Sex differences in the effects of early life Vitamin D deficiency on vascular regulation

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Vitamin D (VitD) is classically known for its actions on calcium homeostasis and regulation of bone growth. VitD is now recognised to have effects on many organ systems including the cardiovascular system, and it is a negative regulator of the renin-angiotensin system. Many women of reproductive age are VitD deficient, including in "sunny" Australia. The effects of early life exposure to VitD deficiency on lifelong cardiovascular health are poorly understood. The aim of this study was to examine the effects of *in utero* and early life VitD deficiency on cardiovascular function in both male and female offspring.

Female Sprague-Dawley rats were fed a diet that was either VitD-replete or VitD-deplete for 6 weeks prior to and throughout pregnancy and lactation. The offspring were maintained on the same diet as their mothers or switched to the opposite diet until 3 months of age, after which, all rats were fed a VitD-replete diet. Arterial pressure was measured in conscious rats. Vascular function was tested using wire and pressure myography in tissues removed from animals anaesthetized by overdose of isofluorane. Arterial pressure and vascular function were measured in offspring at 2 and at 12 months of age.

As previously reported, young VitD deficient male and female offspring have significantly elevated arterial blood pressures compared with their VitD sufficient counterparts (Tare *et al*., 2011). Endothelium-dependent relaxation in small mesenteric arteries was impaired in VitD deficient offspring. Nitric oxide-dependent relaxation was halved in arteries from VitD-deficient males and dioestrus females ($P<0.0001$), while relaxation attributed to endothelium-derived hyperpolarization was all but abolished in VitD-deficient females in oestrus. Sodium nitroprusside-evoked relaxation was significantly reduced ($P<0.004$) in VitD deficient females but unaltered in arteries from males. At 12 months of age, following long term VitD repletion, arterial pressures and mesenteric artery function had normalized. However, early life VitD deficiency had permanent effects on neurovascular function in the renal artery, and sex-dependent effects on vascular reactivity and passive wall stiffness of arteries from other regions. Early life VitD deficiency produces early disturbances in cardiovascular function of the offspring, most of which can be reversed with subsequent VitD supplementation. However, some effects on the vasculature are irreversible and the extent of dysfunction varies between the sexes. Maintenance of VitD sufficiency in women of reproductive age is important for the long-term vascular health of their offspring.

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