HYPERTENSION DURING PREGNANCY AND OFFSPRING MICROVASCULAR STRUCTURE: INSIGHTS FROM THE RETINAL MICROCIRCULATION.

Short Title: HYPERTENSIVE PREGNANCY OFFSPRING MICROCIRCULATION

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ABSTRACT:

Human and experimental studies demonstrate that offspring born to pregnancies affected by common complications such as preeclampsia and preterm birth display developmental phenotypes that relate distinctly to the pregnancy disorder. Several studies have now reported microvascular differences in offspring of hypertensive pregnancies and there is interest in whether these may underlie epidemiological associations between pregnancy hypertension and a higher risk of hypertension and stroke in the offspring. The retinal circulation provides a unique window onto microvascular structure, of likely relevance to both the cerebrovasculature and broader cardiovascular risk. Yesil et al (*Am J Epidemiol*. 2016;000(0):000–000) report in this issue of the Journal that maternal gestational blood pressure elevation associates with reduced retinal vascular caliber in offspring at six years of age, providing a link between variation in pregnancy characteristics and childhood vascular development. Further work to understand the longitudinal association between pregnancy, emergence of microvascular changes and cardiovascular risk may identify opportunities for future preventive interventions.

Key Words: Preeclampsia, pregnancy, blood pressure, microcirculation, fetal programming

Hypertensive Pregnancy Complications and the Offspring Microvasculature

Abnormalities within the microvasculature are recognized as an early marker of hypertensive disease development both preceding and exacerbating rises in blood pressure [1]. This association is evident in the etiology of new onset hypertension during pregnancy, in which very high blood pressures emerge within a few weeks, in young women, in parallel with changes in dermal microvascular density [2]. It is possible that a more generalized microvascular disorder underlies several pathological features of the condition as, for example, defective placental and maternal microvascular interactions during implantation are also observed in severe hypertensive pregnancy syndromes [3]. Recently, it has become apparent that offspring of hypertensive pregnancies also may have microvascular abnormalities, which persist beyond pregnancy [4], which could account for their significantly higher risk of early onset hypertension [5] and raised cardiovascular risk profile [6]. However, the time when differences first emerge and what triggers these changes has remained unclear.

Retinal imaging – a window into microvascular pathology

The advent of retinal microvascular assessment has opened new opportunities for large scale, epidemiological study of the microvasculature in young age groups. The retina is a relatively easily accessed vascular bed, which provides a clear view of microvessel structure through static image analysis. The technique is non-invasive and, with appropriate equipment, can also be extended to allow functional assessment, for example, through dynamic flicker analysis [7] to induce dilatation and assess endothelial responses [8]. Differences in the retina are thought to reflect cerebrovascular changes and also associate with systemic changes in vascular responses [9]. Static retinal imaging primarily measures retinal microvessel caliber. Reductions in arteriolar caliber, particularly when associated with increases in

venular caliber, are seen in individuals at increased cardiovascular risk [10]. Yesil et al. have used static retinal analyses to study participants in the Generation R study and, for the first time, demonstrate arteriolar narrowing, by the age of six years, in those whose mothers developed high blood pressure during pregnancy and that the degree of changes relates to blood pressures in the mother during pregnancy [11].

When do these changes emerge?

The fetal and perinatal period is a time of rapid development and it is plausible that adverse exposures linked with maternal pregnancy hypertension, during key vulnerable periods, could have a permanent impact on microvascular development that explains these differences in childhood [5]. Findings from others provide some support for this hypothesis but suggest the association with microvascular structure may be more nuanced than simply a reflection of an impact of pregnancy hypertension on *in utero* growth or vascular function. Hypertensive pregnancy offspring exhibit different endothelial functional responses from birth [12] through to later life [13], [14]. However, although dermal capillary rarefaction has been noted to be reduced at birth in some offspring of hypertensive pregnancies [15], density was higher at birth in those born more preterm to hypertensive pregnancy [15], despite evidence of reduced microvasculature in preterm offspring at other stages in life [4], [16]. Furthermore, no structural differences were identified at birth or three months in those who just exhibited impaired growth [17]. In longer-term prospective studies differences in dermal capillary density are evident in 20 year olds born preterm to hypertensive pregnancies. Furthermore, by this age, the degree of impairment is proportionally related to the severity of their blood pressure elevation on both clinic and ambulatory blood pressure measures [4]. The study by Yesil et al. [11] has provided specific data on offspring of hypertensive pregnancy during childhood, taking account of differences in *in utero* growth. Cohort structure means there is limited data available from children born preterm and the severity of the hypertensive

syndromes represented in the mothers is relatively mild. Nevertheless, retinal microvessel structural differences are still evident in the group during childhood. These findings support a likely continuity of microvascular differences, across several vascular beds, through childhood and into adult years, specifically related to hypertensive pregnancies.

The Significance of Timing in Exposures and Outcomes

Intriguingly, the arteriolar narrowing was limited to those whose mothers had blood pressures that started to rise earlier in pregnancy, whereas those whose mothers had developed elevated maternal systolic pressure late in pregnancy [18] exhibited only retinal venular narrowing [19]. The timing of the onset of gestational blood pressure elevations therefore seems to be a key component in the association between pregnancy hypertension and adverse differences in offspring microvascular structure. Could there be specific exposures during vulnerable periods that trigger these developmental differences? Previous investigations by the same authors [20] showed links between mid-pregnancy levels of circulating placental growth factors and retinal microvasculature, although this did not appear to explain their current findings. Rätsep et al. have also implicated pregnancy placental growth factor levels [21] in a pilot study of 10 individuals in whom decreased circulating peripartum maternal placental growth factor levels associated with altered cerebrovascular structure in 7-10 year old offspring. Associations may exist because placental growth factor is a sensitive marker of a hypertensive pregnancy and other circulating angiogenic factors may also be of relevance. For example, increases in the antiangiogenic biomarkers soluble fms-like tyrosine kinase 1 and soluble endoglin have been associated with dermal capillary rarefaction in young adults aged 20-30 years born preterm to hypertensive pregnancies [4] and it will be of interest to understand the association between these factors peripartum and offspring microvascular structure.

Conclusion

The observation of decreased retinal arteriolar caliber during childhood in offspring of mothers whose blood pressure starts to rise early in pregnancy is consistent with the observed increased cardiovascular risk in this group later in life [22]. Furthermore, as depicted in Figure 1, the finding provides a temporal continuity, through childhood, between previous neonatal and adult studies of hypertensive pregnancies. The precise timing and trigger of these microvascular developmental changes requires further consideration but a renewed focus on how pregnancy hypertension alters microvessel development in the offspring may provide a unique opportunity to identify ways to manage hypertensive risk in this young population.

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Web Figure 1. Microvascular Alterations Identified in Offspring of Hypertensive Pregnancies

Several pieces of evidence have now identified microvascular changes during childhood and young adulthood in individuals born to a hypertensive pregnancy. Many of these changes are also observed during the hypertensive pregnancy in the mother (right hand column). Recent publications have started to characterise the range of vascular beds that exhibit altered microvascular differences including Yesil et al who have studied the retinal microvasculature. The figure highlights key references that are available in relation to these vascular beds and the time during the early life course when measurements were taken.