EDITORIAL

Feto-maternal interactions: a possible clue to explain the 'missed heritability' in arterial hypertension

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Arterial hypertension is the first cause of mortality worldwide and is the most relevant (and modifiable) cardiovascular risk factor [1]. Although only 5–10% of hypertensive patients have an identifiable cause for it (that is, secondary hypertension), the vast majority have essential (idiopathic or primary) hypertension [2]. The causes are in general poorly understood, even if essential hypertension is characterized as a highly (around 30–40%) hereditable disease [3]. In line with this observation, epidemiological studies could identify several genes and genetic variants associated with increased blood pressure (BP) [4]. However, a surprising result of these studies was that these genetic variants contribute only a minor part of the phenotypic variation in BP. This discrepancy, between the expected and observed contribution of these genetic variants, is termed 'missed heritability' [5]. Several theories have been suggested to explain this phenomenon, and one of the most intriguing hypotheses is that epigenetic regulation of gene expression may importantly account for this variance [6]. The term 'epigenetic' refers to mechanisms that regulate gene expression without affecting the DNA sequence itself. Importantly, epigenetic activity is increased and particularly vulnerable to environmental insults during the embryonic, fetal and early postnatal periods [7]. In line with this concept, vulnerable periods during early life known to be associated with fetal programming of cardiovascular disease coincide with increased epigenetic activity. The review article by Scherrer *et al.* [8] highlights the potential contribution of fetal programming to the pathogenesis of arterial hypertension: studies in young offspring of mothers suffering from preeclampsia [9] and in apparently healthy children conceived by assisted reproductive technologies (ART) [10,11] have shown that these children display premature vascular aging and increased BP. Studies in animal models of these two entities have shown that epigenetic dysregulation with consequent altered expression of genes important for BP regulation [that is, endothelial nitric oxide synthase (eNOS)] plays a central role in the pathogenesis of arterial hypertension [12,13]. An alarming observation is that epigenetic alterations occurring during early life may persist throughout the lifespan of the individual and sometimes can be transmitted to the next generation. Consistently with this concept, vascular dysfunction in the progeny of male ART mice mated with normal females is comparable to that observed in the fathers and is associated with similar alterations of the methylation of genes in the vasculature [13].

The observation that low birth weight in humans is associated with epigenetic alterations [14] and increased BP represents another example for this hypothesis [15]. Bruno *et al.* [16] review the most relevant pathophysiological mechanisms involved in the association between birth weight and increased risk for arterial hypertension in adulthood. An important observation in this context is that adverse events during early life are invariably associated with premature vascular aging (that is, endothelial dysfunction, increased arterial stiffness and increased carotid intima-media thickness) that is already detectable during childhood and may develop into arterial hypertension in adulthood [7,17]. This has two important consequences: the detection of subpopulations at risk at an early stage may allow the prevention of future development of cardiovascular diseases, and as a practical consequence, therefore, 'early life' history and BP measurement in children should be part of the routine workup for the assessment of cardiovascular risk in general practice. The review of Santi *et al.* [18] points out this relevant aspect, which has been recently discussed by the US Preventive Services Task Force [19]. Although

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the Task Force concluded that 'current evidence is insufficient to assess the balance of benefits and harms of screening for elevated blood pressure in apparently healthy children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood', Santi *et al*. (in accordance with other guidelines) underline the importance of screening for high BP at regular intervals, as increased BP during childhood tracks into adulthood [20] and almost half of adults with arterial hypertension had high BP values in childhood [21]. Finally, the review by Raio *et al*. [22] emphasizes the contribution of arterial hypertension in pregnancy to perinatal morbidity and mortality of both the mother and her child and discusses the relevance of adequate prevention and treatment of these hypertensive disorders. An important aspect to consider is the fact that offspring of mothers suffering from pre-eclampsia are at increased risk for stroke in adulthood [23]. Therefore, prevention and/or treatment of hypertension in pregnancy is expected not only to decrease morbidity and mortality in the mother, but also to prevent vascular dysfunction and premature cardiovascular morbidity and mortality in the offspring [9]. In summary, adverse events during early life are associated with arterial hypertension and increased cardiovascular morbidity and mortality in adulthood. Studies in experimental animal models show that pathologic insults during fetal life cause epigenetic alterations of genes regulating important pathways of blood pressure regulation that are heritable. These studies could suggest that epigenetic alterations may also underpin the fetal programming of arterial hypertension (and premature cardiovascular morbidity and mortality) in humans and thereby explain, at least in part, the 'missing heritability' of essential hypertension. As a practical consequence, 'early life' history should become part of the routine in the assessment of cardiovascular risk in children and adolescents, and if suspect, it should be followed by ambulatory BP measurement and assessment of vascular function. This should allow early intervention and prevention of future morbidity and mortality in persons at risk.

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Conflicts of interest

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