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# Fetal programming and vascular dysfunction

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**Abstract** Cardiovascular diseases are the main cause of mortality and morbidity in Western countries, but the underlying mechanisms are still poorly understood. Genetic polymorphisms, once thought to represent a major determinant of cardiovascular risk, individually and collectively, only explain a tiny fraction of phenotypic variation and disease risk in humans. It is now clear that non-genetic factors, i.e., factors that modify gene activity without changing the DNA sequence and that are sensitive to the environment can cause important alterations of the cardiovascular phenotype in experimental animal models and humans. Here, we will review recent studies demonstrating that distinct pathological events during the perinatal (transient perinatal hypoxemia), late foetal (preeclampsia), and early embryonic (assisted reproductive technologies) periods induce profound alterations of the cardiovascular phenotype in humans and experimental animals. Moreover, we will provide evidence that epigenetic modifications are contributing importantly to this problem and are conferring the potential for its transmission to subsequent generations.


## Introduction

Epidemiological observations in humans and studies in experimental animal models support the idea that CVD take their origins during the fetal or perinatal period. 20 years ago, David Barker, a British epidemiologist, was first to hypothesize that the embryonic, fetal, and early postnatal periods are characterized by a high phenotypical plasticity and that insults during these periods lead to alterations that predispose to cardio-metabolic disease during adulthood.[1,2] These pioneering observations set the stage for a large number of epidemiological studies in this field and the term "developmental origins of health and disease" was coined to describe this concept. More recently, direct experimental evidence for this concept has been provided in humans and experimental animal models. Here, we will review recent studies demonstrating that pathological events during the perinatal (transient perinatal hypoxemia), the late fetal (preeclampsia) and early embryonic

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(assisted reproductive technologies, ART) period induce profound alterations of the cardiovascular and metabolic phenotype in humans and experimental animals and discuss underlying mechanisms.

## Transient perinatal hypoxemia predisposes to exaggerated hypoxic pulmonary hypertension later in life

At birth, the transition from fetal to adult circulation is a delicate event, as gas exchange is no more carried out by the placenta but by the lungs.[3] These functional and structural changes are particularly sensitive to noxious stimuli. In line with this concept, in normal rats, transient perinatal exposure to hypoxia during the first week of life predisposes to exaggerated hypoxic pulmonary hypertension when adult animals are re-exposed to hypoxia.[4] To tests whether a similar long-term effect of perinatal hypoxia on the pulmonary vasculature exists in humans, we assessed hypoxic pulmonary vasoreactivity at high altitude (Capanna Margherita, 4559 m) in a group of young adults who had suffered from transient hypoxemia (persistence of the pulmonary hypertension (PTPH)[9]) during their first week of life and a group of age and sex-matched controls born without any perinatal problem.

We found that, similarly to what was observed in rats, the subjects having suffered of transient hypoxemia during their first week of life developed exaggerated pulmonary hypertension at high altitude compared to the controls[5] (Fig. 1). This study represented the first demonstration that a transient insult during the perinatal period has major long-term consequences on the regulation of the vascular function in humans not only in the systemic but also in the pulmonary circulation.

## Preeclampsia in humans induces systemic and pulmonary vascular dysfunction in the offspring

Epidemiological studies have shown that offspring of preeclampsia are predisposed to premature cardiovascular disease,[6,7] as evidenced, for example, by a roughly 3-fold increase of the risk for stroke. The underlying mechanisms are unknown.

During preeclampsia, vasculotoxic factors are released into the maternal circulation by the diseased placenta. We speculated that these factors pass the placental barrier and leave a defect in the circulation of the offspring that predisposes to a pathological response later in life. To test this hypothesis, we assessed pulmonary-artery pressure and flow-mediated dilation of the brachial artery in 48 offspring of preeclampsia and 90 offspring of normal pregnancies born and permanently living at the same high-altitude location (La Paz, Bolivia, 3600 m).

The important new finding was that pulmonary-artery pressure was roughly 30 percent higher and flow-mediated dilation 30 percent smaller in offspring of mothers with preeclampsia than in control subjects (Fig. 2). Vascular dysfunction in the pulmonary and the systemic circulation was a robust finding, since we found a close inverse relationship between pulmonary-artery pressure and flow-mediated dilation ($r = -0.6$, $P < 0.001$).

The preeclampsia-induced vascular dysfunction has clinical consequences. Exaggerated hypoxic pulmonary hypertension is an important underlying mechanism of high-altitude pulmonary edema.[8,9] Offspring of mothers with preeclampsia living at high altitude appear to be at risk for re-entry high-altitude pulmonary edema.[5] Moreover, offspring of preeclampsia living at high altitude or suffering

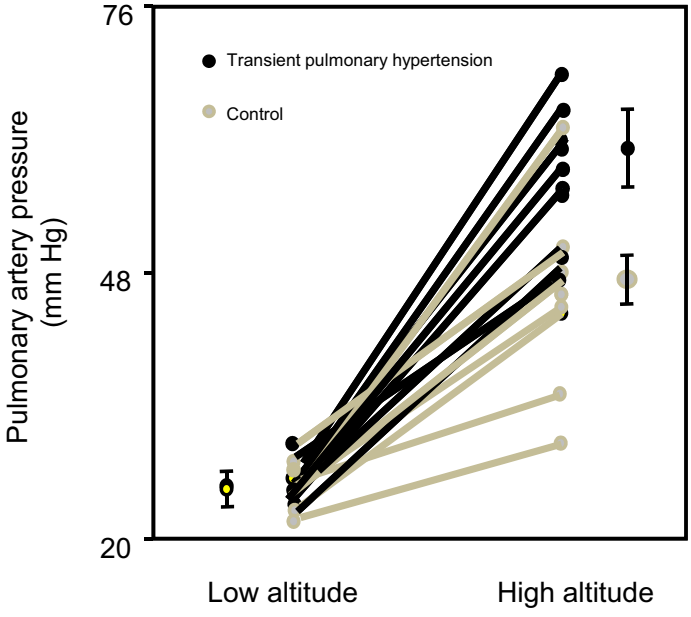


**Figure 1** Transient pulmonary hypertension during the first week of life predisposes to hypoxic pulmonary hypertension later in life. Effects of high-altitude exposure (4559 m) on systolic pulmonary-artery pressure in participants with a history of transient perinatal pulmonary hypertension and in controls. Points with error bars = mean and SE for group (modified from Sartori et al., 1999).[5]

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