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Low birth weight and blood pressure

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Abstract

Evidence supporting the association of normal and pathologically elevated blood pressure with low birth weight is presented and discussed in this article because of the overwhelming global prevalence of hypertension and its impact on individuals and nations. The findings provide strong impetus for the medical and public health communities to consider the concept of the "developmental origins of health and disease" in developing approaches to address the growing burden of hypertension worldwide.

1. Introduction

Elevated blood pressure has a major impact on the health of individuals and the populations of many, if not all, countries. Hypertension is itself a disease but also a risk factor for the development and aggravation of other diseases, especially cardiovascular diseases, that are expected to remain the leading cause of death in all countries, rich or poor. Globally, hypertension is the risk factor attributed to the largest number of deaths [1].

It is estimated that more than 970 million people—15% of the world population—had hypertension in 2000. By 2025, this number will likely reach 1559 million or 19.8% of the world population [2]. In the United States, 60 million people reportedly have hypertension [3], but this may be an underestimate because many affected children and adolescents are undiagnosed [4]. Numerous causes of hypertension have been recognized and, in many instances, have formed the basis for preventive and therapeutic interventions.

In 1986, Barker and Osmond postulated that prenatal and early postnatal nutrition may influence an individual's predisposition to develop ischemic heart disease [5]. Extensive subsequent work led to what is today known as "Barker's early origin of adult disease hypothesis" [6]. This review considers 2 questions. (1) What is the relationship between birth weight and later blood pressure? and (2) is hypertension in later life a consequence, in part, of the relationship between low birth weight and blood pressure?

2. Is there a relationship between low birth weight and later blood pressure?

The first study relating birth weight to subsequent blood pressure showed that lower birth weight was associated with higher blood pressure at 10 and 36 years of age [7]. A further study by the same group demonstrated that within any given birth-weight cohort, adult blood pressure was the highest in those who were born with large placentas [8]. Numerous studies went on to confirm the association of low birth weight with higher blood pressure, but only a few considered placental weight. Later observations revealed that the negative relationship between birth weight and systolic blood pressure found early in life persists and, in fact, is amplified in later life up through the seventh decade (Fig. 1) [9].

In 1996, a review based on 34 studies involving more than 66 000 persons of all ages identified a negative relationship between birth weight and systolic blood pressure in childhood and adulthood [10]. This relationship was independent of body size at the time of blood pressure measurement, and its magnitude tended to increase with age. The difference in systolic blood pressure in children was approximately −2.0 or −4.0 mm Hg per kilogram increment in birth weight, whereas it reached −5.0 mm Hg per kilogram in older subjects.

A similar review [11] in 2001 based on 27 independent observational studies corroborated the finding of "substantial

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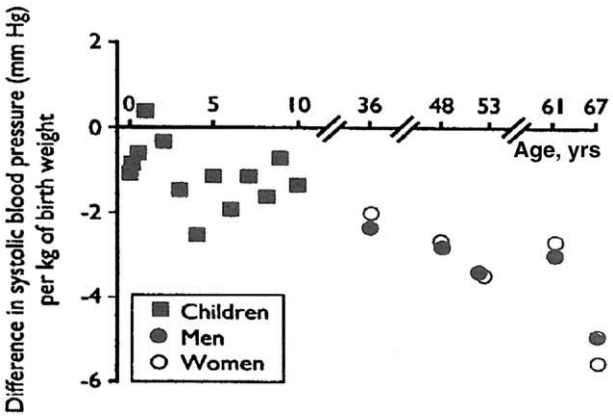

Fig. 1. Relation between systolic pressure and birth weight at different age. Reproduced from Law et al. *BMJ*. 1993;306:24-7 with permission of the *British Medical Journal*.

and consistent evidence of a negative association between birth weight and systolic blood pressure from childhood through the eighth decade of life." Specifically, there was a mean difference in systolic blood pressure of −1.7 mm Hg per kilogram increment in birth weight. As observed previously, this negative association did not depend on body size at the time of blood pressure measurement—if anything, adjustment for body size strengthened the association. Age also amplified the association: the mean difference for each decade of life was −0.35 mm Hg per kilogram increment in birth weight. The review also documented a consistently negative association between birth weight and diastolic blood pressure: in 22 data sets, the decrease in diastolic blood pressure ranged from −0.30 to −1.7 mm Hg per kilogram increment in birth weight. Placental weight and other factors such as head circumference, body length, and fatness were found to influence the relationship between birth weight and blood pressure, but some of the data were weak or even conflicting.

From a historical viewpoint, it is noteworthy that the fetal-origins-of-adult-disease hypothesis received significant support because of its public health implications [12]. However, it also raised some concerns [13,14], mainly because all the reported studies were retrospective, observational, and subject to confounding factors such as subsequent weight of the participants.

In 2002, a new review by Huxley et al [15] included all of the studies that had been evaluated previously [10,11]. The investigators weighted the estimated blood pressure difference associated with a 1-kg increment in birth weight (or the regression coefficient between these 2 variables) by the size of the studies and demonstrated a much weaker regression coefficient in the larger studies. On the basis of this observation, they found a publication bias in the reporting of the studies which included earlier reviews. In addition, they expressed concerns about unwarranted adjustments for current weight and other confounding factors, which they said led to an overestimation of the impact of birth weight on subsequent blood pressure. Instead of a −2.0 to −3.0 mm Hg systolic-blood-pressure difference per kilogram increment in birth weight, this review arrived at an estimated association of only a −0.6 to −0.4 mm Hg difference per kilogram after removing the impact of adjustment for current weight. Consequently, the authors concluded that "the findings suggest that birth weight is of little relevance to blood pressure in later life."

Other studies published from 2004 to 2007 [16-20] carefully considered the criticism of Huxley et al in their methodology. Altogether these publications reported on 28 cohorts comprising 279 352 subjects. With some variations, they showed that a negative association between birth weight and systolic blood pressure had been demonstrated, but it was weaker in larger studies than in smaller ones. One of the publications [17] presented a meta-analysis of data from studies published and not published previously, thereby eliminating the concern that a bias had existed in the selection of the studies included in the previous reviews [13,14]. In several of the cohorts, adjusting for current weight and size resulted in a much stronger birth weight–blood pressure association in both men and women [18]. In contrast, adjusting for parental social class, education, and smoking habits; gestational age; and the age and size of the mother had limited impact. One of the publications [16] underscored caveats about methodological issues, such as how the birth-weight information was obtained (hospital record vs parental recollection), inaccuracies in blood pressure measurement (use of rounding or "fixed-category" blood pressure allocation), and, perhaps most important, the nature of the relationship of birth weight to blood pressure (linear vs. curvilinear). Indeed, this publication and others indicate that the relationship defined by the regression coefficient is linear and negative up to a birth weight of about 4 kg, but then it reverses and becomes positive as the birth weight approaches and exceeds 4 kg, yielding a J curve for the relationship in its entirety.

In all the studies, and in 2 of the 3 reviews assessing the birth weight–blood pressure association discussed in this section, both systolic and diastolic blood pressures were within normal levels except in the investigation by Law et al [9] that included subjects 40 years older who had hypertension (ie, systolic blood pressure greater than 140 mm Hg). From this study, the investigators postulated that "hypertension is initiated in utero and amplified throughout life." The study by Hardy et al [18] of 5 different cohorts ranging from 7 to 62 years of age found that the data from 4 of the cohorts corroborated the observations from Law et al and thus supported the "amplification hypothesis."

3. Is hypertension in later life a consequence, in part, of the relationship of low birth weight with blood pressure?

In 1996, 2 studies by Curhan et al [21,22] reported on the association between birth weight and hypertension—one

derived from the very large Health Professionals Follow-up Study [21] in men and the other, derived from the Nurses' Health Study [22] in women. Hypertension was defined by the use of blood pressure–lowering medications or by a measurement higher than 140/90 mm Hg. Subjects were grouped by 5 birth-weight categories as self-reported and confirmed by the mother. In each group, the cumulative incidence of hypertension was reported for the years 1986 and 1994 in men and the years 1976 and 1992 in women. During the time between the observation points, hypertension incidence increased markedly for men and women in each birth-weight group. Furthermore, in each year that it was measured, the incidence of hypertension was greatest in the lowest birth-weight group (<5.5 lb) and least in the highest birth-weight group (>10.0 lb). Among the men, in 1986, it decreased from 27.1% to 21.3% and in 1994 from 38% to 31.9% as birth weight rose from <5.5 lb to ≥10.0 lb, a nearly linear decrease in hypertension incidence from the lowest to the highest weight (Fig. 2). The same pattern was observed in women: in 1976, hypertension incidence decreased from 15.5% to 9.4%, and in 1992 from 40.9% to 34.5%, from the lowest to the highest birth-weight group.

The 1992 Finnish study reported by Barker et al [23] showed that the cumulative incidence of hypertension (defined by the use of blood pressure–lowering medications) in 55- to 65-year-old men and women grouped by birth weight was smaller in each successive birth-weight group from the lowest (<3000 g) to the highest (>4000 g) (Fig. 2). The authors also considered the relationship between hypertension incidence and the body mass index (BMI) of the subjects at 12 years of age and found that the highest incidence of hypertension occurred in subjects with the lowest birth weight and the highest BMI. In contrast, the lowest incidence of hypertension was found in subjects with the highest birth weight and the lowest BMI at 12 years of age (Fig. 3).

Another study on a subset of the same population [24] again confirmed the inverse relationship between birth weight and

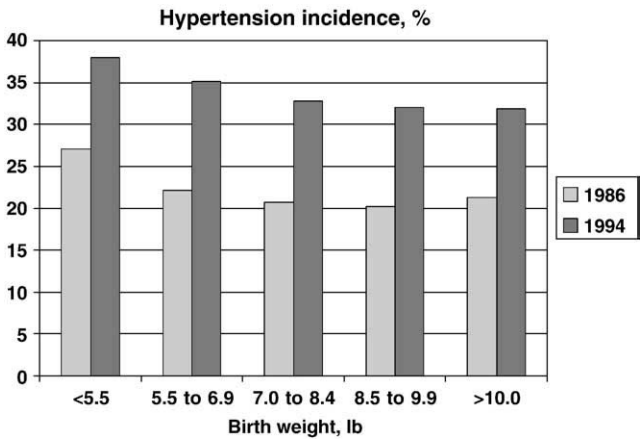

Fig. 2. Age-adjusted cumulative incidence of hypertension at baseline, in 1986 and again in 1994 in men as a function of birth weight. Derived from data reported in reference [21].

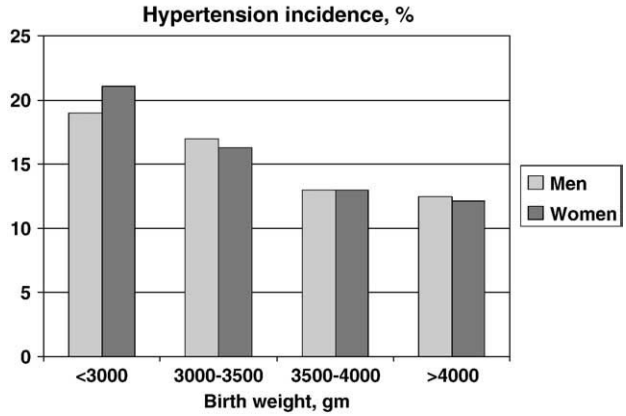

Fig. 3. Cumulative incidence of hypertension in 55- to 65-year-old men and women as a function of their birth weight. Derived from data reported in reference [23].

incidence of hypertension. The authors postulated the existence of a "self-perpetuating" mechanism that begins in utero and extends into adult life—a concept similar to the "amplification" hypothesis advanced earlier by Law et al [9]. It was also proposed that hypertension may be more difficult to control in patients who had a low birth weight. This notion suggests that additional and undoubtedly interactive factors determine the relationship between birth weight and blood pressure, be it normal or elevated, in later life.

Further and stronger evidence of the complexity of the relationship between blood pressure and birth weight comes from the observation that specific antihypertensive therapies are apparently being used preferentially in some patients who had a low birth weight. Lackland et al [25] found greater use of calcium channel blockers in black women and ACE inhibitors in white men with low birth weights. These medications were likely chosen because they worked better than other classes of medications in such patients. That a specific class of medications is more effective one group of patients than another suggests that the pathologic mechanism of hypertension differs between these groups.

Pursuing observations that low birth weight is linked to insulin resistance, Eriksson et al [26] showed that this relationship was stronger in subjects who had the Pro 12 Pro variant of the PPAR-y2 gene (peroxisome proliferator-activated Receptor); they also showed [27] that the systolic blood pressure of hypertensive patients (defined by use of antihypertensive medications) who had the variant Pro 12 Pro fell with increasing weight and length at birth. More important, they found that in the study cohort of 208 hypertensive subjects, those born with low weight and small length had the most use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers undoubtedly because these medications were the most effective. The explanation may be that hypertension results from the interactions between the renin-angiotensin system and insulin or that the patients were also treated for subclinical comorbid conditions such as diabetes or heart failure.

Overall, epidemiologic studies have repeatedly demonstrated the associations of clinical hypertension with low birth weight and also with childhood development. Data from the Helsinki Birth Cohort Study established the interdependence of genetic and environmental factors in determining not only the blood pressure level but also the class of antihypertensive of medication that can be most effective. However, hypertension is not the only chronic disease that is influenced, or even determined, by this interdependence [28,29]—insulin resistance, type 2 diabetes mellitus, and heart disease have been linked to factors that exist in utero and after birth.

4. Conclusion and perspective

The medical and public health communities ought to give serious consideration to the "developmental origins of health and disease," a concept heralded by Gluckman and Hanson [30] that is an extension of Barker's [6] "fetal origins of adult disease." The concept emphasizes that health and disease are determined by influences in fetal life and also by continued development during the earlier years of life. This is important, actually critical, because it recognizes the role of prenatal and later life environmental factors and it also highlights the capacity of health promotion and prevention to overcome the impact of deleterious environmental factors.

The validity of this concept is supported by all the studies discussed in this limited review and by scores of other investigations that could not be mentioned. The impact of environmental factors is in great part determined by an individual's genetic makeup and genetic predispositions. The gene-environment interactions, or epigenetics, are discussed in another article in this journal [29]. Undoubtedly, research advances in this area will assist the medical community and public health officials in designing interventions to ensure the best possible health during development and to avoid, or limit, the initiation and progression of disease. As stated by Gluckman and Hanson [29,30], "it is no longer possible to ignore the developmental phase of life."

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