Fetal and Early Life Determinants of Hypertension in Adults
Implications for Study

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In this issue of Hypertension, Fagerudd et al present results describing the significant association of early life factors and adult blood pressure levels. The concept that adult-onset diseases may have a fetal and/or early life origin has been advanced since the 1980s. This school of thought, also referred to as the “Barker Hypothesis,” was initiated by identifying ecological associations of fetal and early life health indicators (infant mortality, birth size, etc) and adult diseases, such as ischemic heart disease. This epidemiological approach was used to assess the geographic patterns of birth weight and adult-onset stroke in the United States and the United Kingdom, identifying similar associations. The results prompted the expansion to numerous cohort and epidemiological studies that identified the direct association of birth weight and various disease outcomes, indicating greater disease risk and accelerated disease progression among individuals with adverse fetal and early life events. For example, risk for hypertension-related end-stage renal disease was greater among individuals with a birth weight <2500 grams. Similar findings were reported for hypertension and other hypertension-related outcomes.

Clearly, indicators such as birth weight and birth length are influenced by fetal exposures to various maternal factors. Most obvious, maternal nutrition is suggested as a major factor with maternal undernutrition and malnutrition playing a major role. The associations are even greater when low birth weight is coupled with childhood obesity. Greatest risks of hypertension are identified for low-birth-weight individuals with accelerated excess “catch-up weight.” The identification of such factors associated with cardiovascular disease provides an opportunity to devise strategies for disease prevention.

A critical component of the research in this field is the identification of mechanisms that explain the association of hypertension and birth weight. Brenner et al proposed that a reduced number of nephrons in the low-birth-weight infant increases the risk of development of hypertension later in life. Likewise, the blood vessels of premature infants were found to be stiffer than vessels of full-term infants. Thus, the effect on blood pressure could be mediated by either of these mechanisms, a combination of both, or factors yet to be identified. For example, maternal undernutrition and subsequent small birth size are suggested to be associated with increased sensitivity to glucocorticoids, enhanced angiotensin II, and increased insulin sensitivity. The different association of low birth weight and classes of hypertension treatments among adults with high blood pressure suggests that different mechanisms may be playing a role. In a study of Medicaid beneficiaries with hypertension, the use of angiotensin-converting enzyme inhibitors was significantly associated with low birth weight among white men, and calcium channel antagonists were associated with low birth weight among black women. Nonetheless, all studies of birth weight and hypertension have not reported the same strong significant associations. The associations in different populations and different age groups have been weaker or not detected.

Fagerudd et al provide a significant contribution to this body of literature with this study and confirmatory data regarding the increased risks of elevated blood pressure and diabetes in individuals with low birth weight. In addition, these investigators find a strong association of low birth weight with elevated systolic blood pressure, the blood pressure with the greatest cardiovascular disease risks. This assessment in a population with type 1 diabetes provides new information concerning the mechanisms involved in the association of fetal development and elevated systolic blood pressure. This current study also incorporates a unique population that can be examined to assess this association with a thorough and sophisticated longitudinal follow-up registry. Such a population-based and comprehensive study base, found most often in Nordic countries, is ideal for this type of investigation.

The study of the fetal and early life origins of hypertension has significant implications for research. For epidemiology investigations, the results of these analyses contribute to the understanding of the cause of hypertension, the risks of hypertension developing, the factors associated with disease progression, and the risks of adverse hypertension-related outcomes. The risks attributed to fetal and early life events might explain at least part of the geographic and racial disparities in the prevalence of hypertension in which residents of the southeastern United States and, in particular, blacks have an excess burden of high blood pressure. Fetal and early factors may provide clinical investigators with explanations for cardiovascular disease progression by iden-
Identifying markers that are associated with increased risks. The consideration of fetal and early life factors associated with the development of hypertension by basic scientists may also assist in the identification of such markers and mechanisms of disease progression.

Although progress has been made in this field, much work remains to be performed. First, the association of fetal and early life events with adult blood pressure should be assessed in different populations. In particular, such investigations should be completed in populations such as blacks, Asians, and others with excess cardiovascular disease burdens. Likewise, the risks of adverse early life events and the development of elevated blood pressure identified in Nordic cohorts should be compared with the risk patterns determined in other populations. Early life factors and disease progression should also be assessed in various age and birth cohorts. Most important, the role of genetic and environmental factors and the physiological mechanisms involved should be investigated. This novel research arena has the potential to provide new information for the study of hypertension and related cardiovascular diseases.

References