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The fetal origin of adult diseases

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Summary

In the last decade, the development of Barker's hypothesis of fetal programming opened the field for extensive research into the fetal origin of adult diseases. The association between low birth weight, which reflects intrauterine nutritional status, and the development of adult diseases has been confirmed in many studies for type 2 diabetes, hypertension and coronary heart diseases. Many other adulthood diseases were investigated for the same association with variable outcomes. These will be presented in this review.

Introduction

The complex interaction between the maternal and fetal systems maintains fetal growth. Birth weight is one of the most important determinants of perinatal outcome. Intrauterine growth restriction (IUGR) is a major cause of prenatal morbidity and mortality. As well, smaller decrements in growth during the fetal period can have profound consequences for the individual throughout later life. Early fetal development occurs mainly by cell hyperplasia. During the embryonic period, organogenesis is the main focus of the developing embryo. Subsequently, in the fetal period, there is intense growth and cells undergo hyperplasia and hypertrophy during the second trimester and mainly hypertrophy during the third trimester with maturation of the organ systems.

The fetal origins of adult disease hypothesis, which was developed by David Barker, proposes that fetal growth restriction, due to undernutrition, has long-lasting physiological and structural effects that predispose to diseases later in life. There are critical periods of rapid fetal cell division during which an injury or insult to this process can result in permanent metabolic or structural changes. During these periods, fetal adaptations meant to counteract the undernutrition status in the short term can influence long-term health negatively. Small for gestational age (SGA) fetuses have undergone a reduction of growth *in utero* and have therefore modified their intrauterine growth pattern and are more likely to have undergone changes in their programming.

This review will attempt to summarise the effects of maternal nutrition and placental function along with the recent updates in the fetal programming of adult disease.

Fetal adaptation

To accommodate undernutrition, the fetus adapts with metabolic changes. The fetus becomes catabolic and consumes its own substrates to provide energy (Harding and Johnson, 1995). This leads to slowing growth, which helps the fetus to survive by lowering its metabolic rate. There is redistribution of blood flow to the brain, heart and adrenals to protect these tissues which are important for immediate survival (Rudolph, 1984). At the same time there is reduced flow to the liver and abdominal viscera. Another fetal adaptive method to undernutrition is by endocrine and hormonal changes. Maternal undernutrition decreases the insulin and insulin-like growth factors (IGF), which reduces fetal insulin, IGF and glucose concentrations. This leads to reduced transfer of amino acids and glucose to the fetus and slowing the growth rate (Oliver *et al*., 1993). It is these alterations in metabolic function which are believed to be present and lead to pathological health state in adults.

We will now review the adult diseases which have an association with fetal origin.

Coronary heart disease

Many reports had found an association between birth weight and mortality due to coronary heart disease (Osmond *et al*., 1993; Stein *et al*., 1996; Frankel *et al*., 1996; Rich-Edwards *et al*., 1997; Forsen *et al*., 1997; Leon *et al*., 1998). One of the first is the Hertfordshire cohort study (Osmond *et al*., 1993). They followed 15 726 men and women born between 1911 and 1930 and found that death from coronary heart disease decreased twofold with higher birth weights. The association between low birth weight and raised death rate secondary to coronary heart disease has been confirmed by other studies. In south India, a study of 517 men and women born between 1934 and 1954 found the prevalence of coronary heart disease fell from 11% in men and women who weighed 2.5 kg or less at birth to 3% in those weighed 3.1 kg or more at birth (Stein *et al*., 1996). A longitudinal cohort study of 70 297 nurses in United States has provided strong evidence of association between low birth weight and increased risk of non-fatal adult cardiovascular disease (Rich-Edwards *et al*., 1997). A Finish study of 3302 men born between 1924 and 1933 found a strong association with thinness at birth (especially in term men), lower placental weight and increase maternal body mass index during pregnancy and increased cardiovascular risk (Forsen *et al*., 1997). Other studies in Sweden and Wales have the same outcome (Frankel *et al*., 1996; Leon *et al*., 1998).

Size at birth and birth weight were not the only risk factors for cardiovascular risk; catch-up growth during infancy and childhood has been associated with increased

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risk of adult coronary heart disease (Eriksson *et al*., 1999, 2001). A longitudinal study of 3641 men born in Helsinki, Finland between 1924 and 1933 found that the hazard ratio for death from coronary heart disease increased by 14% ($P < 0.0001$) for each unit decrease in ponderal index [weight (kg)/length^3 (m^3)] and increased by 22% ($P < 0.0001$) for each unit increase in body mass index [weight (kg)/length^2 (m^2)] at 11 years of age (Eriksson *et al*., 1999). Two years later, the same group studied 4630 men born between 1934 and 1944 and confirmed the association between low birth weight and low ponderal index and increased risk of coronary heart disease (Eriksson *et al*., 2001). They also found that rapid catch up and weight gain increases the risk of coronary heart disease.

One of the unique studies provided by an unfortunate consequence of the World War II is the Dutch famine study, where investigators looked at the relation between maternal nutrition and coronary heart disease. Investigators studied 296 men and women exposed to undernutrition *in utero* between 1944 and 1945 and 440 control subjects born 1 year before or after (Roseboom *et al*., 2000). The prevalence of coronary heart disease was significantly higher in people exposed to undernutrition in early pregnancy than in those who were not exposed (8.8% vs. 3.2%, OR = 3.0). The prevalence was not increased in those exposed during mid-pregnancy or late pregnancy

The long period between birth and the development of coronary heart disease and different lifestyles can be a valid argument against this association. Furthermore, people whose growth was impaired *in utero* with poor weight gain during infancy may continue to be exposed to an adverse environment that produces the effects attributed to the programming of coronary heart disease. However, studies which collected data on lifestyle factors including smoking, employment, alcohol consumption and exercise found that these confounding factors have little effect on the association between coronary heart disease and birth weight (Frankel *et al*., 1996; Rich-Edwards *et al*., 1997). A Swedish study followed 14 611 men and women born between 1915 and 1929 with data collection at birth and at 1960 and 1970. Full birth data and socio-economic status including paternal occupation, residence, cars, marital status, occupation, education and income was collected (Leon *et al*., 1998). Complete information on all these variables was available in 96% of subjects. They confirmed the inverse association in men between mortality from ischaemic heart disease and birth weight. Gestational age at delivery was not associated with mortality secondary to ischaemic heart disease. Socio-economic circumstances at birth and in adult life had a small effect and cannot explain the association between birth weight and mortality from ischaemic heart disease.

Hypertension

The association between low birth weight and hypertension has been replicated in many studies in different countries. Law and Shiell (1996) published a systematic review of the published literature including more than 66000 subjects aged 0–71 years in 34 studies. They confirmed the inverse relation between birth weight and blood pressure in children and in adults. SGA infants have higher blood pressure levels as children and adults. However, the positive association was inconsistent in adolescence.

The same group published another review for all papers published between 1996 and 2000, a total of 45 papers, including more than 444 000 male and female subjects aged 0–84 years (Huxley *et al*., 2000). They added that postnatal catch-up growth was associated positively with elevated blood pressure. Placental weight and abdominal circumference were associated consistently with raised systolic blood pressure. The highest blood pressures occurred in individuals with low birth weight who had high rates of growth subsequently. Another study reported a significant association between placental volume and abdominal circumference in the second trimester and childhood blood pressure, suggesting that the fetal programming for blood pressure started early *in utero* (Thame *et al*., 2000). Early or late catch-up growth is also associated with increased blood pressure in adolescence (Horta *et al*., 2003).

Confounding socio-economic circumstances may affect this association. However, in twin studies by Poulter *et al*. (1999), little or no confounding supports the inverse relationship between birth weight and blood pressure. Poulter *et al*. (1999) studied 492 pairs of female twins with mean age of 54 years. They excluded any women on antihypertensive drugs. There was an inverse relation between birth weight and adult blood pressure, both systolic ($P = 0.01$) and diastolic ($P = 0.04$). Monozygotic twins have similar trends (Poulter *et al*., 1999), although not statistically significant. They concluded that the effect of low birth weight on subsequent adult blood pressure levels is due to placental insufficiency rather than poor maternal nutrition.

Another twin study examined whether the difference in birth weight is associated with difference in blood pressure at age 7 years (Zhang *et al*., 2001). The study included 119 pairs of monozygotic and 86 pairs of same-sex dizygotic twins. The smaller twin had an average 300-g lower birth weight and was thinner than the larger twin ($P < 0.001$). At age 7 years, body size and blood pressure were similar in the two groups. These results challenge the hypothesis that intrauterine environment affects blood pressure adversely in children at the age of 7 years. Conversely, it may have been too early for manifestations for hypertension to develop.

A recent meta-analysis of 44 papers describing 57 studies demonstrated the association between low birth weight and hypertension later in life, in which the study population contained both males and females (Lawlor *et al*., 2002). Nineteen of those studied presented results stratified by sex and 38 studies presented combined results. Combining all studies, there were no differences in the pooled regression between male and females. There was no sex difference in the association between birth weight and systolic blood pressure in later life.

The possible mechanism of intrauterine programming of adult hypertension secondary to IUGR may be due to redistribution of blood flow away from the liver, viscera and the kidneys, in favour of the brain, which leads to underdevelopment of these organs as suggested by Hinchliffe *et al*. (1992). They demonstrated that the kidneys of growth-restricted human infants are smaller and contain fewer nephrons than those of average for gestational age (AGA) infants. It was reported recently that the renal volume in growth-restricted fetuses was 31% less than the volume in AGA fetuses ($P = 0.0001$) (Silver *et al*., 2003). Another study confirmed that primary hypertensive patients had significantly lower glomeruli per kidney than normal

controls (median 702 379 vs. 1 429 200) (Keller *et al*., 2003). There was no relation between the number of glomeruli and the age of the patients.

In almost all the studies, an increase in birth weight was associated with a fall in blood pressure in childhood and adulthood. The association between low birth weight and raised blood pressure depends on babies who were small-for-dates rather than on babies who were born preterm with AGA (Leom *et al*., 1996).

Type 2 diabetes mellitus

One of the mechanisms for adaptation to undernutrition is through endocrine changes. Insulin has an essential role in fetal growth, and as part of this adaptation insulin production and function could be altered *in utero*, which may predispose to the development of type 2 diabetes in the future.

Many studies confirmed the association between low birth weight and type 2 diabetes (Hales *et al*., 1991; Barker *et al*., 1993; McCance *et al*., 1994; Leger *et al*., 1997; Poulsen *et al*., 1998). One of the first reports is the Hertfordshire study, where they studied 370 men born between 1911 and 1930 aged 59 – 70 years. The prevalence of type 2 diabetes or impaired glucose tolerance was threefold higher in men who weighed < 5.5 lb at birth than those who weighed 9.5 lb (Hales *et al*., 1991). The same result was confirmed in men and women with OR = 3.8 for the development of type 2 diabetes in those individuals who weighed less than 2.5 kg at birth. Furthermore, men and women with a birth weight of more than 4.5 kg had an increased prevalence of type 2 diabetes (McCance *et al*., 1994).

Twin studies support the relationship between birth weight and type 2 diabetes. A study of 28 twin pairs (14 monozygotic and 14 dizygotic) with a mean age of 67 and 64 years demonstrated the relationship between growth discordance and impaired glucose tolerance (IGT) in adult life (Poulsen *et al*., 1998). Birth weights were significantly lower in twins with an abnormal glucose tolerance test (GTT), including both type 2 diabetes and IGT ($P < 0.02$). As well, the twins with the lowest birth weights had the highest plasma glucose concentrations at 120 minutes after the 75-g GTT ($P = 0.02$). The significantly lower birth weights in both monozygotic and dizygotic type 2 diabetic twins decreases the likelihood of confounding. This study supports the hypothesis that intrauterine malnutrition has a major role in the development of type 2 diabetes later in life.

Insulin resistance

The development of insulin resistance has a major role in type 2 diabetes. The Hertfordshire study (Barker *et al*., 1993) reported that 407 men and women aged 59 – 70 years with low birth weight had a high prevalence of insulin resistance syndrome. A French study (Leger *et al*., 1997) found that young adults who were $<$ 10th centile at birth had raised plasma insulin concentrations when fasting and after glucose challenge tests. Men and women who were *in utero* during the Dutch famine were compared to those who were born 1 year before or after (Roseboom *et al*., 2000) and they had significantly higher 2-hour plasma glucose concentrations, fasting proinsulin levels and 2-hour insulin concentrations. The authors concluded that fetal undernutrition can programme insulin resistance and type 2 diabetes.

Insulin deficiency

The pancreas and specifically the insulin-producing β-cells play an important role in intrauterine adaptation and thereby may have consequences in later life. Van Assche *et al*. (1979) confirmed that infants who are small at birth have fewer β-cells. A study in south India involving men and women who were growth-restricted *in utero* and developed type 2 diabetes showed that they had signs of both insulin resistance and insulin deficiency (Fall *et al*., 1998).

The 'thrifty hypothesis'

In an effort to place these data in context, Hales and Barker, in 1992, proposed the 'thrifty phenotype hypothesis', whereby permanent metabolic and endocrine modifications (nutritional thrift) occurring *in utero* as a result of inadequate nutrition are detrimental to the developing pancreas. Fetal and infant undernutrition and impaired growth increases the risk for the development of adulthood type 2 diabetes. Phillips (1996) added later that when nourishment is reduced these fetal metabolic adaptations might include development of tissue insulin resistance to prevent glucose metabolism and cell growth. The development of insulin resistance could be to reduce the cell growth rate in order to survive the undernutritional status and to conserve more glucose and nutrients for the brain development by the brain-sparing effect. This insulin resistance could become permanently programmed and persist into adult life, thus contributing to the development of type 2 diabetes. The growth during childhood and catch-up growth was associated with an increased risk of cardiovascular disease. As well, childhood obesity was found to have a greater risk in the development of type 2 diabetes than adult obesity (Vanhala *et al*., 1998).

There are conflicting data in a Danish twin registry study including 67 twin pairs (20 monozygotic and 47 dizygotic) with type 1 diabetes (Kyvik *et al*., 2000). The mean birth weight in twins with diabetes was 2538 g compared to mean birth weight of 2549 g in non-diabetic twins. Logistic regression analysis showed no relationship between birth weight and diabetic status.

In the Leningrad siege study, Stanner and Yudkin (2001) investigated the relationship between decreased maternal food intake and risk factors for coronary heart disease in adult life, involving 169 subjects exposed to intrauterine starvation during the siege between 1941 and 1944, and compared these subjects with 192 subjects born in Leningrad before the siege and 188 subjects born concurrently with these two groups but outside the area of the siege. There were no differences between the subjects exposed to starvation *in utero* and during infancy and control subjects in glucose tolerance, insulin concentration, blood pressure and lipid concentration or coagulation factors. This study did not find an association between intrauterine starvation and glucose intolerance, dyslipidaemia, hypertension or cardiovascular disease in adult life.

Hypothalamic – pituitary – adrenal (HPA) axis

Low birth weight is associated with diseases in adult life such as hypertension, type 2 diabetes and cardiovascular disease. This association could be influenced by programming the HPA axis and glucocorticoid levels in low birth weight fetuses.

A birth cohort study in Helsinki, Finland examined the relationship between adult HPA axis function and birth weight and body proportions at birth (Kajantie *et al*., 2002). They studied 421 men and women (mean age 69.5 years) born at term between 1924 and 1933. There was no significant correlation between fasting cortisol concentrations and birth weight. However, there was a significant positive association between cortisol and ponderal index. The relationship between size at birth and cortisol concentrations in adult life is different in subjects born at different gestational ages. Subjects born before 39 weeks of gestation have an inverse association between total and free cortisol with weight and length at birth, whereas in subjects born after 40 weeks, there were positive correlations with weight and length at birth. These data suggest that both hyper- and hypocortisolism may be a consequence of fetal programming of HPA axis during intrauterine life (Kajantie *et al*., 2002).

Respiratory system

Intrauterine growth restriction and low birth weight has been associated with altered lung development and function, including an increased risk of respiratory distress (Minnor and Divon, 1998), impaired airway function (Nikolajef *et al*., 1998), as well as reduced lung compliance and impaired ventilatory efficiency in lambs (Joyce *et al*., 2001).

In a study involving 8960 men and women, the prevalence of bronchial asthma and wheeze at the age of 26 years increases with lower birth weight and higher body mass index (BMI) in adult life (Shaheen *et al*., 1999). After controlling for potential confounding factors, the odds ratio comparing the lowest birth weight group (< 2 kg) with the modal group (3–3.5 kg) was 1.99 for the development of bronchial asthma in adult life.

Immunity

Normal nutritional status is important for a competent immune system. It is known that protein malnutrition lowers human immunity. Lymphoid tissues have a high rate of cell proliferation and rapid turnover of proteins. Protein malnutrition leads to decrease in size and weight of the thymus as well as loss of lymphoid cells in the spleen and lymph nodes, which leads to a decrease in cell-mediated immunity (Chandra, 1993). SGA infants were found to have atrophy of the thymus, impaired cell-mediated immunity and hypoimmunoglobulinaemia (specifically IgG) (Moore, 1998). This evidence supports the theory that nutritional programming during intrauterine life may affect immunological development.

Serum cholesterol and blood clotting

Redistribution of blood flow away from the trunk and the liver in IUGR fetuses could have a major effect on liver development. Reduced abdominal circumference (AC) at birth reflects impaired liver growth and may be its function. Men and women who were born in Sheffield, UK between 1939 and 1940 with reduced AC at birth were found to have higher serum concentrations of total cholesterol and low-density lipoproteins (Barker *et al*., 1993). There was a strong association between reduced growth *in utero* and infancy and high plasma concentrations of fibrinogen and factor VII (Barker *et al*., 1992).

Cancers

Breast cancer

Michels *et al*. (1996) reported a case–control study of 582 women with breast cancer and 1569 controls. Three hundred and ninety-three women (67%) were premenopausal at the time of diagnosis. Low birth weight was associated significantly with a reduced risk of breast cancer. The risk for women with a birth weight of 2500 g or less was less than half that for women who weighted 4000 g or more (age adjusted OR = 0.56). Prematurity was not associated significantly with an increased risk of breast cancer. A more recent case–control study, Vatten *et al*. (2002) from Norway reported 373 patients diagnosed between 1959 and 1997 with a mean age at diagnosis of 50 years and 1150 control women born in the same hospitals and in the same period. They found a positive association between birth weight and breast cancer risk (P for trend = 0.02). A higher birth weight of 3730 g was associated with an odds ratio of 1.4 compared to a lower birth weight of 3090 g. Birth length has a positive association with an odds ratio of 1.3 for the highest (51.5 cm) compared with the lowest (50 cm). There was no association between placental weight and breast cancer risk. On the other hand, Sanderson *et al*. (2002) reported 288 premenopausal women with breast cancer diagnosed at 45 years of age or less and matched with 350 controls, 1996–98. Women who weighed 4000 g at birth or more were not at increased risk for the development of breast cancer (OR = 0.7, CI 0.4–1.4) relative to women who weighed 2500–2999g at birth.

Not all the studies showed the same association between birth size and breast cancer. This could be due to genetic or socio-economic status differences?

Testicular cancer

The incidence of testicular cancer peaks during the third decade of life. Akre *et al*. (1996) reported 232 patients, born in Sweden between 1920 and 1978, and 904 matched control subjects. There is a significantly elevated risk with either low (< 2500 g) or high (> 4000 g) birth weights (OR = 2.59 and 1.58, respectively). Low birth weight was associated significantly with non-seminomas testicular cancer (OR = 7.62). Moller and Skakkebaek (1997), in a case–control study, found that birth weights below 3000 g and above 4000 g were associated with increase risk of testicular cancer. Birth weight below 2500 g has OR = 2.6 for the development of testicular cancer. In a more recent study, Richiardi *et al*. (2002) conducted a case–control study of 628 patients born from 1920 to 1980 diagnosed with testicular cancer from 1958 to 1998 and matched them with 2309 controls. The duration of pregnancy was associated negatively with the risk for testicular cancer (P value for linear trend = 0.008). Long gestation and high birth weight appear to be protective.

Hepatoblastoma

Hepatoblastoma is a rare embryonal tumour resulting from developmental disturbance during organogenesis. Very low birth weight infants have a significantly increased incidence (Ikeda *et al*., 1997). Ikeda *et al*. (1998) reported 15 children (nine boys and six girls) who were diagnosed between the ages of 6 and 77 months. The birth weights ranged from 560 to 1380 grams and the gestational age ranged from 23 to 33

weeks (median 25). They found a significant correlation between the development of hepatoblastoma and very low birth weight and extreme prematurity. In a more recent study, Feusner and Plaschkes (2002) reviewed 105 children with hepatoblastoma. The rates were increased 15-fold with low birth weight (< 1000 g) and twofold with prematurity (< 37 weeks).

Psychiatric illnesses

Undernutrition *in utero* and during infancy may influence the development of the central nervous system. In one study, men and women who committed suicide were found to have low rates of weight gain in infancy, and after adjusting for social class the mean weight at 1 year of those who had died from suicide remained 395 g lower ($P = 0.02$) (Barker *et al*., 1995). Other studies found a significant association between low birth weights and increased risk for the development of schizophrenia (Wahlbeck *et al*., 2001) and depression (Thompson *et al*., 2001) in men in late adult life. These findings suggested that the neurodevelopmental aetiology of psychiatric illnesses could be mediated by programming the HPA axis.

Conclusion

More than 100 studies have been performed involving approximately half a million individuals. The association between low birth weight with hypertension and type 2 diabetes has been confirmed in most of these investigations. Type 2 diabetes and hypertension occur frequently together in association with dyslipidaemia, central obesity and insulin resistance, all of which strongly predispose to the development of atherosclerotic vascular disease. The association between birth weight and the development of other adult diseases such as respiratory, immunity, psychiatric illnesses or cancers was demonstrated in some studies, with conflicting results in other studies. Future research directions should now focus on high-risk groups and the implementation of early screening and treatment for these disorders.

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