Birth Weight and Hypertension

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There is substantial literature showing that birth weight is associated with differences in blood pressure within the reference range. These differences are found in children and adults, but they tend to be small. A 1-kg increase in birth weight is associated with \( \approx 3 \) mm Hg lowering in systolic pressure. This association is one of the associations with low birth weight that led to the “fetal origins hypothesis,” which proposes that the different forms of cardiovascular disease and type 2 diabetes originate through undernutrition during fetal life and infancy. Undernutrition at this time permanently changes the body’s structure and physiology. Like other living things, humans are plastic during development, and their form and function is the product of the genes acquired at conception and of environmental influences, importantly nutrition, that regulate gene expression.

Huxley et al. recently reviewed 103 published studies on the association between birth weight and blood pressure. They concluded that the association was weaker in large studies than in small ones and was, therefore, an artifact, the product of a bias by which small studies are published only if they show large effects. The Lancet published the review under the title “Unraveling the Fetal Origins Hypothesis.” This was inappropriate for a number of reasons. A central issue in understanding the intrauterine origins of hypertension is reconciling the small effects of birth weight on blood pressure within the reference range with its large effects on the risk of hypertension requiring medication. One possibility is that lesions that accompany poor fetal growth and tend to elevate blood pressure have small effects on blood pressure within the reference range, because counterregulating mechanisms are able to maintain normal levels. As the lesions progress with ageing, however, these mechanisms are no longer able to maintain homeostasis, and blood pressure rises. There may be a cycle of rise in blood pressure resulting in further progression of the lesions and further rise in blood pressure. Evidence to support the development of self-perpetuating cycles comes from a study of elderly people in Helsinki, Finland, among whom the effect of birth weight on blood pressure was confined to those being treated for hypertension. An inference is that by the time they reached old age, most of the people with lesions acquired in utero had developed clinical hypertension.

There is evidence in both humans and animals that one of the lesions acquired in utero is a reduced number of nephrons. Nephron number is calibrated to body size at the time of nephrogenesis, which occurs at \( \approx 34 \) weeks of gestation, and people who had low birth weight have fewer nephrons. A reduced nephron number leads to glomerular hyperfiltration and, over time, to sclerosis and loss of glomerulae.

The conclusions drawn by Huxley et al. were also unhelpful because birth weight does not have an effect on blood pressure that is best estimated by pooling the results of all of the published studies. Rather, the effects of the intrauterine environment on disease are conditioned by later events. In Helsinki, and in other studies, the effects of low birth weight on blood pressure and hypertension are amplified by rapid weight gain in childhood. This may reflect an increase in glomerular hyperfiltration, and the consequent long-term damage, which results from the greater excretory load imposed on the kidney by a large body. In Helsinki, birth weight also has a greater effect on hypertension among people born into poor families. This and other findings indicate that our understanding of the early origins of hypertension will require biological insights into the long-term effects of different paths of development, in which the effects of low birth weight are modified by subsequent growth and by the postnatal environment.

In the current issue of Hypertension, Davies et al. return to the statistical issues raised by the Lancet. In a study of 25,874 subjects they find that the association between low birth weight and raised blood pressure is robust. They review the literature and conclude that the weaker associations in large studies are the result of error, generated by birth weights that are recalled rather than recorded, and by inaccurate measurement of blood pressure in large studies carried out as part of routine medical examinations rather than for the purposes of research. Davies et al. also confirm that the inverse association between low birth weight and blood pressure amplifies with age. This is consistent with the existence of self-perpetuating cycles of rising blood pressure and renal damage.

The fetal origins hypothesis will not be unraveled by statistical sleight of hand. Rather, we can look forward to a rapid expansion in our knowledge of how blood pressure homeostasis is established before birth and how it may be compromised by events in utero and during early postnatal life.

Disclosures

None.

References

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