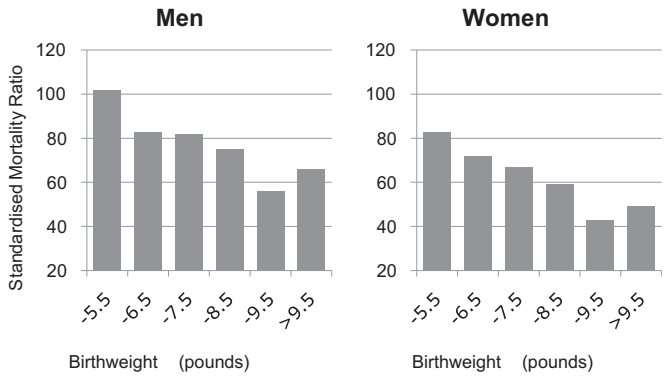

Fig. 1. Mortality from coronary heart disease in 15,726 men and women in Hertfordshire.

trajectory. A rapid trajectory of growth increases the fetus's demand for nutrients [15]. This demand is greatest late in gestation but the trajectory is thought to be primarily determined by genetic and environmental effects in early gestation. Experiments in animals have shown that alterations in maternal diet around the time of conception can change the fetal growth trajectory [16]. The sensitivity of the human embryo to its environment is being increasingly recognized with the development of assisted reproductive technology [17]. The trajectory of fetal growth is thought to increase with improvements in periconceptional nutrition, and is faster in male fetuses.

3. Maternal nutrition

The graded relation between birth weight and coronary heart disease disease (Fig. 1) implies that variations in the supply of food from normal healthy mothers to normal healthy babies have major implications for the long-term health of the babies [18]. A baby does not depend on the mother's diet during pregnancy: that would be too dangerous a strategy. Rather it lives off her stored nutrients and the turnover of protein and fat in her tissues [19]. These are related to her body composition and, therefore, reflect her lifetime nutrition. A girl is born with all the eggs she will ever have and the quality of these therefore reflects her own mother's nutritional state. Fig. 2 shows how the critical first 1000 days of development, from conception to two years of age, reflect 100 years of nutritional flow.

Although a mother's diet during pregnancy is not closely linked to the birth weight of her baby it can, however, programme the baby. Follow-up studies of people who were in utero during the war-time famine in Holland have shown that, although the babies' birth weights were little affected, severe maternal caloric

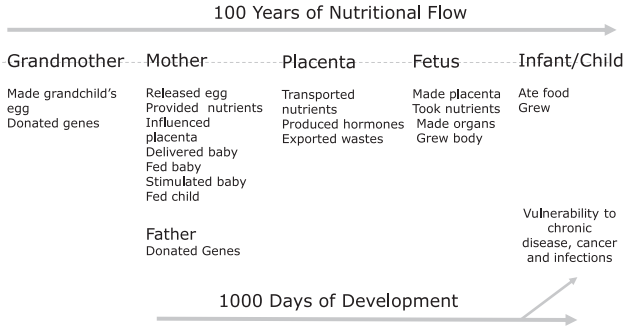

Fig. 2. The transgenerational roots of chronic disease.

restriction at different stages of pregnancy was variously associated with obesity, dyslipidemia, insulin resistance and coronary heart disease in the offspring [20]. In the Dutch studies, maternal rations with a low protein density were associated with raised blood pressure in the adult offspring [21]. This adds to the findings of studies in Aberdeen and Motherwell, UK, which showed that maternal diets with either a low or a high ratio of animal protein to carbohydrate were associated with raised blood pressure in the offspring during adult life [22,23]. While it may seem counter-intuitive that a high-protein diet should have adverse effects, these findings are consistent with the results of controlled trials of protein supplementation in pregnancy, which show that high protein intakes are associated with reduced birth weight [24]. One possibility is that these adverse effects are a consequence of the metabolic stress imposed on the mother by an unbalanced diet in which high intakes of essential amino acids are not accompanied by the micronutrients required to utilize them.

4. The placenta

A baby's birth weight depends not only on the mother's nutrition but also on the placenta's ability to transport nutrients to it from its mother. The placenta seems to act as a nutrient sensor regulating the transfer of nutrients to the fetus according to the mother's ability to deliver them, and the demands of the fetus for them [25]. The weight of the placenta, and the size and shape of its surface, reflect its ability to transfer nutrients. The shape and size of the placental surface at birth has become a new marker for chronic disease in later life [26]. The predictions of later disease depend on combinations of the size and shape of the surface and the mother's body size. Particular combinations have been shown to predict coronary heart disease [27], hypertension [28], chronic heart failure [29] and certain forms of cancer [30]. Variations in placental size and shape reflect variations in the normal processes of placental development, including implantation, unplugging of the spiral arteries, and the growth and compensatory expansion of the chorionic plate [26]. These variations are accompanied by variations in nutrient delivery to the fetus.

5. Maternal effects on the placenta

The placenta responds to the mother's diet and to her body composition. Placental size, shape and efficiency were examined among 2414 term singleton babies born around the time of the wartime famine in Holland [31]. Compared to babies born before the famine, babies who were in utero during the famine had a smaller placental surface area (Table 1). Babies whose mothers conceived after the famine ended also had smaller placental areas. It seems that famine impaired the normal processes of placentation, even among babies who were conceived after it had ended. In babies who were in mid-late gestation during the famine, the placenta was less efficient as measured by a high ratio of placental area to body size. In babies who were in early gestation during the famine, or who were conceived after it had ended, the placenta was more efficient.

Placental growth responds to fasting during pregnancy. Ramadan is an annual period of daytime fasting during which people in Saudi Arabia, including pregnant women, change their diets and physical activity. The birth records of 17,660 singletons born in Unizah, Saudi Arabia, over a ten year period were examined. During the first six years of the study period mean placental weight rose by more than 100 g while mean birth weight was unchanged [32]. This secular increase in placental weight was accompanied by a change in the placenta's response to Ramadan. During the first half of the study period, babies who were in their second or third