

The foetal origins hypothesis, diabetes, and other chronic diseases

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The spread of the pandemic of cardiovascular disease and diabetes is not restricted to Western settings. Many low-income countries also face an increase in such non-communicable diseases (NCDs). For instance, the World Health Organization (WHO) estimates that around 7 million people were living with diabetes in Africa in 2000 and approximately 18 million will be affected in 2030. The same report in the European region of WHO shows that although nearly 33 million people were recorded in 2000, the expected number in 2030 will be around 48 million.¹ This means that, even though the disease is going to increase worldwide, the speed will be greater in developing countries.

The weakness of healthcare systems in many poor countries limits the adequate care of these patients. Diagnosis is often in the late phases and appropriate treatments are commonly not available. Therefore, improving preventive strategies is crucial to minimise the global burden of NCDs in poor settings.²

The relevance of childhood obesity to adult diseases such as stroke or hypercholesterolaemia has been clearly assessed in Europe and the USA.³ Paediatricians include such morbidities in their current care, and the general population is warned about the harmful consequences of being overweight during childhood. But does foetal life have the same effects into adulthood? Should preventive measures start in the uterus rather than in infancy? What consequences might this have in settings like Africa where low birthweight due to malaria results in 100 000 infant deaths each year?⁴ Finding the right answer to these questions would change the approach to these diseases worldwide, and hopefully, will improve their prognosis.

The 'Barker Hypothesis'

A group of British epidemiologists, headed by David Barker, suggested in 1986 the 'thrifty phenotype hypothesis', commonly known as Barker's Hypothesis. They proposed that intrauterine under-nutrition might permanently change or 'programme' the individual, who may then be predisposed to certain diseases later in life.

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Since then, the relevance of low birth-weight into adulthood is the area where most research has been focused. A more detailed analysis of intrauterine growth retardation (IUGR) will be presented here initially, followed by an overview of the most relevant studies on IUGR and its consequences for adult diseases will be explored.

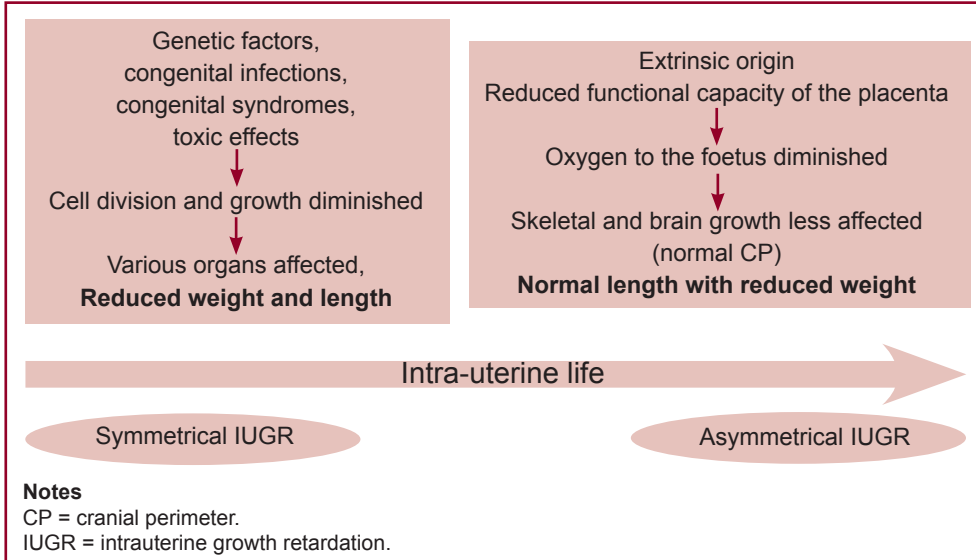
As Kanana-Gantenbein et al suggested, during intrauterine life the new individual goes through a constant process of maturation that will prepare them to face postnatal events.⁵ According to these authors, normal foetal growth has two different phases: embryonal and foetal. The former includes the proliferation, organisation, and differentiation of the embryo, while the latter involves growth and functional maturation of the different organs of the foetus.⁵ Problems in these phases can lead to IUGR, defined as '*all newborns with a birthweight and/or birth length below the 10th percentile for their gestational age with pathologic restriction of foetal growth due to adverse genetic or environmental influences.*' The different effects that any alteration of normal gestational growth has are summarised in Figure 1.

Other authors have proposed a more detailed differentiation, considering that not all small newborns will have suffered any insult in their intrauterine life. Breeze and Lees suggested the distinction between newborns 'constitutionally' small for gestational age (SGA), and those who have suffered any alteration during their intrauterine life resulting in growth restriction (IUGR).⁶ These categories are not merely academic because their relevance into adulthood might be very different. Once an individual has not achieved his or her full development, the consequences would be greater.⁶ However, the distinction might be difficult to perform in clinical practice due to the current limitations for measuring the full development of an individual. In practice, serial measurements (either clinical or with ultrasound) are used to detect growth restriction.⁶

In places where resources are limited, it might be complicated to distinguish between SGA and IUGR, so antenatal care strategies must focus on providing full growth potential for the foetus. As Breeze and Lees reported, identifying high-risk pregnancies for IUGR is the first step in minimising the harmful outcomes that might persist into adulthood.⁶ Factors associated with IUGR and SGA, according to Breeze and Lees, are summarised in Table 1.

Recently, there has been increasing evidence for an association between birthweight (as an indicator of foetal growth) and the risk of certain adult diseases such as the metabolic syndrome, diabetes and hypertension.⁷ As

Figure 1 Different types of intra-uterine growth retardation (adapted from reference 5)



of 'foetal origin of adult diseases' into the medical literature has been particularly relevant after the publication of the studies conducted by the group led by Barker.⁸ This group of UK investigators noticed that in the regions of England with the highest rates of infant mortality in the early 20th century, the highest rates of mortality from coronary heart diseases also happened decades later.^{9,10} The most common cause of infant death reported at the beginning of the century was low birthweight. After these observations, Barker et al proposed the hypothesis that 'a baby's nourishment before birth and during infancy, as manifested in patterns of foetal growth, "programmes" the development of risk factors such as elevated blood pressure, fibrinogen concentration, hyperlipidaemia, and glucose intolerance, and hence these are key determinants of coronary heart diseases.'⁹

In their first reports, no distinction between embryonic and foetal life was made when considering the growth

Table 1 Maternal risk factors for intra-uterine growth retardation or small gestational age (adapted from reference 6)

Risk factor	Risk
Past obstetric history	20% recurrence rate
Diabetes	Especially with microvascular disease
Hypertension	Especially if severe
Renal disease	Incidence of 23% with chronic proteinuria
Inflammatory bowel disease	If active Crohn's disease or ulcerative colitis
Connective tissue disease	Especially if active systemic lupus
Cardiac diseases	Risk of foetal death
Smoking	Especially >20/day
Alcohol	Especially heavy drinking
Drugs abuse	Especially with opiates
Prescribed drugs	Beta-blockers
Malnutrition	Common cause in developing world
Ethnicity and altitude	Varies within countries and ethnic groups
Assisted conception	Reported with in vitro fertilisation
Age	Older mothers have increased risk
Body mass index (BMI)	Maternal BMI <20.0

impairment of the foetus. Nevertheless, in 1994 this group of investigators pointed out the different effects on adult diseases that these two phases have. However, they asserted that in both intra-uterine periods, nutrient deficiencies could lead to growth impairment and functional abnormalities, with deleterious consequences later in life.¹¹ As Ophir et al also suggested, the main adaptation of the foetus to undernutrition is to become catabolic and consume its own substrate to provide energy, thus reducing its rate of cellular division.¹² This is the main mechanism whereby undernutrition (due to maternal malnutrition or

vascular deficiency) might permanently change or 'programme' the individual, which might predispose to diseases later in life. This 'thrifty phenotype' is the result of short-term responses that might be beneficial to the foetus but can have deleterious long-term effects.¹³

Sallout et al have also studied the mechanisms of foetal adaptation to undernutrition, which can lead to pathological health states in adults.¹⁴ They propose the main mechanisms as:

- redistribution of blood flow to the important organs for immediate survival (e.g. brain and heart);
- reducing the blood flow to other organs (e.g. abdominal viscera);
- endocrine and hormonal alterations, e.g. the decrease in maternal insulin and insulin-like-growth factor (IGF) that happens in malnourished mothers, reducing the foetal insulin, IGF, and glucose.

This induces a reduced shift of glucose and amino acids to the foetus and consequently a restriction in its growth. However, when the individual has no nutrient restriction in postnatal life, this pancreatic β -cell deficiency and peripheral insulin-resistance might cause glucose intolerance and subsequent diabetes.¹⁴

These are the bases of the 'thrifty phenotype hypothesis' (Barker Hypothesis). Since 1986, when the first reports were published, many other mechanisms have been proposed to explain how foetal undernutrition might lead to adult diseases; glucocorticoid exposure,¹⁵ or genetic and epigenetic links¹⁶ are some of these mechanisms. De Boo and Harding have reviewed the mechanisms in detail and these

results are summarised in Figure 2.

More than 100 studies enrolling almost half a million individuals have been carried out in both humans and animals to examine the relevance of the Barker Hypothesis.⁶ Many adult diseases have been associated with intra-uterine events.¹⁴ A more detailed review of those studies referring to cardiovascular diseases or diabetes will be given later.

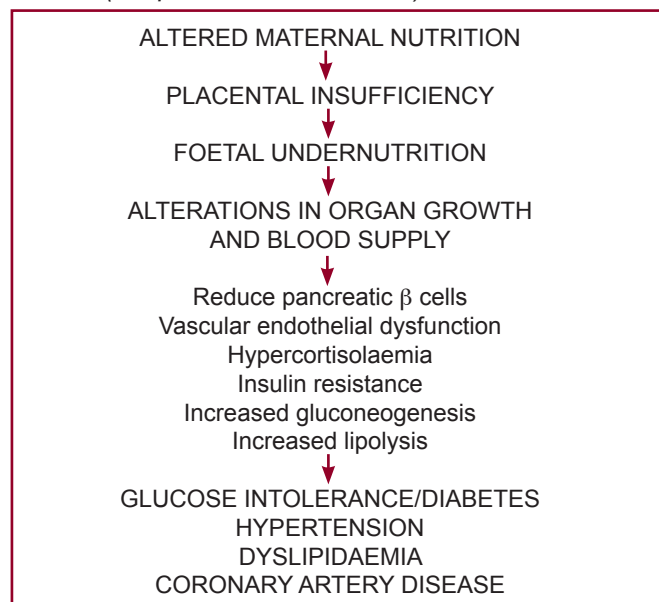
Adult disease with links to foetal under-nutrition

Coronary heart disease and low birthweight have been frequently associated worldwide. Stein et al found in 517 individuals from India that 11% whose birthweight was <2.5 kg had future coronary heart disease, whereas the figure was 3% in those with birthweight >3.1 kg.¹⁷ Reports from Rich-Edwards et al studying North American nurses, and Forsen et al studying 3302 men from Finland, have given similar results.^{18,19} Nevertheless, some of these studies emphasised that birthweight was not the only relevant factor, a marked catch-up growth during infancy and childhood also contributed to an increased risk of adult coronary diseases.²⁰ The relevance of when foetal malnutrition occurred was evident from the Dutch famine study. Those who suffered malnutrition in early pregnancy had a higher risk of coronary heart disease than those who were exposed to undernutrition later.²¹

The long period of observation covered by these studies makes it difficult to exclude other confounding factors, which might reduce the significance of these correlations (e.g. lifestyle factors). Notwithstanding, other studies have suggested that different socio-economic circumstances do not weaken the association significantly.¹⁴

The development of hypertension in adult life among individuals with low birth-weight has also been reported in many countries. Law and Shiell carried out a meta-

Figure 2 Links between intra-uterine malnutrition adult disease (adapted from reference 8)



analysis including more than 444 000 individuals and showed that low birthweight, as well as rapid postnatal catch-up, was associated with an increased risk of hypertension.²² Thame et al showed a significant association between placenta volume with abdominal circumference and raised systolic blood pressure.²³ To analyse the impact of confounding factors in this association, several studies have been carried out among twins. However, they have obtained differing results, such as the meta-analysis of Larwlor et al or the study of Zhang et al.^{24,25} Nevertheless, most studies have highlighted the link between redistribution of blood flow during pregnancy and later.²⁶

As previously discussed, the foetus with undernutrition undergoes several metabolic alterations. These have been known to precede the development of type 2 diabetes or insulin resistance in adult life among IUGR newborns. Hales and Barker reported an odds ratio (OR) of 3.8 for the development of type 2 diabetes in individuals with a weight <2.5 kg at birth.²⁷ Similar results were shown by McCance et al.²⁸ Furthermore, studies on twins such as that conducted by Poulsen et al reached similar conclusions.²⁹

Discussion

There is substantial evidence of the association between birthweight and risk of adult diseases; but as Morley and Dwyer have suggested, does it mean that size at birth is causally related to risk of cardiovascular events or are there other mechanisms involved?³⁰ If birthweight plays a role in the genesis of diseases into adulthood, public health policies should be changed and concentrated on the foetus rather than on children. But is there enough evidence to modify these policies? Finding which factors make adults vulnerable to chronic diseases, like hypertension or diabetes, would help towards their prevention.

Although many studies have corroborated Barker's hypothesis it has also been criticised. For instance, Morley and Dwyer have proposed three alternative explanations to the hypothesis.^{30,31} Firstly, that postnatal growth or size may be related to outcome, rather than foetal growth. According to these authors, postnatal catch-up during childhood is as relevant as birthweight (as Eriksson et al have also shown).²⁰ Another alternative explanation is that social and economic factors have influence on health. Birthweight is also related to the mothers' welfare, so socioeconomic confounding is difficult to assess. However, both Morley and Poulsen have carried out studies among twins that underline the association between birthweight and blood pressure, not explicable only by socioeconomic aspects.^{29,31} Finally, they consider that genetic factors might also be involved. Some genes influence birthweight, and what is even more critical, the gene-environment interactions could explain the different results found within racial groups.

Some view four main problems with Barker's foetal origins hypothesis:³²

- it fails to explain temporal or international variation in heart diseases;
- many studies have obtained different, even opposing results;
- some cofounders are not measured;
- small sample sizes of cohorts have been included in some studies.³²

Singhal and Lucas have proposed another theory linking birthweight and risk of adult diseases derived from their follow-up of preterm babies.³³ According to these authors, accelerated early postnatal growth (common in asymmetrical IUGR) is the basis of increased risk of the metabolic syndrome in adulthood. Other authors have also suggested that postnatal environmental factors might be responsible for more of the differences in adult disease mortality and morbidity than Barker originally suggested.³⁴ Paneth et al proposed a similar theory called the 'early life experience hypothesis',³⁵ suggesting that the Barker hypothesis fails to explain the increasing prevalence of the metabolic syndrome in countries where low birthweight has decreased during the last decade. This 'catch-up growth' or 'early life experience hypothesis' could explain the previous fact and, what is even more relevant, has enormous implications in the current recommendation for infants' nutrition.¹⁴ In countries where malaria or HIV are common causes of low birthweight, adequate nutrition during childhood might help to reverse the susceptibility to metabolic syndrome among IUGR newborns.

Both the original foetal origins hypothesis and 'catch-up growth' or 'early life experience' hypotheses reflect the fact that chronic disease might start early in life. Thus, preventive measures against cardiovascular disease or diabetes should not only focus on adult behaviour. Incorporating this into public health approaches is crucial in developing countries with an increasing prevalence of these 'diseases of lifestyle'.

Although there is a lack of studies in poor-income countries concerning 'foetal origins', the theory still has implications for current public health policies. Sub-Saharan Africa faces the devastating effects of the HIV pandemic. As has been previously mentioned, HIV is a common cause of preterm and IUGR newborns. Moreover, a frequent side-effect of antiretroviral drugs is dyslipidaemia and insulin resistance. Therefore, the earlier preventive strategies start in these settings, the greater health improvement would be achieved.

In conclusion, research has shown that low birthweight is associated with an increased risk of adult disease such as hypertension and diabetes. Although this association might be explained only by the thrifty phenotype hypothesis, other mechanisms may be involved.

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