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## REVIEW ARTICLE

### Fetal nutrition and cardiovascular disease in adult life

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Babies who are small at birth or during infancy have increased rates of cardiovascular disease and non-insulin-dependent diabetes as adults. Some of these babies have low birthweights, some are small in relation to the size of their placentas, some are thin at birth, and some are short at birth and fail to gain weight in infancy. This paper shows how fetal undernutrition at different stages of gestation can be linked to these patterns of early growth. The fetuses' adaptations to undernutrition are associated with changes in the concentrations of fetal and placental hormones. Persisting changes in the levels of hormone secretion, and in the sensitivity of tissues to them, may link fetal undernutrition with abnormal structure, function, and disease in adult life.

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#### Association between early growth pattern and disease in adults

Two English surveys have indicated that low growth rates in utero and during infancy are associated with high death rates from cardiovascular disease. One of them, of 1586 men born in a maternity hospital in Sheffield during 1907-25, showed that death rates from cardiovascular disease fell progressively with increasing weight, head circumference, and ponderal index (weight/length<sup>3</sup>) at birth.<sup>1</sup> In the other, of 5654 men born in Hertfordshire during 1911-30, death rates from coronary heart disease were almost three times higher among those who weighed 18 lb (8.2 kg) or less at age 1 year than among those who weighed 27 lb (12.3 kg) or more.<sup>2</sup>

Examination of men and women in different populations in Britain has shown that low growth rates up to the age of one year are associated with increased prevalence of known risk factors for cardiovascular disease, including blood pressure,<sup>3</sup> and plasma concentrations of glucose, insulin,<sup>4</sup>

fibrinogen,<sup>5</sup> factor VII,<sup>5</sup> and apolipoprotein B.<sup>6</sup> These associations parallel those with death rates from cardiovascular disease. The associations are seen in babies who are born small for their gestational age rather than those born prematurely.<sup>1,3</sup> They are found not only among babies with intrauterine growth retardation, defined by birthweight at the lowest centiles, but are also seen in babies of average or even above average weight at birth. Some of the subjects were small at birth in relation to the size of their placentas;<sup>3</sup> others were thin at birth;<sup>1,7</sup> and yet others, though of average birthweight, were short in relation to head size and had below average infant weight gain.<sup>2,5</sup>

Numerous animal experiments have shown that poor nutrition, and other influences that impair growth during critical periods of early life, may permanently affect (programme) the structure and physiology of a range of organs and tissues, including the endocrine pancreas, liver, and blood vessels.<sup>8,9</sup> For example, retardation of intrauterine growth in the guineapig causes life-long elevation of blood pressure.<sup>10</sup>

A simple example of programming in human beings is the permanent deformity of the pelvic bones caused by rickets in infancy. Since different tissues mature during different, often brief, periods of fetal life and infancy, the long-term consequences of altered nutrition depend on its timing and its duration. Consistent with this, different patterns of early growth are associated with different adult abnormalities. For example, those who are thin at birth, as measured by a low ponderal index (weight/length<sup>3</sup>), tend to develop the

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combination of insulin resistance, hypertension, non-insulin-dependent diabetes, and lipid disorders known as syndrome X.<sup>7</sup> Those who are short in relation to head size tend to develop hypertension and high plasma fibrinogen concentrations.<sup>5</sup>

It has been argued that people whose growth had been impaired in utero and during infancy may continue to be exposed to an adverse environment in childhood and adult life, and it may be this later environment that produces the effects being attributed to programming. The associations with cardiovascular risk factors, however, are independent of known influences in adult lifestyle. They occur in each social class and at each level of cigarette smoking, alcohol consumption, and obesity.<sup>12</sup> Adult lifestyle influences, however, add to the effects of early life. For example, the risk of non-insulin-dependent diabetes was highest in people who had low weight at birth and during infancy but became obese as adults.<sup>4</sup> A low rate of early growth may lead to non-insulin-dependent diabetes only if the resulting impairment of glucose-insulin metabolism is challenged by adult obesity. This observation may explain why rates of diabetes are low in rural areas of the developing world but higher among those who have migrated from these areas to cities or to the western world.

In support of a causal link between impaired early development and cardiovascular disease are the strength and graded nature of the associations. Body weight at birth is only a proxy for the changes in the body's structure, physiology, and metabolism that have been programmed in utero, yet the relative risks associated with low birthweight are large. The risk of syndrome X, for example, is ten times higher among men whose birthweight was 6.5 lb (2.95 kg) or less than in men whose birthweight was more than 9.5 lb (4.31 kg).<sup>7</sup>

### Associations in different populations

Associations between early growth and cardiovascular risk factors are being found in different populations. The association between lower birthweight and impaired glucose tolerance, for example, has been shown in four studies of adults<sup>4,11,12</sup> (and Martyn CN, unpublished). The association with raised blood pressure has also been shown in four studies of adults<sup>3,11,13</sup> (and Martyn CN, unpublished) and is consistently found in children. Blood pressure is known to "track" from childhood to adult life. Tracking is perturbed, however, during adolescence, which may explain why two studies have shown only weak associations between birthweight and blood pressure in teenagers.<sup>14,15</sup> A study of people of different ages suggests that raised blood pressure is initiated in utero and thereafter amplified with increasing age.<sup>13</sup>

Associations between cardiovascular risk factors and placental size are being found less consistently than those with fetal size. For example, the relation between blood pressure and increased placental size found in two studies<sup>3,11</sup> was not evident in a study of teenagers.<sup>14</sup> As will be discussed in this paper, undernutrition in utero may either constrain or stimulate placental growth, depending on its timing and severity. Hence associations between placental size and adult disease are likely to vary from one population to another.

The long-term effects of impaired fetal development raise a number of questions. What are the influences that alter fetal growth? How does the fetus respond? How are the long-term cardiovascular, metabolic, and endocrine consequences programmed? Knowledge is still scanty, but it

is possible to set out a broad framework within which these questions can be explored.

The intrauterine environment is the main influence on fetal growth. It determines nutrient and oxygen supply to the fetus. Fetal growth can also be constrained by maternal size. There is a strong relation between birthweight and mother's height. Embryo transfer and cross-breeding experiments have shown that birth size is related to the size of the uterus to which a fetus is transferred.<sup>16</sup> A baby's birth measurements, however, are predictive of adult disorders independently of maternal pelvic size.<sup>1</sup> This discussion must therefore focus on influences that determine fetal nutrition, rather than on the physiological constraint of fetal growth by the mother.

### Undernutrition in early pregnancy

In the earliest stages of pregnancy, embryonic and trophoblast growth are influenced by the concentrations of nutrients. Animal work shows that suboptimum nutrition before implantation can retard growth and development, with the 1-cell embryo being particularly sensitive. The early embryo is selective in its use of nutrients and, before the late morula stage, respire pyruvate, lactate, and aminoacids such as glutamine rather than glucose.<sup>17</sup> Hyperglycaemia, which is common in man as a consequence of maternal diabetes, delays embryonic growth, and is implicated in the development of malformations.<sup>18</sup> This effect contrasts with the accelerated growth associated with hyperglycaemia in late pregnancy. Before implantation the blastocyst switches to glucose-based metabolism,<sup>19</sup> and hypoglycaemia, which is difficult to record in healthy women, may retard its growth and development. Thus both hyperglycaemia and hypoglycaemia in early embryogenesis may be associated with low birth weight.

### Undernutrition in mid-pregnancy

The placenta grows faster than the fetus in mid-pregnancy. Nutrient deficiency may affect fetal growth by changing the complex interaction between the fetus, the placenta, and the mother. Although severe maternal undernutrition restricts growth of both fetus and placenta, mild undernutrition may lead to increased placental but not fetal size.<sup>20</sup> Mild hypoxaemia associated with high altitude also increases placental size, as does anaemia.<sup>11</sup> This placental overgrowth may be an adaptation to sustain nutrient supply from the mother. Localised placental hypertrophy can also be induced experimentally in sheep by reducing the number of implantation sites. This compensatory growth at the remaining sites<sup>21</sup> occurs before there is noticeable retardation of fetal growth and may be a sensitive, early response to reduced nutrient supply. Subtle changes in the distribution of nutrients may modulate placental growth, either directly or indirectly through endocrine or paracrine signals.

### Undernutrition in late pregnancy

In late gestation maternal undernutrition promptly slows fetal growth and alters the metabolic interaction between fetus and placenta. Fetal growth is sacrificed to maintain placental function. Experimental restriction of placental growth has given an insight into these adaptations. Oxygen, glucose, and aminoacids are re-distributed. The placenta reduces its consumption of oxygen and glucose while maintaining a large output of lactate to the fetus.<sup>22</sup> The lactate is partly derived from aminoacids of fetal origin<sup>23</sup> and

the fetus may waste and be thin at birth. There is evidence for similar metabolic changes in growth-retarded human fetuses.<sup>24,25</sup> The human placenta may also adapt and use aminoacids when its nutrient supply is jeopardised. Wasting of growth-retarded fetuses has been observed by ultrasound.<sup>26</sup>

The effects of undernutrition in late gestation depend on its duration. Acute undernutrition causes prompt slowing of fetal growth associated with fetal catabolism.<sup>27</sup> Fetal growth rapidly resumes when nutrition is restored. In contrast, long periods of undernutrition may irreversibly slow the rate of fetal growth in lambs<sup>28</sup> and lead to reduced length at birth. The basis of this irreversibility is uncertain, but the irreversibility is reflected in the clinical observation that growth-retarded neonates whose postnatal growth fails are the ones who have had long periods of intrauterine growth retardation.<sup>29</sup>

### Hormonal responses to undernutrition

Metabolic adaptations to undernutrition are linked to changes in the concentrations of fetal and placental hormones and influence fetal growth. Insulin and the insulin-like growth factors (IGFs), hormones thought to have a central role in the regulation of fetal growth, rapidly respond to changes in fetal nutrition. For example, maternal starvation lowers fetal IGF-1 concentrations; infusion of glucose, but not of aminoacids, restores them.<sup>30</sup> Concentrations of these hormones influence nutrient availability as well as fetal growth.

Impaired  $\beta$ -cell development is a feature of intrauterine growth retardation.<sup>31</sup> The impairment may be due to the lowering of IGF-1 concentrations associated with hypoglycaemia, or to growth hormone resistance or deficiency. During fetal life there are few growth hormone receptors in the liver.<sup>32,33</sup> Growth-hormone receptors are, however, widely distributed in extrahepatic fetal tissues.<sup>32</sup> Growth hormone is essential to growth of the pancreatic  $\beta$  cells. Anencephalic fetuses in diabetic mothers do not show the islet-cell hyperplasia that is usually associated with fetal hyperglycaemia.

Fetal undernutrition may also induce insulin resistance in tissues. Babies who are thin at birth tend to be insulin resistant as adults, and have a high prevalence of syndrome X.<sup>7</sup> The mechanisms linking fetal wasting with insulin resistance are unknown, but could involve structural changes in skeletal muscle. After birth insulin deficiency and resistance would be manifest through effects on glucose metabolism rather than somatic growth because linear growth becomes driven by growth hormone. Recent findings suggest that both insulin resistance and impaired  $\beta$ -cell development may be important in the pathogenesis of non-insulin-dependent diabetes.<sup>4,7,34</sup>

Infants who were short at birth as a result of a long period of maternal undernutrition may have persisting defects in their growth hormone and IGF axis. They have exaggerated responses to growth-hormone-releasing factor and lower IGF-1 levels<sup>35</sup> suggesting a degree of growth hormone resistance.<sup>36</sup> One interpretation is that the normal evolution of their hepatic growth-hormone receptors may have been attenuated. Postnatally the growth-hormone axis influences cardiovascular function.

Fetal blood pressure may be partly regulated by cortisol. In sheep exogenous cortisol raises the blood pressure of the immature fetus, perhaps by enhancing vascular sensitivity to angiotensin II.<sup>37</sup> In the rat a high ratio of placental weight to birthweight is associated with reduced placental activity of

11- $\beta$  hydroxy-steroid-dehydrogenase,<sup>38</sup> the enzyme that may protect the fetus from excessive maternal cortisol. A high ratio of placental weight to birthweight can be induced in the rat by a low-protein diet, and the products of these pregnancies have raised blood pressure 15 weeks after birth (Jackson AA, unpublished). The growth-retarded human fetus has high plasma cortisol concentrations and these could initiate adult hypertension.

### Conclusion

We have shown how undernutrition can change the pattern of fetal and placental growth. Undernutrition in early pregnancy retards embryonic growth and may result in symmetrically small low birthweight babies. Undernutrition in mid-pregnancy may change the interactions between fetus and placenta, and the placenta may be small or hypertrophied. Undernutrition in late pregnancy may cause fetal wasting as its aminoacids are diverted to the placenta for energy production.

We suggest that undernutrition during gestation reprogrammes the relationships between glucose and insulin and that between growth hormone and IGF. Reprogramming of these relationships may be analogous to the programming of the thyroid-stimulating hormone (TSH)/thyroxine axis in congenital hypothyroidism, where the TSH to thyroxine ratio remains high.

Insulin resistance and deficiency are associated with cardiovascular disease in adult life. Adults with growth-hormone deficiency have an increased mortality from cardiovascular disease.<sup>39</sup> Both growth hormone and IGF-1 increase cardiac output, stimulate ventricular growth, and influence angiogenesis, and IGF-1 has its strongest anabolic effects on cardiac muscle.

Undernutrition at different stages of pregnancy leads to phenotypes characterised by low birthweight, or low birthweight relative to placental weight, or thinness at birth, or shortness at birth with subsequent failure of infant growth. Each of these phenotypes is associated with a particular pattern of metabolic abnormalities in adult life. The abnormalities may depend on the different timing of the undernutrition and its different effects on organs and tissues according to their stage of development. We now need to learn more about the ways in which the fetus adapts to undernutrition. These adaptations enable it to survive but, by permanently changing the body's physiology, structure, and metabolism, they may lead to cardiovascular disease in later life.

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## MEDICAL EDUCATION

### The changing clinical experience of British medical students

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The UK National Health Service is undergoing fundamental reforms, which might have a detrimental effect on the training of doctors, not least with respect to the amount of clinical experience that medical students get.

We compared the practical experience gained by two cohorts of students at medical schools throughout the UK, who had started their training in 1981 or 1986. The assessment was made by questionnaire at the end of their final clinical year. Experience of acute medical conditions, surgical operations, and practical procedures differed significantly between groups of medical schools, and

showed a significant decline in the past five years.

This decline in the clinical experience of medical students has coincided with the introduction of the health service reforms. We suspect that the university-based clinical education designed for a lifetime of change is in danger of being replaced by a dispersed clinical apprenticeship for current practice.

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