COMMENTARY

Intrauterine growth and disease in later life — Barker and beyond

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'When a variation in characteristic is of the slightest use to a being, we cannot tell how much to attribute to natural selection and how much to attribute to the conditions of life.'

Charles Darwin, 1899

The Barker hypothesis

Coronary heart disease (CHD), hypertension, and diabetes mellitus (DM) occur in epidemic proportions worldwide. Unhealthy lifestyle practices and behaviours are well accepted as contributing factors, but the true origins of these diseases may actually be found *in utero*. According to the Barker hypothesis, disturbed intrauterine growth has a negative influence on the development of the cardiovascular system and favours the occurrence of hypertension, insulin resistance, hypercholesterolaemia, and hyperuricaemia in adult life.[1]

Many chronic disorders that manifest later in life may be related to two seemingly opposing factors potentially present early in life: (*i*) poverty, i.e. malnourished mothers give birth to malnourished infants with low birth weight (LBW); and (*ii*) prosperity, i.e. exposure of an infant with LBW phenotype to a high-energy (caloric) diet. These factors contribute to the biological phenomenon of developmental plasticity, or the ability of a genotype to produce multiple forms and behaviours in response to environmental conditioning.

Living things are often plastic during early development, and consequently can be moulded by the environment. By adapting to a limited supply of nutrients, it appears that the human fetus trades off the development of non-essential organs, such as kidney (nephron mass) and pancreas (beta cell mass), in favour of more essential organs such as the brain. These developmental adaptations may be the origins of a number of diseases in later life[2] and are thought to be consequences of fetal programming, whereby adaptations invoked in response to deficient maternal-placental nutrient supply have permanent effects on structure, physiology, and metabolism.[3]

Geoffrey Bihl's interest in intrauterine growth and chronic disease developed during undergraduate and prostgraduate training at Wits University. As a nephrologist researching in Cambridge and while practising in the Western Cape, both in the state and the private sector, the health and cost implications of such afflictions have captured his attention.

Inverse relationship between birth weight and disease

The combination of LBW and small size during infancy, followed by accelerated weight gain from age 3 - 11 years, is predictive of hypertension, CHD, and type 2 DM, according to Professor D J P Barker, of the Medical Research Council, Southampton General Hospital, UK. In his address at the 9th Asian Pacific Congress of Nephrology,[4] Barker discussed his research findings showing the delayed effects, especially on heart disease, of the early developmental environment. On the basis of these and related studies, Barker contends that optimal nutrition is crucial during fetal development and throughout infancy.[5]

In support of the Barker hypothesis, numerous studies (reviewed by Phenekos[6]) have unequivocally shown an inverse relationship between the birth weight of infants born preterm or at term and the increased incidence of hypertension, CHD, impaired glucose tolerance, insulin resistance, and type 2 DM. These associations have been extensively replicated in studies conducted in a number of countries and do not appear to be the result of confounding variables.[3]

Relationship between birth weight, glomerular mass, and chronic kidney disease

LBW has been hypothesised to affect normal renal development adversely, thereby contributing to an increased risk of acute renal failure and transient imbalance of fluid and electrolyte homeostasis soon after birth[7] and an increased risk of developing chronic kidney disease later in life.[8,9] Although the number of nephrons in the human kidney varies considerably under normal circumstances, retarded intrauterine growth has been reported to be associated specifically with a significant reduction in nephron numbers. In turn, low nephron numbers may be an independent risk factor for the development of hypertension.

Manalich and colleagues[10] evaluated the relationship between birth weight and the number of glomeruli and

glomerular volume by examining coronal sections of the kidneys of 35 neonates who died within 2 weeks of birth as a result of hyaline membrane disease, infectious complications, brain haemorrhage, or perinatal hypoxia. There were significant differences in the number of glomeruli ($p < 0.0001$) and glomerular volume ($p < 0.0001$) between the LBW and normal birth weight (NBW) groups. Essential arterial hypertension was present in 38.9% of the mothers of LBW children v. 5.9% of the mothers of NBW children ($p < 0.05$). It appears therefore that endowment with decreased nephron mass may be a risk factor for hypertension and the rate of progression of renal disease.

In contrast, the findings of Nyengaard and colleagues[11] did not support associations between LBW and low kidney weight or between LBW and a decrease in number and/or small glomeruli in patients with type 2 DM. To determine whether there was a correlation between LBW and the development of type 2 DM and high blood pressure, Nyengaard and colleagues examined 79 autopsy kidneys (with known weight) from normal and type 2 DM patients, which had previously been used for studies of glomerular number and volume. There were no significant correlations between birth weight and glomerular number, glomerular volume, or kidney weight.

Relationship between birth weight and blood pressure

Hypertension may originate from retarded growth *in utero*, followed by accelerated postnatal growth. Retarded fetal growth leads to permanently reduced cell numbers in the kidney and other tissues, and subsequent accelerated growth may lead to excessive metabolic demand on this limited cell mass.

To determine whether diminished number of nephrons is a factor contributing to the development of primary hypertension, Keller and colleagues[12] compared the number and volume of glomeruli in 10 middle-aged white patients with a history of primary hypertension, left ventricular hypertrophy, or both, and renal arteriolar lesions with the number and volume of glomeruli in 10 normotensive subjects. Hypertensive patients had significantly fewer glomeruli per kidney and significantly greater glomerular volume than matched normotensive controls ($p < 0.001$). These data demonstrate that the number of nephrons is reduced among white patients with primary hypertension.

Law and colleagues[13] were among the first to assess the association between blood pressure (BP) and LBW and to determine whether a relationship was established *in utero* or during infancy, and if it changed over time. The study included 1 895 children aged 0 - 10 years, 3 240 men and women aged 36 - 40 years, 459 men and women aged 46 - 54 years, and 1 231 men and women aged 59 - 71 years. All participants had a recorded birth weight. Increased systolic blood pressure (SBP) was found in all groups beyond infancy among participants with LBW compared with NBW individuals. The relationship became more pronounced with increasing age; SBP at age 64 - 71 years decreased by 5.2 mmHg (95% confidence interval (CI): 1.8 - 8.6) for every kilogram increase in birth weight after allowing for current body mass. The researchers concluded that essential hypertension was established during the fetal period and amplified over time.

A number of subsequent studies have examined the relationship between birth weight and BP during adolescence. In a retrospective study, 330 participants who were LBW at term delivery were matched with controls of NBW.[14] The mean SBP was not significantly different between groups: 105.8 mmHg for the LBW individuals v. 107.5 mmHg for the NBW controls. Nilsson and colleagues[15] prospectively studied the association between birth weight and BP in 18-year-old males. Weight, height, and mean BP were measured and stratified according to birth weight. SBP, but not diastolic blood pressure (DBP), differed significantly ($p < 0.001$) between birth weight strata; SBP was higher in the LBW strata. An increase in birth weight of 1 000 g decreased SBP by 0.8 mmHg, and was most pronounced in participants who had experienced rapid growth and development. The investigators concluded that LBW was inversely associated with SBP, supporting the concept of an *in utero* programming effect of fetal growth retardation on haemodynamics in early adult life.

In a study of 165 136 Swedish men aged 18 years, SBP was independently and inversely associated with both gestational age and birth weight for gestational age.[16] The difference in SBP between the top and bottom quintiles of birth weight for gestational age was –1.61 mmHg (95% CI: –1.82 - –1.40) after adjustment for birth length for gestational age, height, and weight. A similar study demonstrated that BP was significantly higher in late adolescence among individuals born preterm at very low birth weight (VLBW) (birth weight ≤ 1 500 g) compared with NBW controls. In a cohort study, Doyle and colleagues[17] compared BP between VLBW preterm survivors ($N = 156$) and randomly selected NBW subjects ($N = 38$) at age ≥ 18 years. BP was assessed using both a standard mercury sphygmomanometer and an ambulatory BP monitor. Higher SBP and DBP (as measured by sphygmomanometer) were observed in the VLBW group compared with the NBW group (mean difference (95% CI): SBP 8.6 mmHg (3.4 - 13.9); DBP 4.3 mmHg (1.0 - 7.6)). Although there was no difference between the groups with regard to ambulatory DBP, the VLBW group had significantly higher mean SBP compared with controls (mean difference (95% CI) for the 24-hour period: 4.7 mmHg (1.4 - 8.0)). Differences persisted during periods of waking and sleeping.

A longitudinal study conducted by Law and colleagues[18] assessed BP at age 22 years among 346 participants (males and females) who were measured at birth, then yearly for the first 10 years of life. Individuals who were small at birth but gained

weight rapidly between 1 and 5 years of age had the highest BP at age 22. Again, the most significant effect observed was in SBP, which increased by 1.3 mmHg (95% CI: 0.3 - 2.3) for every standard deviation decrease in birth weight. SBP also increased independently by 1.6 mmHg (95% CI: 0.6 - 2.7) for every standard deviation increase in weight gain during age 1 - 5 years. Relationships were less significant for DBP. Although adjustment for adult body mass attenuated the effect of rapid weight gain during early childhood (age 2 - 5 years), it did not influence the relationship between birth weight and BP. On the basis of these data, the authors concluded that even though a significant risk for adult hypertension is established during fetal development, accelerated weight gain during early childhood also contributes to the burden of risk.

Relationship between birth body length and BP

In addition to finding a negative association between birth weight and SBP at age 20 in men and women, research by Moore and colleagues[19] also demonstrated that decreased body length and thinness at birth and LBW relative to placental weight were associated with elevated SBP in later life. BP effects were greatest among individuals with increased weight or excess weight for height at age 20 years. The effects of birth weight on BP were more pronounced at age 20 years than at age 8 years ($p < 0.01$ for men and $p = 0.03$ for women).

A prospective study[20] from Sweden supported the hypothesis that poor fetal growth, as measured by LBW or decreased body length at birth, may contribute to the development of hypertension in later life, and that these associations increase with age. BP was assessed at age 50 years and at 60 years in 438 women born at term. There was a significantly higher risk of hypertension in the lowest birth weight quintile (odds ratio (OR) 2.0, 95% CI: 1.1 - 3.8) and lowest birth length tertile (OR 1.8, 95% CI: 1.1 - 3.0) compared with the middle quintile and tertile, with or without adjustment for adult body size (as measured by body mass index (BMI)) at age 60 years. At 60 years of age hypertension risk decreased by 4% (95% CI: 0.92 - 0.99) per 100 g birth weight and 10% (95% CI: 0.81 - 0.99) per cm body length. No significant increased risk was observed in the 50-year-old age group.

Relationship between birth weight and coronary heart disease

There is emerging evidence from experimental and clinical studies of a link between LBW and cardiovascular disease in adulthood.[21] Barker[22] hypothesised that individuals who develop CHD experience slowed growth during fetal life and infancy, followed by accelerated weight gain in childhood. Hypertension and type 2 DM, disorders that predispose to the development of CHD, have been linked to similar paths of growth. Specific underlying mechanisms for CHD may include reduced number of nephrons associated with LBW, the development of insulin resistance *in utero*, and altered programming of the microarchitecture and function of the liver.

A longitudinal study[23] conducted in Finland assessed the associations between birth size, growth during infancy and childhood, and risk for CHD, using the outcome measure of hospitalisation for or death from cardiac disease. Data from 4 630 males born between 1934 and 1944 who attended child welfare clinics were analysed. Individuals in the data set had an average of 18 measures of weight and height recorded between birth and age 12 years. Low weight and decreased height at birth and at age 1 year were associated with an increased risk of heart disease. Rapid weight gain and an increased BMI after age 1 year also increased the risk of CHD, but this increase was confined to those who were thin at birth. The adverse effects of rapid weight gain were apparent by 3 years of age in this cohort.

Relationship between birth weight and diabetes mellitus

A number of studies conducted during the past decade have established a relationship between suboptimal fetal and infant growth and the development of metabolic syndrome and type 2 DM. It is believed that poor nutrition in early life results in permanent changes in glucose-insulin metabolism, leading to a decreased capacity for insulin secretion and insulin resistance. Although the strength of this association has varied among studies, the link between early growth and insulin resistance has been documented in all age groups.

Forsen and colleagues[24] determined that type 2 DM is programmed *in utero* in association with low rates of fetal growth. In a large cohort study, they examined the relationship between type 2 DM and size at birth and childhood growth in men ($N = 3\,639$) and women ($N = 3\,447$) born in Helsinki, Finland, between 1924 and 1933, who still lived in Finland in 1971, and for whom detailed birth and school health records were available. The prevalence of DM (7.9%) was ascertained from a national register. The main predictors were size at birth and childhood growth in terms of height, weight, and BMI. The incidence of DM increased with decreasing birth weight, birth body length, ponderal index (birth weight/body length), and placental weight. The OR for development of type 2 DM was 1.38 (95% CI: 1.15 - 1.66, $p < 0.001$) for each 1 kg decrease in birth weight. The OR for development of type 2 DM was 1.39 (95% CI: 1.21 - 1.61, $p < 0.001$) for each standard deviation increase in weight between 7 and 15 years of age. Children whose mothers had a high BMI during pregnancy had more rapid growth during childhood and an increased incidence of type 2 DM.

In a recent study,[25] LBW and high birth weight (HBW) were associated with an increased risk of type 2 DM in children. All

children in Taiwan Province aged 6 - 18 years were assessed for the presence of DM over a 5-year period; 429 children with type 2 DM and 549 with a normal fasting blood glucose level were included in the analyses. After adjusting for the variables of family history, socioeconomic status, age, sex, and BMI, the ORs for development of type 2 DM were 2.91 (1.25 - 6.76) for children with LBW (< 2 500 g) and 1.78 (1.04 - 3.06) for children with HBW (≥ 4 000 g), compared with the control group (birth weight 3 000 - 3 499 g).

Conclusion

A strong case has been made for the delayed effects of suboptimal fetal development. More data supporting the Barker hypothesis are continuing to emerge. However, alternative interpretations of these findings include socio-economic conditions present at birth that tend to persist throughout the lifespan, and the prevailing conditions of childhood that have greater influence on adult health than adverse conditions during fetal life and early infancy. Additional studies will further help to define the relative contributions of birth weight, weight change, and the environment in which a child develops to adulthood with chronic, adult-onset disease.

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