Hypertensive Disorders During Pregnancy and Offspring Retinal Microvasculature During Adolescence

[*]Maria C. Magnus, PhD, Alun D. Hughes, MD, PhD Cathy Williams, PhD Nishi Chaturvedi, MD, PhD, Janet Catov, PhD, Abigail Fraser, PhD

[*] MRC Integrative Epidemiology Unit at the University of Bristol, Oakfield House Oakfield Grove BS8 2BN Bristol, United Kingdom, E-mail: Maria.Christine.Magnus@bristol.ac.uk Twitter: @mariachmagnus1, @BristolUni

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Offspring of mothers with hypertensive disorders during pregnancy (HDP) have increased risk of cardiovascular disease (CVD) (1). Whether this is due to a direct intrauterine effect, such as maternal inflammation, endothelial dysfunction, or poor placentation linked to pre-eclampsia (PE), or due to shared genetics or environment that predispose to increased blood pressure, as seen in gestational hypertension (GH), remains undetermined (1). Regardless, it has been postulated that microvascular changes that predate cardiovascular events by decades could play a role (2). Retinal scans are a noninvasive way to directly observe the human microvasculature. We examined whether exposure to maternal HDP was associated with retinal microvascular features in adolescents in a U.K. pregnancy cohort.

We included 1,082 singletons with information on maternal HDP and retinal microvasculature at age 13 years from the ALSPAC (Avon Longitudinal Study of Parents and Children). Ethical approval was granted by the ALSPAC Law and Ethics Committee and local research ethics committees. Women without pre- existing hypertension were classified with GH if they had systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on at least 2 occasions first occurring after 20 gestational weeks. PE was defined as GH in combination with proteinuria (≥1+ dipstick test). We compared children of mothers with GH and PE to children of mothers without pre-existing hypertension. Measures of retinal microvasculature included arteriolar diameters, venular diameters, arteriolar length diameter ratio, arteriolar tortuosity, arteriovenous ratio, and optimality deviance. Multi- variable linear regression models adjusted for sex and ametropia (model 1), in addition to maternal age, parity, education, pre-pregnancy body mass index, smoking, and grandparental history of CVD (model 2).

A total of 159 mothers (15%) had GH, whereas 18 (2%) had PE. Mean age at the time of the retinal scans was 12.8 years (SD 0.2). Maternal GH showed modest associations with offspring retinal venular diameter (adjusted mean difference 2.56 mm; 95% confidence interval [CI]: 0.20 to 4.92 mm), and arteriovenous ratio (adjusted mean difference -0.02; 95% CI: -0.04 to -0.01) (Table 1). Similar associations were not observed for PE, with an adjusted mean difference of 0.88 mm (95% CI: -5.57 to 7.32 mm) for retinal venular diameter, and an adjusted mean difference of -0.01 (95% CI: -0.05 to 0.04) for arteriovenous ratio (Table 1). There was no strong evidence of any additional associations. Excluding children with childhood-onset diabetes (n = 3) did not change the results.

Our findings indicate that children born to mothers with GH (but not PE) have a greater venular diameter and a lower arteriovenous ratio compared with children of mothers without pre-existing hypertension before pregnancy. In contrast to findings from the Generation R cohort, which examined children at age 6 years, our findings do not support a narrower arteriolar diameter among children exposed to HDP (3). The differences between our findings and those from Generation R may be explained by the fact that they measured retinal microvasculature at age 6 years, or that they did not separate GH from PE. However, both narrower arterioles and wider venules are known to predict future hypertension and CVD events. It is therefore plausible that there is a microvascular pathway linking HDP and increased CVD risk in offspring (4). The association of GH—but not of PE—with offspring retinal microvasculature is also in line with previously reported results for offspring blood pressure in ALSPAC (5). Based on our results, the associations between maternal GH and offspring microvasculature might reflect a common role of an underlying genetic predisposition or life- style characteristics linked to hypertension/CVD as opposed to a direct intrauterine effect. In conclusion, our results indicate that children of mothers with GH have a wider venular diameter and lower arteriovenous ratio. This might be explained by a common role of genetic or lifestyle characteristics linked to CVD risk.

REFERENCES

1. Thoulass JC, Robertson L, Denadai L, et al. Hypertensive disorders of pregnancy and adult offspring cardiometabolic outcomes: a systematic review of the literature and meta-analysis. J Epidemiol Community Health 2016;70:414–22.
2. Li LJ, Ikram MK, Wong TY. Retinal vascular imaging in early life: insights into processes and risk of cardiovascular disease. J Physiol 2016;594:

2175–203.
3. Yesil GD, Gishti O, Felix JF, et al. Influence of maternal gestational hypertensive disorders on microvasculature in school-age children: the Generation R Study. Am J Epidemiol 2016;184:605–15.
4. Newman AR, Andrew NH, Casson RJ. Review of paediatric retinal micro- vascular changes as a predictor of cardiovascular disease. Clin Exp Ophthalmol
2017;45:33–44.
5. Fraser A, Nelson SM, Macdonald-Wallis C, Sattar N, Lawlor DA. Hypertensive disorders of pregnancy and cardiometabolic health in adolescent offspring. Hypertension 2013;62:614–20.

TABLE 1 Mean Difference in Measures of Retinal Microvasculature Between Offspring of Mothers With Hypertensive Disorders During Pregnancy and Offspring of Normotensive Mothers

Measure of Microvasculature	Gestational Hypertension Mean Difference (95% CI)	Pre-Eclampsia Mean Difference (95% CI)	Direction of the Association Between the Microvascular Measures and Later Risk of Cardiovascular Events
Arteriolar diameter, μm			↓
Model 1	0.19 (−1.60 to 1.97)	0.41 (−4.52 to 5.35)	
Model 2	0.26 (−1.58 to 2.10)	0.92 (−4.10 to 5.95)	
Venular diameter, μm			↑
Model 1	3.01 (0.71 to 5.30)	1.18 (−5.15 to 7.51)	
Model 2	2.56 (0.20 to 4.92)	0.88 (−5.57 to 7.32)	
Arteriolar length diameter ratio			↑
Model 1	−0.38 (−0.94 to 0.18)	−0.84 (−2.38 to 0.71)	
Model 2	−0.40 (−0.98 to 0.17)	−0.96 (−2.54 to 0.61)	
Arteriolar tortuosity			↓
Model 1	−0.002 (−0.006 to 0.002)	−0.004 (−0.015 to 0.007)	
Model 2	−0.001 (−0.006 to 0.003)	−0.003 (−0.014 to 0.009)	
Arteriovenous ratio			↓
Model 1	−0.03 (−0.04 to −0.01)	−0.01 (−0.06 to 0.03)	
Model 2	−0.02 (−0.04 to −0.01)	−0.01 (−0.05 to 0.04)	
Optimality deviance*			↑
Model 1	−0.002 (−0.017 to 0.012)	0.009 (−0.032 to 0.050)	
Model 2	−0.003 (−0.019 to 0.012)	0.008 (−0.034 to 0.049)	

Values are mean difference (95% confidence interval). Model 1 is adjusted for sex and ametropia. Model 2 is adjusted for sex and ametropia, in addition to maternal age, parity, education, pre-pregnancy body mass index, smoking during pregnancy, and genetic predisposition to cardiovascular disease (parental history of hypertension, stroke, or heart disease). Multiple imputation of missing covariate information was conducted using chained equations. *For a theoretically optimal bifurcation, the optimality ratio should be 0.79, and the optimality deviance was calculated as the absolute value of the optimality ratio minus 0.79.