Chapter 1

Introduction

Graham J. Burton, David J. P. Barker, Ashley Moffett and Kent Thornburg

Developmental programming of the fetus is a phenomenon that has profound implications for the health of individuals and societies. The term describes the process by which gene expression in the fetus is influenced by the intrauterine environment, such that the structure of major organs and the homoeostatic points of metabolic and endocrine systems are set for life. Through this mechanism, perturbations in the intrauterine experience that affect development may predispose to a spectrum of adult diseases, depending on the system principally affected. Thus, in a recent review the National Institute of Child Health concluded that 'coronary heart disease, the number one cause of death among adult men and women, is more closely related to low birth weight than to known behavioural risk factors'. The list of diseases continues to grow, and now also includes diverse metabolic, neoplastic and neurological disorders.

This striking effect first came to light through epidemiological studies of men in Hertfordshire, UK, who had died from cardiovascular disease. Through the records maintained by the midwives attending the births of these men it was possible to show that death rates from the disease fell across the normal range of birth weight. In a later study of blood pressure levels among men and women in Preston, UK, it was possible to relate birth weight to the weight of the placenta. People with small placentas and people with large placentas in relation to their birth weights had the highest blood pressure levels. Although these data highlighted the importance of the fetoplacental relationship to developmental programming, the mechanistic role of the placenta in the phenomenon has received little attention to date. This is a remarkable oversight, given that the placenta evolved to support the fetus *in utero*, and must therefore reasonably be expected to be a key determinant of fetal growth.

This book records the proceedings of a scientific meeting convened to rectify this situation. The meeting, held over two days in Cambridge in December 2009, brought together invited experts from a wide variety of disciplines to present and discuss their data in depth under the skilful and diplomatic guidance of the Chair, Professor Sir Robert Boyd. The contributions presented here explore our current knowledge of the ways in which various aspects of placental development and function may influence fetal programming, and aim to promote further scientific research in their respective fields. When structuring the meeting, we aimed to consider the development of the placenta from the level of molecular genetics through to epidemiological biomarkers, and from pre-conception through to maturity, with the emphasis being placed on human data.

The starting point of the meeting was that changes in the shape of the placental surface, whether it is round or oval, are related to developmental programming. Little attention has been paid to the importance of placental shape in recent years, or to its determinants. What is so striking, however, is that placental shape changed radically over the 20-year period of the Helsinki study, indicating that it is surprisingly plastic and responsive to intrauterine cues. Equally, it is not known whether the tissues along the major and minor axes of the placenta perform the same functional roles. The placenta has a wide variety of functions, including passive and active transport, hormone synthesis, metabolic regulation, acting as a selective barrier to maternal hormones and as an immunological shield. We must therefore be precise when we talk in terms of placental efficiency and insufficiency, and refer to the specific function being monitored.

Morphologically, placental development starts at the time of implantation, but can of course be

The Placenta and Human Developmental Programming, ed. Graham J. Burton, David J. P. Barker, Ashley Moffett and Kent Thornburg. Published by Cambridge University Press.

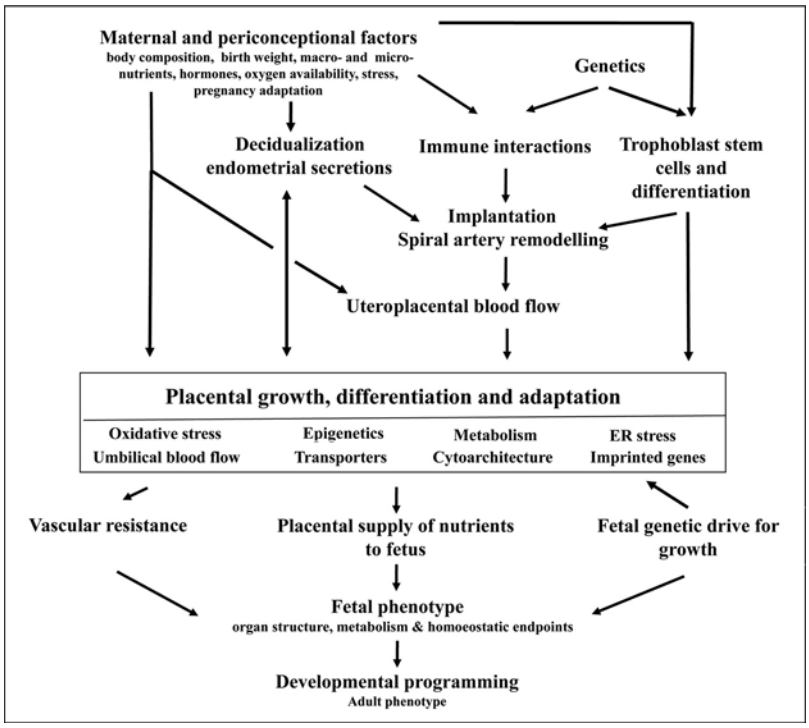

Figure 1.1 Diagrammatic representation of the major factors affecting placental development and function, and the ways in which these may affect the developmental programming of the fetus.

influenced by a variety of preceding events. For example, micronutrients influence the antioxidant composition of the antral fluid during folliculogenesis and the quality of the ovum released. Equally, in animal models maternal diet alters the allocation of cell lineage during formation of the blastocyst, affecting the development of the extraembryonic membranes. Similar perturbations have been observed following culture during *in vitro* fertilization procedures, particularly when the conditions are suboptimal and operate through epigenetic modifications. Thus, greater attention should be given to the pre- and periconceptional care of women in terms of their diet, body mass index and general well-being.

The development of the placenta is not autonomous, but is clearly heavily influenced by the uterine mucosa with which the trophoblast interacts. Appropriate preparation of the endometrium in each menstrual cycle is of central importance to successful implantation, yet surprisingly little is known about either the process of decidualization or, conversely, the triggers for endometrial breakdown at menstruation. Maternal nutrition has a profound impact on the hypothalamopituitary axis, and the effects of anorexia on ovarian function are well documented. In contrast, nothing is known regarding its possible impact on the endometrium and decidualization. It is now appreciated that the influence of the endometrium and its glandular secretions extends well beyond the time of implantation, and that the placenta and fetus are supported by the secretions until the end of the first trimester. Evidence from animal species indicates that the conceptus signals to the glands to upregulate the supply of nutrients and growth factors to meet its needs. Whether a similar mechanism operates in the human remains to be elucidated, but this is of key importance given that the major organ systems are differentiating at this time.

Towards the end of the first trimester there is a need for a greater oxygen supply, which can only be provided by the maternal arterial system. Establishing the intraplacental circulation in the highly invasive haemochorial form of placentation displayed by the human is fraught with immunological and haemodynamic challenges. During implantation, trophoblast cells migrate from the conceptus deep into the decidua and inner myometrium, where their function is to transform the maternal spiral arteries (Figure 1.1). This invasion is far more extensive in humans and closely related great apes than in other primates, raising questions about the evolutionary drive for such a complex and potentially hazardous process. The

molecular mechanisms underpinning spiral arterial conversion are not fully understood, but after being surrounded by trophoblast, the smooth muscle in the arterial walls is replaced by an inert fibrinoid material so that the arteries are no longer able to contract and potentially compromise placental blood flow. To achieve this end, the semi-allogeneic trophoblast cells must negotiate components of the maternal uterine immune system. It is now appreciated that interactions between parental MHC ligands expressed by the invading trophoblast cells (HLA-C molecules) and the NK receptors on the maternal decidual natural killer cells (KIR) are an important determinant of pregnancy outcome. This interaction is thought to have a physiological function in terms of regulating trophoblast invasion, necessitating a paradigm shift in our understanding of the roles of these immune cells. Macrophages, dendritic cells and T cells – including T regulatory cells – are also present in the decidua and myometrium, and their role during early placentation requires further research.

The importance of an adequate uterine blood flow bringing a supply of nutrients and oxygen to support fetal growth is highlighted by studies of populations living at high altitude, which can be considered experiments of nature. Blood flow is maintained or even increased in indigenous populations, but reduced in recent migrants, in whom it correlates with a reduction in birth weight. Understanding the mechanisms underlying these adaptations may throw light on important placental homoeostatic pathways.

Maternal factors such as stress and cigarette smoking have a profound but transient impact on uteroplacental blood flow. Stress may also cause elevated levels of glucocorticoids, and recent research on laboratory rodents has shown that these can adversely affect placental differentiation. Glucocorticoids are administered routinely in cases of threatened preterm deliveries to accelerate maturation of the lungs and other organ systems. Although this may provide immediate clinical benefits postnatally, there may be later consequences in terms of fetal programming.

The placenta is not passive to these insults but highly adaptive, responding to various challenges with changes in cellular architecture, vascularity and transporter expression (Figure 1.1). Hence, placental size is not an accurate estimate of placental capacity, and thought should be given to whether the efficiency is best expressed per unit exchange surface area or in some other form. Many of these structural adaptations and changes in transporter expression are regulated through imprinted genes, which allow gene dosage to be strictly controlled and are thought to play crucial roles in the partitioning of nutrients between the mother and her fetus. There are clearly important signals that pass from the fetus back to the placenta regulating expression of these genes: members of the insulin-like growth factor family appear to be strong candidates for these signalling functions. Further research is required to elucidate the components of this fascinating dialogue.

A central question in this respect is whether the placenta, the fetus or both act as the nutrient sensor. The mTOR signalling pathway performs this function at the cellular level, regulating proliferation and differentiation in response to amino acid availability. Activity in this pathway is, however, perturbed by the closely interacting conditions of oxidative and endoplasmic reticulum stress. Thus, although adaptations in placental function in response to fluctuations in nutrient supply may occur in the normal placenta, this may not be possible in cases of pathology secondary to malperfusion, when these stresses are present.

Assessment of placental function *in vivo* is obviously important for clinical diagnosis and monitoring. Most of the biochemical tests used to predict poor placentation and fetal growth originate from other screening tests, for example for trisomy 21, and are therefore not specific for fetal growth retardation. However, in these cases placental products such as pregnancy-associated placental protein-A (PAPP-A) are reduced during the first trimester. Whether this reflects a small placental mass or impaired placental secretory activity due, for example, to endoplasmic reticulum stress, is not known. The difficulty of obtaining placental samples from ongoing pregnancies represents a major problem for research in this area. Ultrasonography of the placenta and uterine artery waveforms combined with a wider range of placental biomarkers may provide a way forward.

The capacity of the placenta to supply adequate nutrients to the fetus is obviously of central importance to the role of the organ in developmental programming, but other aspects of placental function may also operate. The placenta represents a major component of the fetal circulation, and changes in umbilical vascular resistance, through, for example, a reduction in villous vascularization or an imbalance in vasoreactive agents, will affect the mechanical loadings on the developing heart (Figure 1.1). Proliferation and

differentiation of cardiomyocytes is sensitive to such factors, and so cardiac development may be impaired as a result.

Ultimately, developmental programming arises through the tension between the genetic drive for growth of the fetus and the intrauterine environment to which the fetus is exposed. Changes in the supply of macro- and micronutrients can heavily influence the differentiation of fetal organs and tissues, and alter the homoeostatic set points of endocrine axes. It is important for public health to stress that these effects operate across the birth weight range and are not confined to extreme low-birth weight individuals.

We thank all our participants for their stimulating contributions, the Centre for Trophoblast Research (www.trophoblast.cam.ac.uk) for sponsoring the meeting, and Cambridge University Press for publishing this book, which we hope will provoke interest into the role of a fascinating but often neglected organ, the placenta, in developmental programming.

Chapter 2

The maternal and placental origins of chronic disease

David J. P. Barker, Johan G. Eriksson, Eero Kajantie, Saleh H. Alwasel, Caroline H. D. Fall, Tessa J. Roseboom and Clive Osmond

Introduction

Fetal programming is the process whereby environmental influences acting during development alter gene expression and program the body's structures and functions for life. There is now a body of evidence showing that chronic diseases of adult life, including cardiovascular disease, type 2 diabetes and certain cancers, originate through this process. These diseases are initiated by adverse influences during development [1]. These adverse influences may also slow the growth of the fetus and reduce its body size at birth and during infancy. Compared with people whose birth weights were towards the upper end of the normal range, those whose birth weights were towards the lower end have (a) reduced functional capacity, including fewer nephrons in the kidney; (b) altered metabolic settings, including insulin resistance; and (c) altered production of hormones, including stress and sex hormones. In a recent review the National Institute of Child Health concluded that 'coronary heart disease, the number one cause of death among adult men and women, is more closely related to low birth weight than to known behavioural risk factors' [2]. To date, most epidemiological observations that have demonstrated this link between prenatal life and later disease have used birth weight as the marker of early life. A baby's birth weight reflects its success in obtaining nutrients from its mother [3]. The source of these nutrients is not only the mother's current diet, but her nutritional stores and metabolism, which are the product of her lifetime's nutrition [4]. A baby's birth weight also depends on the placenta's ability to transport nutrients to it from its mother [3]. 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 fetus's demands for them [5]. At the outset it is reasonable to assume that how the placenta programs the fetus will depend on the mother's lifetime nutrition.

This review uses new epidemiological data to examine the role of materno-placental interactions in initiating chronic disease in the offspring. It has been possible to pursue this issue epidemiologically because placental function and maternal nutrition are reflected in placental size at birth and in maternal body size, and these can be related to the later occurrence of disease.

Measurements of placental size and shape that reflect its function

The size, weight and shape of the placenta are all subject to wide variations [6]. Its size reflects its ability to transfer nutrients [7]. Small babies generally have small placentas but, in some circumstances, an undernourished baby can expand its placental surface to extract more nutrients from the mother [8]. Low placental weight at birth has been shown to predict hypertension and coronary heart disease in later life [9,10]. The weight of the placenta, however, does not distinguish its surface area from its thickness. In order to increase the surface for nutrient and oxygen exchange, the placenta can increase the surface of its villi, expand its invasion across the surface of the uterine lining or invade the maternal spiral arteries more deeply. The long-term consequences of these three responses may be different.

Placental shape

In the last century the surface of the placenta was described as being either 'oval' or 'round' [11–13]. In order to describe the extent to which the surface was more oval than round, two so-called 'diameters' of the surface were routinely recorded in some hospitals, a maximal diameter (the length of the

The Placenta and Human Developmental Programming, ed. Graham J. Burton, David J. P. Barker, Ashley Moffett and Kent Thornburg. Published by Cambridge University Press.

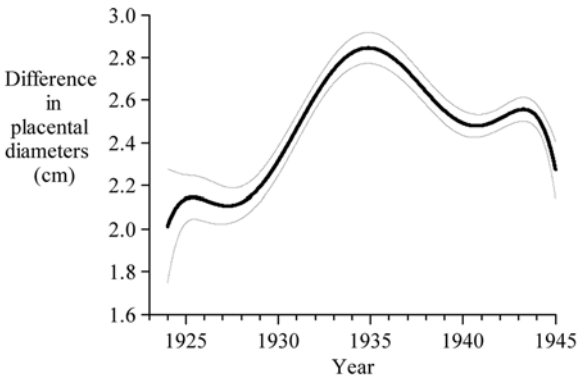

Figure 2.1 Trend line (95% confidence interval) for the difference between the two placental diameters over 21 years in the Helsinki Birth Cohort.

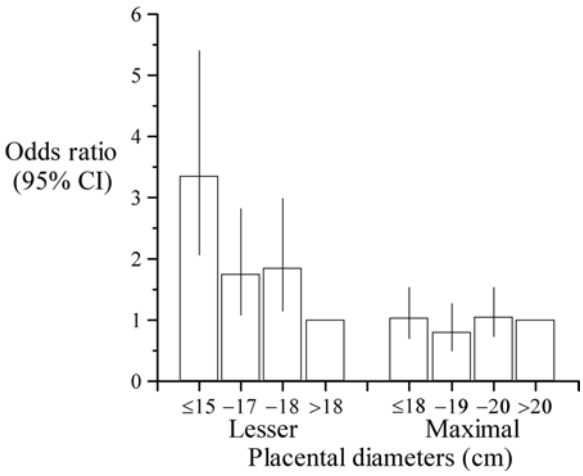

Figure 2.2 Hazard ratios for pre-eclampsia according to the lesser and maximal placental diameters.

surface), and a lesser one bisecting it at right-angles (the breadth) [14]. These measurements are available in the Helsinki Birth Cohort Study. The cohort comprised 20 431 men and women born in the city during 1924–44 [15]. The mean lengths of the two diameters, which were measured to the nearest centimeter, were 19.5 cm and 16.9 cm, and their lengths were highly correlated (correlation coefficient = 0.63). Figure 2.1 shows that the difference between the lengths of the two diameters fluctuated during the 21 years of births, the general trend being for the difference to increase so that the placental surfaces became more oval. The diameters were used to estimate the surface area ($\pi \times/\times$ lesser $\times/\times$ maximal diameter $\times/\times$ 4]. How closely this area reflects the total surface area for materno-fetal exchange through the gestational period is not known, but it is reasonable to suppose that they correlate. Combined with placental weight, the two diameters gave an estimate of placental thickness (weight/area).

Pre-eclampsia is associated with reduced placental size. The abnormal placentation is a result of impaired invasion of the maternal spiral arteries by the trophoblast at implantation [16]. Of the mothers of the younger part of the Helsinki birth cohort, born 1934–44, 6410 had their blood pressures and the results of urinary protein tests recorded after 20 weeks of pregnancy. Of these pregnancies, 284 were complicated by pre-eclampsia [17]. Compared to those from normotensive pregnancies, the placentas from these pregnancies had a reduced surface area but the thickness was increased. The increase in thickness in pre-eclampsia could be compensatory for restricted expansion of the surface.

Placentas from pregnancies complicated by pre-eclampsia had a more oval surface than those from normotensive pregnancies because of a disproportionate reduction in the breadth. When the two diameters were analysed together, pre-eclampsia was not associated with the size of the maximal diameter but was strongly associated with a short lesser diameter. Figure 2.2 shows that the relation with the lesser diameter was graded: the shorter the lesser diameter, the greater the risk for and severity of pre-eclampsia. This association with a short lesser diameter depended on its absolute length rather than on its length in relation to the surface area or weight. Processes that underlie the disease may therefore be closely linked to the absolute amount of placental tissue on the lesser diameter. This link may be through a structure or function that it does not share with tissue on the maximal diameter. Alternatively, growth along the lesser diameter may be controlled differently from growth along the major axis. Placental growth may be polarized from the time of implantation, so that growth along the major axis, defined by the maximal diameter, is qualitatively different from that along the minor axis [17]. One possibility is that growth along the major axis is aligned with the rostrocaudal axis of the embryo, whereas tissue along the minor axis may be the nutrient sensor. Tissue on the minor axis may be more sensitive to the mother's nutrition than tissue along the major axis, and it may be more important for nutrient transfer to the fetus.

Table 2.1 Mean systolic blood pressure of men and women aged 50, born at term.

Birth weight (pounds)	Placental weight (pounds)			
	≤1.0	–1.25	–1.5	>1.5
≤6. 5	149	152	151	167
–7. 5	139	148	146	159
>7. 5	131	143	148	153

Placental enlargement

Low placental weight is associated with an increased risk of hypertension in later life [9]. However, a study of men and women born in a maternity hospital in Preston, UK, showed that high placental weight in relation to birth weight is also associated with later hypertension [18]. Table 2.1 shows that, as expected, at any placental weight lower birth weight was associated with higher systolic pressure but at any birth weight higher placental weight was associated with higher systolic pressure. The highest systolic pressure was in people who had the lowest birth weights but the highest placental weights. This observation has been replicated, and high placental weight in relation to birth weight has also been shown to predict coronary heart disease [9,19]. Observations in sheep show that in response to undernutrition in mid-gestation the fetus is able to extend the area of the placenta by expanding the individual cotyledons [8,20]. This increases the area available for nutrient and oxygen exchange, and results in a larger lamb than there would otherwise have been. This is profitable for the farmer, and manipulation of placental size by changing the pasture of pregnant ewes is standard practice in sheep farming. The associations with large placental size suggest that cardiovascular disease can be programmed in association with placental overgrowth as well as restricted placental growth.

Placental efficiency

In Table 2.1, at any birth weight people who had lower placental weights had lower systolic pressures. People in the highest birth weight group but the lowest placental weight group had the lowest systolic pressure. A low ratio of placental weight to birth weight may be an index of placental efficiency, as proportionately more resource has been invested in the growth of the baby as opposed to placental growth. In a recent study of 7000 newborn babies born between 2000 and 2004 in Unizah, a small city in Saudi Arabia, the mean birth weight approached the mean for western populations (Alwasel, unpublished); but the mean placental weight, 473 g in boys and 467 g in girls, and the mean placental to birth weight ratios, 14.6 and 14.9%, were well below those in a recent compilation of European reference values [21]. These differences do not seem to be the result of differences in the procedures used to weigh the placentas. In experimental studies in which uterine blood flow is reduced [22], and in clinical studies [23], a relative decrease in placental size is evident before changes in fetal growth. An interpretation of the findings in Saudi Arabia is that placentas respond to mothers' limited ability to deliver nutrients to them. Placental growth slows but efficiency is increased, so that fetal growth is sustained, albeit with a reduced reserve capacity.

Maternal influences on placental size and shape

In humans, placental growth responds to maternal influences. Maternal anemia and high maternal body mass index are associated with a high placental weight to birth weight ratio [24,25]. Maternal smoking reduces both placental weight and birth weight. The diets of mothers during pregnancy, and their physical activity, are also known to be associated with altered placental weight [5,25].

Changing lifestyle during Ramadan

In Islam, Ramadan is an annual period of day-time fasting that lasts for one month. During Ramadan people in Saudi Arabia change their life style. They take no food or water from dawn until sunset, when they break their fast by eating sweet and fried meals. The next meal is 'Sahoor', which is usually eaten before dawn and comprises foods rich in fat. People reduce their activities during the day, but are more active at night. Although pregnant women are allowed to defer fasting until after the pregnancy, they often prefer to share the spiritual and social experiences of Ramadan with their families. In the studies in Unizah the mean birth weight of babies who were *in utero* during Ramadan was the same as that of babies who were not. However, the mean placental weight of those in the second or third trimester of gestation during Ramadan was lower than in those who were not *in utero* during Ramadan (Alwasel, unpublished). The mean ratio of placental

weight to birth weight was also lower. Among boys the mean was 14.4% compared to 14.9 in those not *in utero* during Ramadan. The corresponding figures for girls were 14.7 and 15.0. These findings suggest that the Ramadan lifestyle increases placental efficiency.

The Dutch famine

The 'Dutch famine' was a six-month period of severe food restriction in the west of Holland during the last years of the Second World War, 1944–5. The Dutch famine birth cohort consists of 2414 men and women who were born as term singletons in the Wilhelmina Gasthuis in Amsterdam between 1 November 1943 and 28 February 1947 [26]. The birth records do not include placental weight, but the two diameters were recorded and thickness measured using calipers. Babies who were *in utero* during the famine had lower birth weight and placental area than babies born before, or conceived after, the famine, but their placental thickness was increased (van Abeelen, unpublished).

Maternal/placental programming

Blood pressure

Placental weight predicts the risk of hypertension in the offspring in later life [9,18,27]. Associations with both low placental weight and a high ratio of placental weight to birth weight have been reported. Similarly, placental weight has inconsistent associations with blood pressure levels in children. Again, there are reported associations between increased blood pressure levels and low placental weight and a high ratio of placental weight to birth weight [28,29]. Other studies have found no associations [30]. The observations on hypertension, reviewed below, suggest that these different findings may reflect different materno-placental phenotypes that programme hypertension.

Hypertension in adults

Compensatory expansion of the placental surface in the sheep fetus, in response to undernutrition in mid-gestation, has already been described. This response only occurs, however, if the ewe was well nourished before conceiving [8]. There is evidence of a similar constraint in humans: 2003 members of the Helsinki Birth Cohort were randomly selected to attend a clinic,

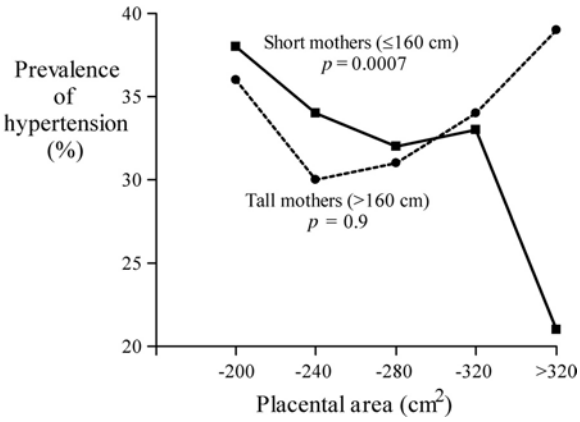

Figure 2.3 Prevalence of hypertension according to placental area in the offspring of short and tall mothers.

644 of them were being treated for hypertension. The prevalence of hypertension fell as placental area increased [14]. The effects of placental area on hypertension, however, varied with the mother's height. Figure 2.3 shows the trends in the prevalence of hypertension in people divided according to whether their mother's height was above or below the median of 160 cm. In people whose mothers were short the prevalence of hypertension fell progressively with increasing placental area. In people with tall mothers the association was U-shaped.

The strong effects of small placental area in people born to short mothers suggest a link between hypertension and the lifetime nutrition of the mother. Short maternal stature is a product of poor fetal or childhood nutrition, or recurrent exposure to infections, though there are also genetic influences [31]. Protein metabolism is established in early life and is related to visceral mass. Short women have less visceral mass than tall women, and have lower rates of amino acid synthesis in pregnancy [32]. An explanation for the combined effect of a short mother and a small placental area on hypertension is that the effects of reduced availability of amino acids in the maternal circulation are exacerbated by restricted placental growth, which limits the transport of amino acids from mother to baby.

Among people with tall mothers there was no overall effect of placental area on hypertension (Figure 2.3). However, when these people were subdivided by their parents' socio-economic status, opposing trends were revealed. In lower social class families, hypertension was associated with small placental area and low

placental weight. In middle class families, hypertension was associated with large placental area and high placental weight in relation to birth weight. Tall mothers in middle-class families are likely to have been the best nourished before conceiving. During pregnancy, however, they would have been subject to the food scarcities that occurred in Finland before and during the Second World War [33]. Similarly to sheep, their fetuses may have responded to this by expanding the placental surface. Compensatory placental growth may be beneficial in some circumstances, but if the compensation is inadequate and the fetus continues to be undernourished, the need to share its nutrients with an enlarged placenta may become an added metabolic burden. A long-term cost of this added burden is hypertension, possibly as a result of impaired development of low-priority organs such as the kidney [34].

Of the two diameters of the placental surface the lesser was more closely associated with hypertension [14]. The interaction between the effects of maternal height and placental area (Figure 2.3) was reflected in a similar interaction between the effects of maternal height and the lesser placental diameter; but there was no interaction between mother's height and the maximal diameter. These findings support the idea that growth along the breadth of the placental surface is more nutritionally sensitive than growth along the length. Expansion of the placental surface along its breadth may be one way in which a fetus may compensate for undernutrition.

Blood pressure in children

The first observations on the relationship between placental surface and blood pressure in children were made on 471 children born in the city of Mysore in India [35, Fall unpublished]. Their blood pressures at nine years of age were inversely related to their birth weights. In boys, systolic pressures rose as placental weight and area decreased. The pressures also rose as the breadth of the surface decreased, but there was no similar trend with the length of the surface. This is consistent with the findings among adults in Finland and Holland, in whom hypertension was more closely related to the breadth of the surface than to its length [14, van Abeelen, unpublished]. It is again consistent with the idea that tissue along the breadth of the surface is more closely related to nutrient delivery to the fetus than tissue along the length of the surface, so that shorter breadth is associated with lesser delivery.

The effects of placental size on blood pressure levels among the girls interacted with the mothers' height. Among girls whose mother's height was below the median, systolic pressure rose as the ratio of placental area to birth weight increased. This association depended more on expansion of the surface along its breadth than along its length. The finding can be interpreted as further evidence that raised blood pressure is programmed in association with compensatory placental expansion, though in this instance the compensatory expansion occurred in the offspring of short mothers. Among girls whose mothers' height was above the median, systolic blood pressure rose as the difference between the length and breadth of the surface increased, that is, as the surface became more oval. On its own, small breadth was not related to systolic pressure. It was small breadth in relation to the length that predicted blood pressure. An oval placental surface may be a marker of maternal malnutrition that selectively affects growth in the breadth of the surface, because this is more sensitive to the mother's nutrition than growth in length.

Coronary heart disease

The observations on hypertension established that the relation between placental size/shape and fetal programming depend on the mother. In short mothers a large placental area was beneficial (Figure 2.3); in tall mothers it was deleterious, presumably reflecting the metabolic costs of compensatory placental expansion. There are similar materno-placental interactions in the programming of coronary heart disease. In the Helsinki Birth Cohort coronary heart disease is associated with low birth weight, an association that has been shown in studies around the world [15,36]. Among men, three different materno-placental–fetal phenotypes were associated with coronary heart disease (Erikkson unpublished). The phenotypes were defined by the mother's height and body mass index, and by the placenta having either a small surface, an oval surface, or being heavy in relation to birth weight. Common to each of the phenotypes was that the babies were thin at birth, which suggests that the materno-placental phenotypes led to fetal undernutrition. This may have affected the development of the heart (see Chapter 16).

Chronic heart failure

People in the Helsinki Birth Cohort who developed chronic heart failure were born with a small placental surface area. This association with a small surface was the result of reduced growth along the lesser axis of the surface. The effects of a reduced surface area were confined to people whose mothers were below the median height and whose fathers were manual workers. The reduced rates of protein synthesis in short mothers may have amplified the adverse effects of impaired placentation on the fetus. These effects may have been exacerbated by poor maternal nutrition during pregnancy. There were food shortages in Helsinki before and during the Second World War, the time when our subjects were born [33]. These may have been more severe in families of low socio-economic status. Animal studies support a relationship between fetal malnutrition and heart failure (see Chapter 16). Increased loading of the heart in fetuses with a small placenta is likely to reduce cardiomyocyte numbers for life and hence make the heart vulnerable to developing chronic failure.

Lung cancer

The findings for coronary heart disease suggest that different combinations of maternal and placental size and shape lead to fetal undernutrition and thinness at birth. Findings for lung cancer suggest that different materno-placental combinations also lead to an imbalanced nutrient supply to the fetus. In the Helsinki Birth Cohort men and women who developed lung cancer were short at birth in relation to their weight, so that they had a high ponderal index [37]. One possibility is that this reflected low amino acid – high glucose delivery to the fetus, which impaired the development of its antioxidant systems and made the lungs vulnerable to tobacco smoke and other carcinogens in later life. Three different materno-placental–fetal phenotypes were associated with lung cancer [38]. Common to each was a short mother and a newborn baby that was short in relation to its weight.

The three phenotypes, defined by the mother's height, body mass index (weight/height^2, BMI) were:

(1) *short, low BMI mother: small placental area*. In people whose mothers were short and whose BMI was below the median, lung cancer was associated with a small placental area. The reduced area for amino acid transfer from mother to fetus may have added to the effects of low maternal amino acid synthesis associated with the mother's short stature [32]. Birth weight was less severely affected than length, because it reflects the supply of glucose as well as amino acids.

(2) *Short, high BMI mother: large placental area*. In people whose mothers were short but whose BMI was above the median, lung cancer was associated with a large placental area. This could have led to a high ponderal index through low amino acid availability to the fetus, accompanied by high glucose availability, associated with high maternal BMI. Maternal glucose metabolism is an important determinant of fetoplacental growth [39]. It may be a key environmental cue to which the placenta responds in order to match fetal growth rate with the resources made available by the mother.

(3) *Short, low BMI mother: large placental area*. In people whose mothers were short and whose BMI was below the median, lung cancer was also predicted by large placental area. This contrasts with the second of the three phenotypes and suggests that lung cancer may be associated with large placental area through two different aspects of placental growth. One possibility is that whereas in the second phenotype large placental area depended on high maternal BMI and high circulating maternal glucose, in this third phenotype it was the result of compensatory expansion of the placental surface in late gestation.

Sex differences in placental growth and programming

Sex differences in placental growth

Boys grow faster than girls from an early stage of gestation and this makes them more vulnerable if their nutrition is compromised [31,40]. Among boys and girls in the Helsinki Birth Cohort the small differences in the average measurements of the baby and placenta concealed large differences in body proportions [41]. At any placental weight boys tended to be longer than girls; and boys' placentas were smaller than girls' placentas in relation to the weight of the baby [42]. Similarly, in the Saudi Arabian study the ratio of placental weight to birth weight was similarly lower in boys than, at 14.6% compared to 14.9%, girls