Invited Review

The developmental origins of adult disease (Barker) hypothesis

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Abstract
Many studies have provided evidence for the hypothesis that size at birth is related to the risk of developing disease in later life. In particular, links are well established between reduced birthweight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. These relationships are modified by patterns of postnatal growth. The most widely accepted mechanisms thought to underlie these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure. It is suggested that the fetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life. These changes may include epigenetic modification of gene expression. Less clear at this time are the relevance of fetal programming phenomena to twins and preterm babies, and whether any of these effects can be reversed after birth. Much current active research in this field will be of direct relevance to future obstetric practice.

Key words: coronary heart disease, developmental origins of adult disease, diabetes, hypertension, programming.

The developmental origins of adult disease

The ‘developmental origins of adult disease’ hypothesis, often called the ‘Barker hypothesis’ after one of its leading proponents, states that adverse influences early in development, and particularly during intrauterine life, can result in permanent changes in physiology and metabolism, which result in increased disease risk in adulthood. This hypothesis originally evolved from observations by Barker and colleagues that the regions in England that had the highest rates of infant mortality in the early twentieth century also had the highest rates of mortality from coronary heart disease decades later. As the most commonly registered cause of infant death at the start of the twentieth century was low birthweight, these observations led to the hypothesis that low birthweight babies who survived infancy and childhood might be at increased risk of coronary heart disease later in life.

Two large studies of men born in Sheffield and Hertfordshire in the first quarter of the 20th century showed a strong relationship between death from coronary heart disease and decreasing birthweight, head circumference or ponderal index. It was particularly people who were born growth restricted rather than premature who were at risk. These results have since been replicated in other studies from many different countries, as well as in women.

Initially, it seemed likely that both low birthweight and coronary heart disease were caused by environmental or lifestyle factors, and that people who suffered poor growth early in life would continue to be exposed to these factors. However, although changes in western diet and lifestyle during the last century have contributed to the increase in incidence of coronary heart disease, adult lifestyle risk factors for coronary heart disease are not predictive of who will develop the disease and who will not. Furthermore, correction for known risk factors such as diet, smoking and exercise did not have a major effect on the relationships between birth size and subsequent disease risk.

Relationships have now been described between reduced size at birth and other diseases that are known risk factors for coronary heart disease, including hypertension, type 2 diabetes mellitus and hyperlipidaemia. A recent systematic review reported that the majority of 80 studies on adults and children showed that there is a 2-mmHg decrease in systolic blood pressure per kilogram increase in birthweight. This relationship is less well defined in adolescence, possibly because ‘tracking’ of blood pressure with age is disturbed at the time of the adolescent growth spurt.

The many reports of relationships between birth size and disadvantageous glucose and insulin metabolism have also recently been reviewed. In particular, lower birthweight has been associated with increased insulin resistance, higher fasting insulin concentrations and increased incidence of type 2 diabetes mellitus. There is also some evidence of a relationship between lower birthweight and impaired insulin secretion, but this is less consistent.

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Neonatal abdominal circumference has been shown to predict plasma cholesterol and fibrinogen levels in men later in life. Both of these are risk factors for the development of coronary heart disease.\textsuperscript{14,15} It has been suggested that abdominal circumference at birth is at least partly reflecting liver size, growth of which may be impaired in babies born small, perhaps as a result of blood flow redistribution to vital organs such as the heart and brain at the expense of abdominal organs such as the liver. However, there is not yet any direct evidence of such a causal link.

Many other outcomes in adult life have been linked to size at birth. Reduced birthweight has been associated with an increased incidence of chronic lung disease,\textsuperscript{16} and psychological outcomes,\textsuperscript{17} and with characteristic changes in fingerprint patterns,\textsuperscript{18,19} while larger birthweight has been associated with increased risk of polycystic ovarian disease and the hormone-related cancers: breast, prostate and testicular cancer.\textsuperscript{20} However, only the diseases that have been confirmed in studies across many different populations and are widely accepted as related to small birth size will be discussed further in this review (Table 1).

It is important to note that these relationships between size at birth and later disease risk are continuous across the range of birth sizes, and are not merely confined to those infants born extremely small or recognised as growth restricted. This suggests that, whatever the mechanisms underlying these relationships, they must act within the normal physiological processes regulating intrauterine development, rather than involving pathological mechanisms applying only to abnormal pregnancy.

### Early childhood growth and disease in later life

The effect of small size at birth is modulated by patterns of childhood growth. Children born in Helsinki between 1934 and 1944 who went on to develop coronary heart disease, hypertension and diabetes as adults were generally short and thin at birth, had poor growth in the first year of life, but then accelerated weight gain in later childhood.\textsuperscript{21–24} Thus, it appears that the increased risk of these diseases in adulthood in individuals with impaired growth before birth can be aggravated by growth failure in the first year after birth, and by rapid weight gain in childhood. However, it is not yet clear whether intervention at either of these times will alter these outcomes.

### Links with placental weight

Increased risk of various adult diseases has been described not only in babies born small, but also in those with unusual relationships between birthweight and placental weight. Babies born small in relation to the size of their placenta have an increased risk of developing hypertension.\textsuperscript{23,25} It is interesting in this regard to note that low birthweight in relation to placental weight has also been associated with failure of catch-up growth in the first 18 months in babies born growth restricted.\textsuperscript{26} On the other hand, babies who later developed type 2 diabetes, sometimes in combination with hypertension, were reported to have small placentas in relation to their birthweight.\textsuperscript{23,27} This may indicate that there are different underlying mechanisms in the development of the different disorders.

### Possible mechanisms

The most widely accepted phenomenon proposed to underlie the developmental origins hypothesis is that of programming. This is the process whereby a stimulus or insult during a sensitive or critical period has irreversible long-term effects on development. Well-recognised mechanisms include altered fetal nutrition and increased glucocorticoid exposure. However, there may also be genetic and epigenetic links.

### Altered fetal nutrition

Fetal nutrition is a key regulator of fetal growth, and thus an obvious candidate as a possible programming influence.\textsuperscript{28} It has proved remarkably easy in experimental animals to permanently alter postnatal physiology in a way analogous to that seen in the human studies by manipulation of maternal diet during pregnancy. In rats, both global maternal undernutrition and specific protein restriction result in reduced birthweight,\textsuperscript{29,30} increased blood pressure,\textsuperscript{31,32} and impaired glucose tolerance\textsuperscript{33} in the offspring. Similar effects have been reported in guinea pigs\textsuperscript{34,35} and sheep.\textsuperscript{36,37}

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**Table 1** Diseases linked with birthweight

<table>
<thead>
<tr>
<th>Replicated and widely accepted association with small birth size</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>9</td>
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<tr>
<td>Coronary artery disease</td>
<td>2–7</td>
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<tr>
<td>Non-insulin dependent diabetes</td>
<td>10</td>
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<tr>
<td>Stroke</td>
<td>145,146</td>
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<td>Dislipidaemia</td>
<td>147–149</td>
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<td>Elevated clotting factors</td>
<td>149</td>
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<td>Impaired neurodevelopment</td>
<td>150–154</td>
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<th>Described but less well replicated and accepted association with small birth size</th>
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<tr>
<td>Chronic lung disease</td>
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<td>Depression</td>
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<td>Schizophrenia</td>
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<td>Behavioural problems</td>
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<td>Marriage</td>
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<td>Fingerprint patterns</td>
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<td>Left handedness</td>
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<td>Reduced uterine and ovarian size</td>
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<td>Precocious pubarche</td>
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<td>Breast cancer</td>
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<td>Testicular cancer</td>
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<th>Described association with large birth size</th>
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<tr>
<td>Polycystic ovary disease</td>
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<td>Breast cancer</td>
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<tr>
<td>Prostate cancer</td>
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<td>Testicular cancer</td>
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<td>Childhood leukaemia</td>
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It is less straightforward to demonstrate such relationships with global nutrition in human pregnancy. However, both birthweight and placental weight are affected by the balance of macronutrients in the maternal diet.\textsuperscript{38,39} Imbalance of protein and carbohydrate intake during pregnancy has been associated with reduced birthweight and increased blood pressure in the offspring.\textsuperscript{40,42} Micronutrients may also play an important role in programming of postnatal pathophysiology. In an Indian study, maternal intake of fruit and green vegetables during pregnancy was positively associated with birth size and glucose tolerance in the offspring.\textsuperscript{42,43} Higher calcium intake during pregnancy has been associated with lower blood pressure in the offspring in childhood.\textsuperscript{44,45}

Fetal overnutrition may be an increasingly common programming stimulus in many communities. Rats that overeat during pregnancy because of experimentally induced impairment of hypothalamic satiety control give birth to offspring that have impaired glucose tolerance in later life.\textsuperscript{46} Similarly, the offspring of rats fed a high-fat diet during pregnancy show impaired glucose homeostasis and hypertension as adults.\textsuperscript{47,48} Infants of diabetic mothers also experience fetal overnutrition, as they are exposed to increased glucose and fatty acid concentrations before birth. There is now good evidence that these babies are at increased risk of glucose intolerance and type 2 diabetes in later life.\textsuperscript{49–51}

There are many possible mechanisms by which altered fetal nutrition might lead to increased risk of disease in the offspring.\textsuperscript{52} However, as a general schema, it is useful to think of altered fetal nutrition as leading, directly or indirectly, to altered growth and maturation of various fetal organ systems (Fig. 1). Permanent changes in the homeostatic regulation of these systems could then lead to increased risk of subsequent disease, especially when placed under increased stress after birth by additional risk factors such as ageing and obesity.

**Glucocorticoids**

Another mechanism by which adult cardiovascular and metabolic disease may be programmed is via exposure to excess glucocorticoids. This may occur \textit{in utero} if maternal

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**Figure 1** Described effects of altered fetal nutrition on growth and maturation of fetal organ systems and their links with adult disease.
glucocorticoid levels are elevated, if exogenous synthetic glucocorticoids are administered, or if the placental barrier that protects the fetus from high levels of maternal glucocorticoids is impaired. Elevated levels of cortisol of either maternal or fetal origin are associated with elevated blood pressure in the sheep fetus. In rats, offspring of dams given dexamethasone during pregnancy have reduced birthweight and increased blood pressure and glucose intolerance in adulthood. Repeat doses of betamethasone given to pregnant sheep have similar effects. Similar effects are seen in rats after inhibition of placental 11β-hydroxysteroid dehydrogenase type 2 (11βHSD-2), the enzyme that inactivates cortisol in the placenta. These effects appear to be mediated at least in part via permanent changes in the regulation of the hypothalamo-pituitary–adrenal axis in the offspring. Intrauterine glucocorticoid exposure leads to reduced numbers of glucocorticoid receptors in the hypothalamus, resulting in impaired negative feedback and hence long-term up-regulation of the hypothalamo-pituitary–adrenal axis after birth. This, in turn, could contribute to increased blood pressure and glucose intolerance in the offspring.

There are intriguing data suggesting that similar mechanisms may pertain in human pregnancy. Babies born small tend to have higher basal plasma cortisol levels as adults. Smaller babies also tend to have lower activity of 11βHSD-2 in their placentas. Repeated administration of betamethasone or dexamethasone during pregnancy has been associated with reduced size at birth, but no data are yet available regarding any possible long-term effects of such exposure. On the other hand, administration of a single course of corticosteroids to women at risk of preterm birth has no effect on the offspring before and after birth. Thus, in contrast with rats, human babies born before their due date do not show the same increased blood pressure and glucose intolerance as observed in rats.

It should be noted that in some circumstances, altered nutrition and glucocorticoid exposure may overlap as programming influences. Maternal dietary restriction increases maternal glucocorticoid secretion in rats, reduces placental 11β-HSD-2 activity and alters neonatal hypothalamo-pituitary–adrenal axis function. Prevention of the rise in maternal glucocorticoid levels by maternal adrenalectomy abolishes the effect of a low protein diet on the outcomes of interest in the offspring. Maternal undernutrition in sheep also alters hypothalamic–pituitary–adrenal axis function in the offspring before and after birth. Thus, the effects of nutrition and glucocorticoids as programming stimuli may act via similar pathways to produce long-term changes in homeostatic regulation leading to increased risk of adult disease.

The thrifty phenotype hypothesis and predictive adaptive responses

The ‘thrifty phenotype’ hypothesis first proposed by Hales and Barker suggested that adult insulin resistance and type 2 diabetes could result from the persistence of a fetal glucose-conserving adaptation in response to intrauterine hypoglycaemia. During periods of maternal undernutrition the fetus reduces insulin secretion and increases peripheral insulin resistance, thus directing more glucose to the brain and heart and less to insulin-dependent tissues such as skeletal muscle. When nutrient availability is abundant in postnatal life, this pancreatic β-cell defect and peripheral insulin resistance could then cause glucose intolerance and eventually diabetes. This would explain why it is mainly thin babies who then become overweight during childhood who are prone to developing type 2 diabetes later in life.

Gluckman and Hanson have recently revised and extended this hypothesis. They propose that when there is a change in the intrauterine environment, for example, nutrient restriction or high glucocorticoid levels, the fetus will make adaptations to improve its immediate chances of survival. These adaptations are often reversible. However, if the environmental changes persist, the fetus is forced to make irreversible adaptations that may or may not be immediately beneficial, but that will manifest themselves in later life. In this way the fetus is preparing itself for life in an extraterine environment with, for example, low food availability or high levels of stress. Gluckman and Hanson coined the term ‘predictive adaptive response’ (PAR) for this phenomenon. There are many examples of PARs from the animal world. For example, the meadow vole pup is born with a thicker coat in autumn than in spring. In this case changes in day length, signalled to the pup in utero by maternal melatonin levels, result in adaptive changes in coat thickness in anticipation of the extraterine environment being cold or warm. Successful adaptation to the predicted environment (a thick coat in a pup who must survive the winter) improves biological fitness. Disparities between the predicted environment and the actual environment into which the fetus is born may result in disease. This might occur if undernutrition in utero is followed by an abundant diet postnatally, such as a small baby born into a food-rich western society. Intriguingly, there is some evidence that the converse may also occur. Rat dams fed a high-fat diet in pregnancy have offspring with altered endothelial function and hypertension as adults. If the offspring are also fed a high-fat diet after birth, the endothelial dysfunction, although not the hypertension, is prevented.

Fetal insulin hypothesis

Hattersley proposed that the relationship between small size at birth and impaired glucose tolerance in adulthood could be explained by inherited deficits in insulin secretion or action. Since insulin is an important regulator of fetal growth, affected individuals with impaired insulin secretion would have impaired growth before birth, and would also go...
on to have impaired glucose tolerance in adulthood. Isolated genetic polymorphisms have been described that clearly support this hypothesis. However, these relatively rare changes seem unlikely to explain the very widespread relationships between birth size and later glucose tolerance described in many different populations and across the range of normal birthweights. Intriguingly, two recent studies have reported lower birthweight in the offspring of diabetic fathers. Furthermore, fathers of low birthweight infants, who were not diabetic at the time of the birth of their child, had a nearly twofold increase in the risk of developing diabetes later in life. These data suggest a link between birthweight and diabetes that is not dependent on the intrauterine environment.

**Genetic and epigenetic links**

The link between fetal growth and adult onset disease must ultimately involve changes in gene expression, which are very likely to involve epigenetic phenomena. During early embryogenesis, DNA undergoes demethylation and remethylation; a process that involves ‘labeling’ of some genes as of maternal or paternal origin, and marks these genes for subsequent inactivation. This epigenetic process of imprinting is thought to particularly affect many of the genes regulating fetal and placental growth. In the mouse, methylation of DNA in the offspring has been shown to be altered by the level of methyl donors in the maternal diet. Methylation of DNA in the fetal liver is also altered by low-protein diet during pregnancy in rats. Thus, changes in the intrauterine environment may ultimately lead to altered gene expression via alterations in DNA methylation and other epigenetic mechanisms, resulting in an increased susceptibility to chronic disease in adulthood.

**Intergenerational effects**

It is now becoming clear that adverse events during pregnancy can affect not only the offspring of that pregnancy but also the next generation. It has long been recognised that the birthweight of the mother is related to the birthweight of her children. A colony of rats fed a low-protein diet for several generations and then re-fed took three generations for fetal growth and development to return to normal. A similar effect was seen during the Dutch hunger winter of 1944–1945; a 5-month period of severe famine at the end of the Second World War. Women who were severely undernourished during the first trimester of pregnancy gave birth to babies who were on average of normal birthweight, but those babies themselves then went on to give birth to smaller babies in the next generation.

There are several possible explanations for these intergenerational effects on birthweight. First, the hormonal environment of the uterus of undernourished mothers may affect the developing reproductive tract of the fetus. Indeed, mothers who were small at birth have reduced uterine and ovarian size. It is proposed that smaller uterine size may impose a greater ‘maternal constraint’ on the fetus, thereby reducing its growth, although there is not yet any direct evidence for such an effect. Second, any epigenetic changes to the genome may be passed on to the second generation.

There are also intergenerational effects on risk factors for cardiovascular disease. Lower maternal birthweight is associated with an increased risk of hypertension during pregnancy, which in turn is associated with lower birthweight of the offspring. Furthermore, maternal birthweight is negatively related to blood pressure in the offspring, regardless of maternal blood pressure during adult life. This effect may be mediated by exposure to excess glucocorticoids. Second generation offspring of rats exposed to dexamethasone during pregnancy not only have reduced birthweight, but also impaired glucose tolerance.

**Periconceptional events**

Birthweight is a very crude measure of fetal growth and changes in the intrauterine environment that lead to altered risk of adult disease may not necessarily result in altered birthweight. Several studies both in experimental animals and in human pregnancy suggest that altered risk of adult disease may be linked with the maternal nutritional status around conception and implantation in the absence of altered size at birth.

In sheep, maternal undernutrition only around the time of conception is associated with preterm birth, prematurity maturation of the fetal hypothalamo–pituitary–adrenal axis, altered fetal growth trajectory and altered insulin secretion in the fetus. In rats, maternal protein malnutrition only during the preimplantation period has also been shown to reduce cell numbers in the developing blastocyst, reduce birthweight and increase adult blood pressure in the offspring.

Human evidence about the importance of nutrition in the periconceptional period again comes from the Dutch hunger winter studies. The offspring of women exposed to famine mid and late gestation were born smaller than unexposed babies and had an increased risk of impaired glucose tolerance as adults. However, the offspring of women exposed to famine in early gestation, although of normal birthweight, had a threefold increased risk of coronary heart disease as adults, increased risk of obesity and raised plasma fibrinogen levels.

Although exposure to severe famine is rare in Western societies, maternal undernutrition around the time of conception may be more common than previously recognised. One study of an unselected series of low birthweight babies in Sydney reported that one third of mothers of the small for gestational age babies had been previously diagnosed with an eating disorder. A doubling in the risk of preterm, low birthweight and small for gestational age babies have also been reported for women whose eating disorder had been treated before the beginning of pregnancy.

**Current controversies**

**Size of the effect**

Although many studies have confirmed Barker’s original description of the link between size at birth and risk of adult
disease, there have also been many criticisms. It has been suggested that recent systematic reviews of the link between birthweight and blood pressure are biased due to the small sample size of many of the studies. Smaller studies were more likely to report more negative effects than larger studies, suggesting publication bias. However, although controlling for publication bias lessened the relationship between systolic blood pressure and birthweight, the relationship did remain significant.

The reported 2-mmHg increase in systolic blood pressure per kilogram decrease in birthweight appears to be a very small effect. However, a distinction needs to be made between physiological and pathological effects. In the American Nurses Study, the relationship with birthweight was present but weak for blood pressure, a physiological measure, and much stronger for the incidence of diagnosed hypertension, a pathological measure of much greater clinical significance. Similarly, in a study of treated hypertensives, blood pressure was markedly higher in those of lower birthweight (6.4–9.4 mmHg per kilogram birthweight), although there was no relationship between blood pressure and birthweight in normotensive subjects from the same cohort.

**Twins**

Twins generally have lower birthweights than singletons, so the fetal origins hypothesis might predict a higher incidence of adult disease in this population. However, mortality rates from coronary heart disease were not found to be increased in twins compared to singletons. Furthermore, adult blood pressure did not differ between twins and their singleton siblings. In contrast, there is some evidence for an increased incidence of diabetes in the twin population, and twins have been found to have increased insulin resistance compared to singletons independent of birthweight.

Studies on the relationship between birthweight and blood pressure in twins have been inconclusive. Some have shown that low birthweight is linked with elevated blood pressure but others could not find this relationship. However, most studies have reported an association between birthweight and glucose intolerance or type 2 diabetes in twins. In twins discordant for glucose tolerance or diabetes the affected twin was found to have a lower birthweight than the unaffected twin, although again, not all studies found this connection.

It has been argued that twin studies can be used to separate the effects of genes and environment on the development of disease. This is based on the premise that monozygotic twins share both their genes and their uterine environment while dizygotic twins share their uterine environment but only part of their genes. However, the uterine environment may not be the same for monozygotic and dizygotic twins. The possible effects of sharing different proportions of a common placenta on fetal growth and development are well recognised, as are the effects of placental anastomoses leading to partially shared circulations, and these effects may also have long-term consequences.

Finally, it has been argued that the regulation of fetal growth in twins may be fundamentally different from that in singletons. The relationship between birthweight and later disease may therefore also be different from that in singletons. Some support for this has been found in the fact that birthweight-specific mortality is lower in twins than in singletons. Furthermore, the offspring of twins are generally of average birthweight while the offspring of growth restricted singletons are themselves at increased risk of being born growth restricted. Few studies have compared long-term outcomes of twins with appropriate singleton controls. Thus, studies on the fetal origins of adult disease in twins need to be interpreted with caution.

**Prematurity**

An important but as yet unanswered question is to what extent the associations with low birthweight may be influenced by gestation length rather than fetal growth. Many of the early epidemiological studies had quite limited data on gestational age of the subjects, and survival of large numbers of preterm babies is a relatively recent phenomenon so that long-term outcome studies are extremely limited. Furthermore, most of the experimental work has focused on impaired fetal growth, largely because of the lack of suitable animal models of prematurity. Nevertheless, there are now a number of studies suggesting that prematurity itself may increase the risk of several of the diseases of interest, although the relative contributions of fetal growth and gestational age remain uncertain. Blood pressure is elevated in some cohorts of young adults born preterm, and is reported to be inversely related to gestational age in some larger population studies. Insulin resistance, elevated fasting insulin levels, and elevated plasma cortisol levels have also been reported in young adults born preterm. If a relationship between adult disease risk and gestational length is confirmed, then this may provide some interesting new challenges for obstetric practice, since elective early delivery, even close to term, may have implications for life-long health of the baby.

**Reversibility**

If the risk of many common diseases of adulthood in our communities is largely determined before birth, then a critical question to be addressed is the extent to which these risks may be aggravated or ameliorated by subsequent events. Since poor fetal growth is most commonly diagnosed in late gestation or even after birth, and since there are not yet any effective intrauterine treatments for the baby who is growing poorly, there has not yet been an opportunity to test directly if reversing the intrauterine growth deficit may or may not also reverse the physiological changes, although work in this area is continuing.

There is some exciting new evidence that some of the programming effects of intrauterine undernutrition may be reversible after birth. The adult offspring of rats that were undernourished during pregnancy developed hyperinsulinaemia and obesity as a result of reduced locomotor activity.
and overeating.\textsuperscript{142,143} These animals also had low plasma concentrations of leptin, a hormone released by adipocytes, which is involved in the regulation of food intake, energy balance and reproduction. When they were treated with leptin in the early postnatal period, the physiological changes caused by \textit{in utero} undernutrition were completely reversed.\textsuperscript{144} Many more studies are needed to fully understand the biology of this and other potential treatment approaches.

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