MINI-SYMPOSIUM

Is there a fetal origin of peripheral vascular disease?

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Peripheral vascular disease (PVD) is an atherosclerotic disease of the distal arterial system typically affecting the lower limbs. This syndrome encompasses a wide range of patients from those with asymptomatic arterial narrowing to those with intermittent claudication, and at the extreme end of the spectrum, patients with critical limb ischaemia and gangrene. The common pathophysiological mechanisms underlying the development of PVD and other atherosclerotic diseases are reflected in the fact that patients often have concomitant coronary artery and cerebrovascular disease. Over the last 20 years, a number of studies have established the importance of birth weight as a determinant of both coronary heart disease and cerebrovascular mortality.^{1,2} By contrast there has been very little work investigating the possible influence of the prenatal environment on the later development of peripheral vascular disease. In this review, we will summarise the epidemiological work conducted on peripheral vascular disease. In addition, we will appraise the evidence that birth weight is associated with the development of this disease. Finally, we will analyse the possible mechanisms underlying such an association using the information gained from both human and animal studies.

EPIDEMIOLOGY OF PERIPHERAL VASCULAR DISEASE

Symptomatic PVD is a relatively common condition with a prevalence of around 7% in adults over the age of 55 years.³ This disease has a relatively benign course—only one quarter of patients with intermittent claudication experience deterioration of symptoms and the annual risk of amputation for a patient with PVD has been estimated at only 1%.³ Unfortunately, there have to date been relatively few epidemiological studies examining risk factors for the development of PVD. Part of the reason for this may lie in the lower public profile of PVD, as compared with coronary heart disease. In addition, unlike coronary artery and cerebrovascular disease, PVD is not a fatal condition in itself, and is rarely listed as a contributory factor on death certificates. This makes the extraction of information on this disease from public health records very difficult, and severely reduces the available epidemiological data. Nonetheless, a number of studies have focused on risk factors for the development of PVD. Unsurprisingly, smoking has been identified as a strong predictor of PVD—over 90% of patients with PVD have a history of tobacco use.⁴ Similarly, hyperlipidaemia and diabetes mellitus have also been shown to increase the risk of developing PVD.⁴ In addition, coronary heart disease has been strongly associated with the incidence of PVD; in one study over 90% of patients with symptomatic PVD had evidence of atheroma in their coronary arteries.⁵ Moreover, there has been a growing awareness of the importance of PVD as not only a marker, but a predictor of coronary artery disease. Leng *et al*⁶ have shown that the presence of symptomatic or asymptomatic PVD are both highly sensitive indicators of future cardiovascular mortality.

Given the close relation between PVD and coronary heart disease, a condition which itself has been shown to be

associated with low birth weight,¹ it is surprising that only one study has directly analysed the influence of fetal environment on the risk of developing PVD. Martyn *et al*⁷ performed non-invasive assessment of lower limb atherosclerosis in 186 patients aged between 66–70 years and attempted to correlate these data with their birth weight and head circumference. Although this study showed a trend towards a higher risk of atherosclerosis in patients with a smaller head size and low birth weight, this association was not significant. While these findings appear to cast doubt on the concept of a “fetal origin of peripheral vascular disease”, this study did suffer from a number of limitations. Firstly, the size of the cohort was relatively small. Moreover in this study, lower limb atherosclerosis was quantified using ankle-brachial pressure index, as opposed to clinical severity. This physiological measurement is, however, most useful as a marker of early peripheral vascular disease,⁷ and it is notable that only 5% of the patients in this study had actual clinical evidence of PVD. By contrast, the majority of studies which have implicated low birth weight in the development of coronary heart disease have used cardiovascular mortality as their marker of disease. We therefore believe there is a need to conduct a large scale study on patients with symptomatic PVD in order to ascertain the importance of birth weight on the development of lower limb atherosclerosis.

ANIMAL MODELS

The concept that adult disease may be determined by prenatal factors has led to the development of a number of animal models to analyse the pathophysiological effects of the fetal environment. The focus of these studies has, however, been on the importance of maternal nutrition on the development of systemic hypertension. Recently, however, there have been some studies examining the role of the fetal environment on specific vascular beds. Ozaki *et al*⁸ have demonstrated that in rats, global undernutrition during gestation causes enhanced thromboxane induced contraction in the femoral arteries of the male offspring. Koukkou *et al*⁹ have also reported that mothers fed a high fat diet produce offspring whose femoral arteries show reduced endothelium dependent vasodilatation. In addition, further work by the same group has demonstrated that the aortas of these offspring have an altered fatty acid content.¹⁰ Using a sheep model, Nishina *et al*¹¹ have shown that protein and global nutrient restriction in early gestation produce offspring with impaired endothelium dependent and independent femoral artery dilation, and that this dysfunction is most pronounced in the protein restricted group. Although these animal models provide indirect evidence that maternal nutrition may contribute to the development of lower limb vascular dysfunction in humans, it is important to inject a degree of caution in reviewing these data. After all, the relative calibre of the femoral artery in humans is far larger than that of rats and sheep, and it is questionable whether data from a quadruped species has relevance to a bipedal human.

So what evidence, if any, is there from human studies on the effects of uterine environment on peripheral vascular

function? Unfortunately, to date no group has performed detailed examination of the pathopharmacological properties of femoral arteries in the context of birth weight. There have, however, been several studies examining the in vivo function of other arteries. Martin *et al*¹² have shown that low birth weight neonates show impaired endothelial function in skin arterioles. Additional studies have demonstrated that low birth weight is associated with reduced flow mediated dilatation of the brachial artery and that this dysfunction persists into adult life.^{13, 14} In addition to demonstrating the role of the fetal environment in affecting peripheral vascular tone, Napoli *et al*¹⁵ have shown that maternal hypercholesterolaemia can cause an increase in the number of fatty streaks in fetal aortas. Furthermore, children of hypercholesterolaemic mothers appear to show faster progression of atherosclerosis, and this finding cannot be explained by conventional postnatal risk factors for atherosclerosis or genetic factors. Interestingly these studies appear to correlate with the findings of the animal studies in emphasising the importance of both maternal dietary imbalance and global undernutrition in influencing vascular dysfunction.

Although these studies add strong circumstantial evidence to the hypothesis that impaired fetal growth causes an increased susceptibility to PVD, several provisos must be made. Firstly, there is a lack of consistency in these findings, with several groups failing to find an association between birth weight and vascular dysfunction¹⁶ or accelerated atherosclerosis.¹⁷ Moreover, the differing geometries and haemodynamics of the femoral and brachial arteries raise questions about the validity of extrapolating data from different vascular beds. Finally, it should be noted that although endothelial dysfunction has been shown to be a reliable marker of atherogenesis,¹⁶ the presence of atherosclerosis is not necessarily an indicator of symptomatic disease. Indeed the progression of atherosclerotic plaques into clinically significant lesions is a highly complex process and as yet there are virtually no data on exactly how the fetal environment might influence this progression.

CONCLUSIONS

Peripheral vascular disease has long been regarded a Cinderella syndrome, lacking the high public profile of coronary heart disease and stroke. As a consequence of this, there has been relatively little epidemiological or clinical research into this condition, and more specifically whether this disease has its origins in part in the fetal environment. Nonetheless, there does appear to be strong circumstantial evidence from epidemiological and clinical studies linking low birth weight and peripheral vascular dysfunction. Indeed, given the close clinical associations between ischaemic heart disease, stroke, and PVD, it would be quite surprising if fetal "stressors" were shown to have an effect on the development of atherosclerotic lesions in carotid and coronary arteries, but not in femoral vessels. Finally, it should be noted that human and animal studies appear to suggest that the vascular function is influenced by both specific nutritional imbalances as well as calorific restriction during

gestation. These findings highlight the fact that although birth weight may be a useful marker of maternal global undernutrition, it is a poor indicator of subtle nutritional abnormalities. This illustrates the need to develop more sophisticated markers of maternal nutritional status during pregnancy in order to provide a comprehensive analysis of the potential role of this factor in peripheral vascular disease.

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