Impaired Fetal Growth, Cardiovascular Disease, and the Need to Move on

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The final step in the acceptance of a new medical hypothesis is often the approval of significant funding to investigate it. In the case of developmental programming (ie, the notion that the in utero environment determines susceptibility to many diseases later in life), this has recently come in the form of support by the US Congress for the National Children’s Study, a $3 billion project to follow the impact of environmental factors before, during, and after pregnancy on disease manifestation in some 100 000 children up to the age of 25 years. This initiative will, no doubt, yield a wealth of correlative data and identify many new factors potentially affecting developmental programming.

Much of the concept underlying the National Children’s Study stems from the pioneering work of Barker and colleagues, whose epidemiological observation of increased cardiovascular risk in children with low birth weight has spurred a large number of retrospective studies during the past 30 years. Indeed, maternal diabetes may result not only from the pathogenic mechanisms of fetal programming but also its evolutionary significance, if any. It has been proposed that developmental programming constitutes an attempt by the fetus to prospectively adapt to detrimental conditions in utero such as undernutrition. Such “predictive adaptive programming” would be protective if the same conditions are encountered after birth but constitute a misadaption to the conditions of excessive caloric and fat consumption prevalent in most Western countries. It would also be difficult to correct after birth. Although many early indicators of cardiovascular risk encountered in childhood correlate with adult risk such as endothelial dysfunction and early atherosclerotic lesions and therefore constitute promising targets for intervention, compensating for low birth weight does not appear to be beneficial. In fact, accelerated growth during childhood seems to increase, not decrease, long-term risk, in particular in prematurely born children, in whom rapid early weight gain enhances insulin resistance and hypertension later in life. Thus, it appears that until the mechanisms of programming are better understood, little can be done after birth to reduce the effect of pathogenic in utero programming, except for a more rigorous avoidance of conventional cardiovascular risk factors. At least the need for earlier and more aggressive treatment of high-risk children is now beginning to be recognized in the latest guidelines.

The focus on outcome parameters such as low birth weight or impaired fetal growth also has not been helpful in identifying specific maternal risk factors responsible for developmental programming. Low birth weight may result from a broad range of pathogenetically diverse maternal conditions, including mechanical obstructions of the uterine artery, severe maternal undernutrition or dysnutrition, corticosteroid treatment, and a number of metabolic diseases, most notably diabetes. It appears unlikely that these conditions would cause uniform pathogenic programming. Indeed, maternal diabetes may result not...
only in reduced birth weight but more frequently in macrosomia. Even if the maternal conditions were to influence birth weight in a consistent manner, sibling competition leads to wide disparities in birth weight, complicating the search for the factors responsible for developmental programming and enhanced disease susceptibility in offspring. Finally, it is now well recognized that maternal overnutrition, not undernutrition, will be the main health threat in the coming decades. The call to shift the emphasis away from birth weight and to focus on specific maternal risk factors and outcome parameters contributing to cardiovascular disease is therefore growing louder. We also should keep in mind that correlative epidemiological studies cannot establish causal relationships. Now that the influence of developmental programming has been established beyond doubt and the translational need is becoming more urgent, we need to go beyond epidemiology and put greater emphasis on experimental models suitable to investigate the mechanisms and causal relationships.

In contrast to animal models of low birth weight, which have yielded inconsistent results, much progress has been made recently in modeling some maternal conditions enhancing atherogenesis in human progeny such as maternal hypercholesterolemia. It has been established experimentally that maternal hypercholesterolemia and the ensuing increased oxidative stress not only accelerate atherosclerosis, as they do in humans, but also that they affect early predictors of cardiovascular disease in offspring such as arterial gene expression, endothelial function, and vascular reactivity. More important, multiple interventions in mothers have been shown to reduce or prevent this form of developmental programming. Programming by pregestational or gestational diabetes is more difficult to mimic, given the complexity of metabolic changes involved, and work on the role of maternal obesity and insulin resistance is only in its infancy. Increased inflammatory stress associated with these conditions, as well as with maternal hypercholesterolemia and smoking, is likely to be of central importance, as are immune mechanisms. Even mild inflammation may modulate immune responses in both the mother and fetus. In fact, evidence in animal models and humans indicates that maternal adaptive immunity programs B- or T-cell–dependent IgM responses in offspring. Maternal immunizations have already been shown to protect against postnatal atherogenesis, even in the absence of gestational hypercholesterolemia or hyperglycemia.

Figure. Developmental programming of cardiovascular disease. Note that many of the maternal conditions and pathogenic factors are still hypothetical.
In addressing causal relationships, mechanisms, and preventive measures in experimental models, it is important to remember that maternal risk factors are not necessarily the same as those affecting the fetus. In addition to factors crossing the placental barrier by passive diffusion or active transport mechanisms (eg, maternal cholesterol), the placenta is both the target and a source of pathogenic factors reaching the fetus (the Figure). It can, for example, protect against or contribute to fetal oxidative stress induced by maternal hypercholesterolemia and/or vascular inflammation. The mechanisms shielding the placenta from recognition by the maternal immune system also may play a role in mediating inflammatory stress from mother to fetus. Another issue to be considered is the extent to which in utero programming is continued in the immediate postnatal period or during childhood. In humans, drastic changes in diet or exposure to environmental risk factors at birth are unlikely. We will therefore have to treat in utero programming, effects of lactation, and early postnatal programming as a single pathogenic entity.

The National Children’s Study will investigate some of the maternal conditions thought to enhance cardiovascular risk in offspring, in particular maternal diabetic conditions, oxidative stress, and inflammation, but it will focus on outcomes that are most prevalent in childhood such as diabetes mellitus, not on cardiovascular risk, which can only be extrapolated from the early consequences of developmental programming (the Figure). Even under the most optimistic conditions, it will not be feasible to carry out large-scale clinical trials for each putative maternal risk factor and to extend them to the onset of clinical manifestations. The contribution of the Barker hypothesis and the extensive epidemiological work validating it has been to prove, in principle, that developmental programming matters for cardiovascular disease. It is now time to complement human epidemiology by studies focusing on intervention and mechanistic studies in experimental models. This should enable us not only to elucidate the in utero programming mechanisms but also to identify potential new targets for prevention that go beyond the standard advice to treat preexisting maternal conditions. After all, interventions targeting developmental programming are most appealing because they may yield lifelong benefits yet involve very little risk for the fetus when effected before pregnancy.

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References

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