The prodromal stage of atherosclerotic lesions (known as lipidotic fatty streak accumulation) is already formed during human fetal development. Fatty streaks containing characteristic accumulations of lipids, lipid peroxidation products, and macrophages occur in the aorta of premature fetuses. Intimal thickening is also observed in fetal coronary arteries. During infancy, fatty streaks become increasingly prevalent, and some of them progress to advanced stages of atherosclerotic lesions. Once initiated, the progression of atherosclerosis is influenced by classic risk factors that promote vascular inflammation and plaque rupture. The observation that maternal hypercholesterolemia is associated with greatly enhanced fatty streak formation in fetal arteries indicates that hypercholesterolemia may play a pathogenic role in early fetal atherosclerotic lesions. Maternal hypercholesterolemia is also able to influence fetal sterol metabolism during pregnancy in animal models. Consistently, direct evidence for a causal role of maternal hypercholesterolemia and the involvement of oxidative stress has been obtained in a rabbit model and in LDL receptor–deficient mice. From a molecular standpoint, many signaling pathways are affected by increased oxidation of LDL or the intracellular formation of reactive oxygen species, and this phenomenon can be exacerbated by concomitant hypercholesterolemia. Interestingly, deletion of the p66shc longevity gene reduces systemic and tissue oxidative stress, vascular cell apoptosis, and early atherogenesis in mice fed a very highly hypercholesterolemic diet. Finally, growing evidence in the literature suggests that vascular damage occurs early and is mediated by polynsaturated fatty acids secondary to a maternal hypercholesterolemic diet. Nevertheless, it is not clear to what extent proteic undernutrition during pregnancy can affect vascular function. Taken together, to date, there is considerable evidence that the pathogenesis of endothelial dysfunction and atherogenesis in childhood is related to hypercholesterolemia and oxidation-sensitive mechanisms during early stages of human development. These mechanisms can affect the subsequent fate of vascular lesions in adult and elderly life.

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It is necessary to perform an accurate analysis of the classic risk factors for atherosclerosis during childhood. This analysis can dissect the causal role of risk factors during pregnancy from the impact of genetic predisposition and classic risk factors after delivery. Indeed, an inherited genetic predisposition can be greater in children of hypercholesterolemic mothers during pregnancy and is thought to contribute to atherosclerotic lesion formation. In their intriguing work in this issue of Circulation, Charakida and coworkers and the ALSPAC (Avon Longitudinal Study of Parents and Children) Group attempt to describe the impact of acute common childhood infections on vascular endothelial function. Results were obtained with high-resolution ultrasound to measure brachial artery flow–mediated dilatation in 600 children aged 10 years who had been allocated to 3 groups: those with current acute infections (n = 135), a convalescent group with infection in the past 2 weeks (n = 166), and a healthy control group (n = 299). The authors’ conclusions were that acute infections in childhood could be associated with impaired brachial endothelium–dependent vasodilatation and might be important in the initiation of vascular damage in childhood. The corollary of this finding could be that these events profoundly affect the subsequent development of vascular damage in adult life. The clinical meaning of brachial vasodilatation is at least questionable when compared with the coronary or peripheral circulation. Indeed, the human brachial artery virtually does not develop atherosclerosis. In this regard, positron emission tomography and carotid thickness measurements have emerged as potentially useful tools for the identification of endothelial dysfunction and, as such, early atherosclerosis. The authors reported that brachial reactivity is acquired, is reproducible, and can be correlated with coronary endothelial function, however. Above all, the hypothesis of Charakida et al remains interesting but needs further causal relationship studies with other noninvasive methods for assessing endothelial function, coupled with plasma markers of endothelial function and oxidative stress (such as isoprostanes, thiobarbituric acid–substances, prosta-cyclin, and nitrates). The issue of evaluating lesions in early infancy (<5 years) in comparison with those at an older age should also be explored. Finally, the contribution of specific infectious agents must be examined in future investigations.

Chronic infection has been found to be significantly associated with the development of atherosclerosis. For the most part, these relationships are still just associations. Specific causative relationships on par with that determined between Helicobacter pylori and peptic ulcer disease have not yet been established. Potential mecha-
nisms whereby chronic infections may play a role in vascular damage are myriad. In the case of *Chlamydia pneumoniae*, the effect may result from direct vessel wall colonization that may damage the arterial wall or indirectly by initiating immunologic responses. In other cases, the effect may simply be that of enhancing the preexisting chronic inflammatory response of the body to standard risk factors such as hypercholesterolemia. Even though the infectious agent may not directly infect the arterial wall, it may perform its critical role from afar. Chronic infection might also influence preexisting plaque by enhancing T-cell activation or other inflammatory responses that may participate in destabilization of the intimal cap.22 Evidence is mounting for a variety of other potential agents, including other herpes viruses, influenza, other specific bacteria (eg, *Mycoplasma pneumoniae*), and chronic infections with common bacterial agents (periodontal disease, chronic bronchitis, and chronic urinary tract infection, among others).22 Future clinical trials are expected to elucidate further the pathophysiological relationship between chronic infection and atherosclerosis and to evaluate further the potential of a variety of treatment approaches, including antibiotics, during early childhood. Large antibiotic trials targeting specific infectious agents to treat advanced atherosclerotic disease have reported disappointing results, indicating a limited benefit of treatment in patients with extensive atherosclerotic lesions.23 Nevertheless, it has been suggested in the present study18 that acute infections might play a more important pathogenic role in the early phase of atherogenesis and may be suitable to intervention at this stage (suggesting a possible novel preventive role for antibiotics), ideally with a coupled clinical intervention for hypercholesterolemic mothers during pregnancy.24 Future studies will have to address the effects of maternal hypercholesterolemia on placental exchange to explore the pathophysiological mechanisms through which maternal hypercholesterolemia may promote fetal atherogenesis. After delivery, especially those children exposed to severe maternal hypercholesterolemia should be followed up for the onset and development of acute and chronic infections and be included in clinical and noninvasive examinations of vascular function. This is particularly relevant because, as acknowledged by the authors, mild childhood infections relevant to normal daily life usually do not require a visit to the doctor or antibiotic therapy. These suggestions could be evaluated by the American Heart Association Pediatric Nursing Subcommittee of the Council on Cardiovascular Nursing and the Council on Cardiovascular Diseases of the Young.25

As suggested by the Fate of Early Lesions in Children (FELIC) study4 and in the present study,18 individual genetic predisposition, environmental factors, and pathogenic events during pregnancy may influence the long-term vascular effects of infections that may take years to become clinically manifest. This is the reason why carefully conducted prospective studies should be designed to validate these assumptions in the pathogenesis of the first cause of death in the world.

References


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