The cause of essential hypertension is multifactorial involving genetic aspects and accumulation of risk factors in adult life, including sedentary lifestyle, adiposity, smoking, and stress. Accumulating evidence exists, however, that the development of future hypertension in the offspring can be directly related to adverse conditions during pregnancy and early life span, like intrauterine malnutrition, stress-induced constriction of placental vessels, exposure of the fetus to nicotine, alcohol, pesticides, drugs, and environmental toxins. Pregnant women display a 5% to 7% risk of developing new onset high blood pressure with a variety of hypertensive complications ranging from gestational hypertension to severe preeclampsia leading to organ damage. Furthermore, offspring of these mothers have a markedly increased risk for development of hypertension.

This delayed evolution of hypertension seems to be linked to the phenomenon of epigenetic changes occurring during pregnancy and early life span which was confirmed by numerous studies in animals and humans. Epigenetic modifications lead to alterations in gene expression or phenotype without any changes in the underlying DNA sequence. They include DNA methylation, post-translational histone modifications, and noncoding RNAs. In preeclampsia, for example, epigenetic changes are found in the placenta with differences in the expression profiles of endogenous serine protease inhibitors.

Reduced nitric oxide (NO) levels leading to endothelial dysfunction have been implicated in the onset and progression of essential hypertension as well as in pregnancy-associated hypertension. Nitric oxide (NO) is oxidized by superoxide anions to peroxynitrite and subsequently nitrite and nitrate. NO-mediated vasodilatation thereby is diminished and vasoconstriction augmented with a subsequent increase in systemic vascular resistance.

Increasing NO availability therefore is an interesting treatment target. Organic nitrates liberating NO or a related molecule are part of the standard drug treatment for patients with angina pectoris secondary to coronary artery disease. NO liberation stimulates soluble guanylate cyclase in smooth muscle cells to enhance formation of cyclic guanosine monophosphate leading to relaxation, thus replacing the diminished endogenous vasodilator capacity. However, the potential of most organic nitrates is limited by the development of tolerance and induction of reactive oxygen formation and endothelial dysfunction. Pentaerythritol tetranitrate (PETN), an organic nitrate devoid of adverse effects such as the induction of nitrate tolerance, vascular oxidative stress, and endothelial dysfunction, improves vascular function in diabetes mellitus and angiotensin II–induced vascular dysfunction.

In the present issue of *Hypertension*, Wu et al report that treatment with PETN during pregnancy and lactation period in spontaneously hypertensive rats (SHR) reduced blood pressure in female offspring (Figure). Besides reduction of blood pressure at 6 and 8 months through maternal PETN treatment, endothelium-dependent relaxation was improved accompanied by increased NO bioavailability. This was likely secondary to increased expression of the endothelial NO synthase and the elevation of the antioxidant enzymes superoxide dismutase 2, glutathione peroxidase 1, and heme oxygenase-1 (HO-1). Racasan et al previously showed that supplementation with l-arginine, the precursor of NO, during pregnancy in SHR reduces hypertension in the offspring. Now, Wu et al nicely demonstrate that epigenetic alterations in the vessel wall most likely underly this observed blood pressure reduction. CHIP analysis revealed that histone 3 lysine 27 acetylation and histone 3 lysine 4 trimethylation at the proximal promoter regions close to the transcription start site of endothelial NO synthase, superoxide dismutase 2, and HO-1 genes were enhanced in the aortae of the offspring as was the binding of RNA polymerase 2a. Epigenetic alterations in other organs involved in blood pressure regulation like the heart or kidney have been described and could also be involved in blood pressure reduction in female offspring induced by maternal PETN treatment. Indeed, changes in mRNA expression of the hypertension regulating genes elastin 1, epoxide hydrolase 2, and acyl-CoA synthetase medium-chain-family member 3 were found in the kidney of female offspring by Wu et al. How PETN did induce histone 3 lysine 27 acetylation and histone 3 lysine 4 trimethylation is not completely clear. Evidence exists that reactive oxygen species, in part, regulate histone modifications. PETN liberates NO, induces antioxidant enzymes in the vessel wall, and enhances circulating endothelial progenitor cells and endothelial function.

Furthermore, the risk of intrauterine growth restriction and perinatal death is reduced by PETN treatment in pregnant
women with abnormal placental perfusion. It is, therefore, likely that maternal PETN treatment improved uteroplacental blood flow and redox environment that triggered the histone 3 lysine 27 acetylation and histone 3 lysine 4 trimethylation. Recently, increased histone 3 lysine 27 methylation was also described in vessels of rats with DOCA salt-induced hypertension by treatment with resveratrol, which is known for its antioxidative capacity.

Interestingly, in male offspring, no effects on blood pressure occurred in the study by Wu et al. Whether maternal PETN treatment induced the same epigenetic alteration as in females was, therefore, not investigated. Female and male SHRs have equal blood pressure levels until 12 weeks, and thereafter sex difference develops with consistently higher blood pressure in male SHR. The late time points at 6 and 8 months, as well as the sex difference in blood pressure regulation, may explain why no effects on development of hypertension were detected in males by maternal PETN treatment. Also, it has to be noted that blood pressure in female offspring was not normalized although significantly lowered by maternal PETN treatment.

In summary, Wu et al clearly demonstrate that maternal treatment with the organic nitrate donor PETN in SHR during pregnancy and lactation reduced hypertension in female offspring by epigenetic alterations.

**Disclosures**

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**References**

NO for the Pregnant Mother: No Hypertension for the Daughter?
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