Elevated Blood Pressure in Offspring Born Premature to Hypertensive Pregnancy

Is Endothelial Dysfunction the Underlying Vascular Mechanism?

Merzaka Lazdam, Arancha de la Horra, Alex Pitcher, Zola Mannie, Jonathan Diesch, Corinne Trevitt, Ilias Kylintireas, Hussain Contractor, Atul Singhal, Alan Lucas, Stefan Neubauer, Rajesh Kharbanda, Nicholas Alp, Brenda Kelly, Paul Leeson

Abstract—Offspring born to mothers with hypertensive pregnancy have higher childhood blood pressure. We hypothesized this relates to prenatally programmed differences in the underlying vascular pathophysiology of the offspring and that these would be most apparent in those born preterm because of severe hypertension. We carried out a 20-year follow-up study of 71 subjects born preterm, 19 to a hypertensive pregnancy and 52 to a normotensive pregnancy. Findings were compared with 38 subjects born at term to uncomplicated pregnancies. Peripheral and central blood pressures were measured, and then central arterial stiffness was assessed by carotid-femoral pulse wave velocity using applanation tonometry. Ultrasound was used to assess flow-mediated endothelial-dependent and independent brachial artery responses and common carotid artery intima-media thickness. Offspring born preterm to either hypertensive or normotensive pregnancy had higher peripheral and central blood pressure compared with full-term born offspring (central mean arterial pressure after preterm hypertensive pregnancy: 84.92 ± 7.0 mm Hg; preterm normotensive pregnancy: 84.13 ± 8.9 mm Hg; full-term pregnancy: 76.24 ± 7.96 mm Hg; P = 0.0009). However, underlying vascular phenotype differed. Preterm offspring of normotensive pregnancy had greater arterial stiffness than offspring of hypertensive pregnancy (5.92 ± 0.84 versus 5.42 ± 0.73 m/s; P = 0.039), whereas offspring of hypertensive pregnancy had greater carotid intima-media thickness (0.52 ± 0.04 versus 0.48 ± 0.06 mm; P = 0.013) and 30% lower flow-mediated dilatation (4.25 ± 4.02% versus 6.79 ± 4.38%; P = 0.05). Prematurity is associated with elevated blood pressure in later life. However, predominant underlying vascular phenotype depends on maternal pathology. Targeting endothelial function may be particularly important for primary prevention after hypertension in pregnancy. (Hypertension. 2010; 56:159-165.)

Key Words: blood pressure ■ preeclampsia ■ endothelial function ■ fetal programming ■ prematurity

De novo onset hypertension affects 5% to 7% of all pregnancies1 and is manifest as a spectrum of hypertensive complications ranging from gestational hypertension to severe preeclampsia.2 Hypertensive pregnancy has3,4 emerged as an independent risk factor for premature maternal cardiovascular disease,1,5,6 and recently offspring of hypertensive pregnancies have also been found to be at greater risk of higher blood pressure in childhood7–11 and stroke in later life.12 Furthermore, the risk to the offspring is graded and greatest in those whose mothers had more severe hypertensive signs, such as early onset hypertension or preeclampsia.12

Severe hypertensive pregnancy is commonly associated with premature delivery and intrauterine growth restriction.13 Prematurity and growth restriction, in turn, have been independently linked with hypertension and cardiovascular complications in the offspring,14–16 and it is postulated that this is mediated through intrauterine conditions adversely affecting the development of the offspring vascular system.17 Interestingly, despite both prematurity and intrauterine growth restriction leading to the same clinical sequelae of hypertension, the persistent underlying vascular phenotype appears to vary with, for example, only the term intrauterine growth-restricted offspring exhibiting endothelial dysfunction.15,18–20 Better understanding of the long-term changes in vascular pathophysiology related to different pregnancy complications may allow novel primary cardiovascular prevention strategies targeted at key aspects of vascular function.21
Whether offspring of hypertensive pregnancy have a vascular phenotype distinct from other pregnancy complications is not known but, if defined, might give insight into the underlying mechanism for their predisposition to hypertension. We hypothesized that any vascular dysfunction would be most apparent in those born premature because of early onset gestational hypertension or preeclampsia, because they have the greatest risk of later cardiovascular complications. We, therefore, performed a 20-year prospective follow-up study of a cohort born premature and compared their vascular phenotype with that of young adults born at term to uncomplicated pregnancies. We then sought to determine whether the vascular phenotype of young adults born preterm to pregnancies complicated by maternal hypertension was distinct from that associated with prematurity when the mother does not have hypertension.

Methods

Study Population
We performed a 20-year prospective follow-up study of a preterm cohort enrolled from 5 centers in the United Kingdom between 1982 and 1985. Participants were born before 37 weeks’ gestation, and obstetric and neonatal details were recorded at birth. Maternal gestational hypertension was defined as a systolic blood pressure (SBP) >140 mm Hg and/or diastolic pressure of >90 mm Hg in the absence of significant proteinuria, whereas preeclampsia was determined by the new onset of hypertension during the second half of pregnancy in the presence of 2+ of proteinuria or 300 mg in 24-hour urine collection. Follow-up of the children had been performed at 18 months22 and 7 years,23 with a substudy at 15 years.24 The initial preterm cohort consisted of 927 subjects. We recontacted 140 of the cohort who had agreed to be contacted about future studies, of whom 71 returned for characterization of cardiovascular risk and to undergo vascular imaging. In addition, we recruited a control group of healthy volunteers matched for age and born at term to uncomplicated pregnancies to provide normal reference ranges for the vascular measures, performed using the same techniques, in our laboratory. There were no differences in birth weight (1297.14 ± 280.26 versus 1329.33 ± 330.08; P = 0.42), gestation (30.23 ± 2.48 versus 30.31 ± 2.93 weeks; P = 0.81), percentage of male offspring (39% versus 55%; P = 0.33), or frequency of hypertensive pregnancy (28% versus 27%; P = 0.76) between those in the original cohort and those who took part. All of the studies were approved by relevant institution research ethics committees, and participants provided signed informed consent in accordance with the Declaration of Helsinki.

Demographic, Anthropometric, and Metabolic Characteristics
Subjects attended in the morning after a 12-hour overnight fast. Height was measured without shoes to the nearest 1 cm and weight to the nearest 0.2 kg, with subjects wearing light clothing, using a combined digital height and weight measurement station (Seca). Hip and waist circumference were measured with a tape measure and skinfold thickness using skinfold calipers (Holtain Ltd) to the nearest 0.1 mm. Data on medical history, smoking history, and parental medical history were obtained by questionnaire.18 Blood samples were drawn, centrifuged, and separated within 30 minutes, then stored for later analysis at ~80°C. Fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured at the Oxford John Radcliffe Hospital Biochemistry Laboratory using routine validated clinical biochemistry assays, with clinical level quality controls. Low-density lipoprotein was calculated using the Friedewald formula.

Blood Pressure Measurement
Three measurements of peripheral SBP, diastolic blood pressure, mean arterial pressure, and pulse pressure were recorded after 10 minutes of supine rest for each participant with an OMRON automatic digital monitor (HEM-705CP, OMRON) using the appropriate cuff size for arm circumference and averaged for analysis. Central aortic systolic blood pressure, diastolic blood pressure, mean arterial pressure, and pulse pressure readings were derived automatically from an applanation tonometry device using a mathematical transformation of the brachial artery blood pressure based on the radial waveform (SphygmoCor System-AtCor Medical).

Vascular Measurements

Aortic Stiffness
Carotid femoral pulse wave velocity, a robust measure of aortic stiffness, was measured using applanation tonometry (SphygmoCor, AtCor Medical). Pulse wave velocity was derived by recording the time delay between the pressure wave at the femoral and carotid pulses relative to the distance between pulse sites based on measurements from the suprasternal notch.

Endothelial Vasomotor Function
Subjects underwent measurement of flow-mediated dilatation using standard protocols.26 Briefly, the right brachial artery was imaged proximal to the antecubital fossa using a high-resolution Philips Sonos 5500 ultrasound machine equipped with a 10-MHz linear array ultrasound transducer. Flow-mediated dilatation, a quantitative measure of endothelial-dependent vasodilatation, was measured as a proportional change in brachial artery diameter in response to shear stress induced by forearm pneumocutaneous cuff inflation to suprasystolic pressure. Nitrate-mediated dilatation of the brachial artery, a quantitative measure of endothelial-independent vasodilatation, was measured 3 minutes after subjects received 400 μg of sublingual nitroglycerine. Images were analyzed offline with automated software (Vascular Analyser, MIA Inc.). Reproducibility data from our laboratory show a coefficient of variation for interstudy measurements of <10%.27

Carotid Intima-Media Thickness
The right and left common carotid arteries were imaged using high-resolution ultrasound (Philips Sonos 5500 equipped with a 10-MHz linear array transducer), in accordance with published guidelines,28 1 cm proximal to the carotid bifurcation to obtain the clearest demarcation of the intima-media layer in the posterior wall. Images were analyzed offline by automated wall tracking software. Carotid intima-media thickness was measured as the distance between the lumen-intima and media-adventitia interface, and the mean of the right and left carotid intima-media was used for analysis.

Statistical Analysis
Statistical analysis was carried out using SPSS (version 16, SPSS Inc) and GraphPad Prism (version 5). The study was powered based on 20 offspring of hypertensive pregnancies and 50 preterm offspring of normotensive pregnancy to have 90% power at P = 0.05 to identify a 0.85-SD difference in vascular measures. Post hoc analysis demonstrates that, in the final patient group, differences of 0.80 SD in carotid intima-media thickness, 1.90 SD in central SBP, 0.57 SD in flow-mediated dilatation, and 0.58 SD in pulse wave velocity were identified by t test for continuous variables of normally distributed data and Mann-Whitney U test for nonnormally distributed data. Spearman bivariate correlations were performed to identify relations among blood pressure, cardiovascular measures, and other characteristics. Stepwise multiple linear regression analysis was used with blood pressure as a dependent variable and variables from bivariate analysis that were
associated with blood pressure with a $P$ value $\leq 0.1$. Results are presented as mean±SD. Two tailed $P$ values $<0.05$ were considered statistically significant.

## Results

### Subject Characteristics

Subject demographics are presented in Table 1. Premature offspring were significantly shorter than those delivered at term, but body mass index and waist:hip ratio were comparable among the 3 groups. Subjects born preterm, whether to hypertensive or normotensive pregnancy, had significantly higher fasting plasma glucose, total cholesterol, and low-density lipoprotein cholesterol compared with those born at term. However, fasting insulin and high-density lipoprotein levels were similar. There were no differences in body size, lipid profile, or glucose levels between subjects born preterm either to a normotensive or hypertensive pregnancy.

### Birth Characteristics

Preeclampsia accounted for 85% of cases born to a hypertensive pregnancy. Preterm offspring born to a hypertensive or normotensive pregnancy did not differ in the length of gestation (31.05±2.34 versus 29.96±2.5 weeks; $P=0.1$), birth weight (1293.9±315.38 versus 1306.9±267.44 g; $P=0.86$) or the proportion of those born small for gestation (37% versus 23%; $P=0.25$). Maternal smoking was reported in 18% of the preterm hypertensive pregnancies and 46% of the preterm normotensive pregnancies ($P=0.062$). Antenatal steroids were administered in 16% of preterm hypertensive pregnancies and 19% of preterm normotensive pregnancies ($P=0.74$).

### Peripheral and Central Blood Pressure

Table 2 demonstrates that preterm subjects from both normotensive and hypertensive pregnancies had significantly higher measures of peripheral and central blood pressure than term controls. Using peripheral measures, the differences were strongest for peripheral diastolic and mean arterial blood pressures ($P=0.0001$ for both groups), although there were similar patterns for systolic pressure ($P=0.06$ for hypertensive group and $P=0.006$ for normotensive group). Based on estimates of central blood pressure, there were consistent differences in SBP, mean arterial pressure, and pulse pressure for both groups ($P=0.0001$) compared with term controls. The absolute difference in central SBP according to birth history was 9 mm Hg. In these study groups, subjects born preterm small for gestational age had no significant difference in blood pressure from those born preterm appropriate for gestation (for SBP 120 versus 121 mm Hg; $P=0.65$), and there was no correlation between blood pressure in early adulthood and birth weight (for SBP $r = −0.26$; $P=0.83$). We then studied the relationship between blood pressure and vascular parameters. Peripheral SBP was significantly correlated with pulse wave velocity ($r=0.308$; $P=0.008$) and flow-mediated dilatation ($r=−0.198$; $P=0.04$).

### Pulse Wave Velocity and Flow-Mediated Dilatation

We, therefore, investigated whether pulse wave velocity was greater in the young adults born preterm to normotensive and hypertensive pregnancies. Results are reported in Table 2. We confirmed significantly higher aortic stiffness in preterm infants born to normotensive pregnancies compared with term control subjects (5.92±0.84 versus 5.56±1.09 m/s; $P=0.03$). However, preterm subjects born to hypertensive...
Table 2. Blood Pressure and Vascular Measures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensive Pregnancy (n=19)</th>
<th>Normotensive Pregnancy (n=52)</th>
<th>Term Uncomplicated Pregnancy (n=38)</th>
<th>P (Preterm vs Term Offspring)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>measurements</td>
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<tr>
<td>SBP, mm Hg</td>
<td>120.21±11.84</td>
<td>120.66±10.35</td>
<td>114.0±11.01</td>
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<td>DBP, mm Hg</td>
<td>71.79±7.37</td>
<td>71.61±6.52</td>
<td>66.12±7.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87.93±7.61</td>
<td>88.07±6.9</td>
<td>82.07±7.66</td>
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</tr>
<tr>
<td>PPBP, mm Hg</td>
<td>48.42±10.62</td>
<td>48.88±8.49</td>
<td>47.88±8.23</td>
<td>0.64</td>
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<tr>
<td>Central SBP, mm Hg</td>
<td>115.96±10.86</td>
<td>115.78±10.55</td>
<td>96.71±9.86</td>
<td>0.0001</td>
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<tr>
<td>Central DBP, mm Hg</td>
<td>69.4±6.28</td>
<td>68.48±9.79</td>
<td>66.6±7.36</td>
<td>0.20</td>
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<td>Central MAP, mm Hg</td>
<td>84.92±7.0</td>
<td>84.13±8.9</td>
<td>76.24±7.96</td>
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<tr>
<td>Central PPBP, mm Hg</td>
<td>46.56±8.63</td>
<td>46.94±10.27</td>
<td>30.71±4.82</td>
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<tr>
<td>Vascular measurements</td>
<td></td>
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<tr>
<td>PWV, ms</td>
<td>5.42±0.73</td>
<td>5.92±0.84</td>
<td>5.56±1.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Carotid IMT, mm</td>
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<td>0.48±0.06</td>
<td>0.36±0.06</td>
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<tr>
<td>FMD, %</td>
<td>4.25±4.02</td>
<td>6.79±4.38</td>
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<tr>
<td>NMD, %</td>
<td>25.95±10.68</td>
<td>26.43±7.41</td>
<td>23.15±10.33</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. No significant differences were demonstrated in blood pressure measures between preterm offspring of hypertensive or normotensive pregnancy. Differences in vascular measures between preterm offspring of hypertensive pregnancy and preterm offspring of normotensive pregnancy are presented in the Figure. DBP indicates diastolic blood pressure; MAP, mean arterial pressure; PPBP, pulse pressure blood pressure; PWV, pulse wave velocity; FMD, flow-mediated dilatation; NMD, nitrate-mediated dilatation; IMT, intima-media thickness.

pregnancies had similar pulse wave velocity to term controls (5.42±0.73 versus 5.56±1.09 m/s; P=0.97) and significantly lower pulse wave velocity compared with those born preterm to normotensive pregnancies (P=0.039) (Figure A), suggesting that differences in aortic stiffness are not the main determinant of higher blood pressure in offspring of hypertensive pregnancy.

We then examined whether variation in endothelial function differed based on maternal pathology during pregnancy. We observed that offspring born to hypertensive pregnancies tended to have 30% lower endothelial-mediated vasodilatation compared with preterm offspring of normotensive pregnancy (4.25±4.02 versus 6.79±4.38; P=0.05; Figure B) who had similar levels of flow-mediated dilatation as term controls (6.79±4.38 versus 6.87±4.88; P=0.94). Therefore, offspring of hypertensive pregnancy had a more selective vascular disturbance of endothelial function.

Carotid Intima-Media Thickness
In view of the variation in functional vascular phenotype, we looked for structural differences between the groups based on carotid intima-media thickness as a robust measure of subclinical development of atherosclerosis. Figure C demonstrates that offspring born to hypertensive pregnancy had significantly higher common carotid intima-media thickness than those born prematurity to a normotensive gestation (0.52±0.04 versus 0.48±0.06 mm; P=0.013), and the difference was even greater when compared with those born at term (0.52±0.04 versus 0.36±0.06; P=0.002; Table 2).

Discussion
This study shows that subjects born preterm have 5 to 10 mm Hg higher blood pressure in young adult life, but the vascular phenotype of the adult depends on the background pregnancy-related pathology. Preterm offspring of hypertensive pregnancies have evidence of impaired endothelial function and greater subclinical atherosclerosis, assessed from increased carotid intima-media thickness. In contrast, preterm offspring of normotensive pregnancies have significantly less carotid wall thickening with normal endothelial responses, and the predominant finding is increased aortic stiffness.

Our finding of increased blood pressure in offspring of premature deliveries and of pregnancies complicated by hypertension is consistent with previously published studies of children4 and young teenagers10 and extends these earlier observations into adulthood.7,8,11,32 Although none of our subjects were hypertensive, a 10-mm Hg difference in SBP represents a substantial variation. Blood pressure is known to track throughout life, and in the 35- to 64-year–old age group a 10-mmHg difference equates to a 20% increase in age-adjusted risk of cardiovascular events.33 Therefore, a better understanding of the underlying vascular pathologies may offer opportunities for novel primary interventions with potentially large long-term clinical benefits. Pregnancy-related complications represent a clinical scenario where cardiovascular risk for the offspring is known from birth, and there may be opportunities to start prevention very early.21 There is now substantial evidence of “programming” of aspects of vascular biology during fetal development, in particular endothelial responses19 and arterial stiffness.16 These differences may be established in response to the intrauterine milieu or because of genetic variation that determines both general and vascular development of the fetus.

Reduced birth weight has been studied in detail because of its association with later risk of cardiovascular disease, and a
consistent finding in both humans and animal models is of endothelial dysfunction. The early period of organogenesis is susceptible to changes in materno-fetal nutrient supply resulting in long-term changes to offspring vascular function even in the absence of gross morphological changes. In fact, periconceptional nutrient restriction leads to raised fetal blood pressure in sheep, as well as endothelial dysfunction in rats. This has been shown to transmit through generations in sheep in the absence of additional dietary challenge. One exception is in the premature infant in whom endothelial function appears to be preserved. In our current study we also show the same levels of endothelial response in preterm infants of normotensive pregnancies compared with term controls despite differences in blood pressure and other cardiovascular risk factors. Rather, the predominant finding in preterm offspring of normotensive pregnancies is of increased arterial stiffness. Arterial stiffness is a composite measure of vascular tone, in part determined by endothelial function, and of vascular structure. Because endothelial function did not differ, our observations may be accounted for by inadequate structural vascular development and differentiation of the central arteries in premature infants with insufficient elastin deposition in central arteries predisposing to abnormalities in aortic elasticity.

A defining feature of preeclampsia is endothelial dysfunction in the mother, and endothelial dysfunction has also been reported in mothers who have gestational hypertension. Furthermore, the degree of maternal endothelial dysfunction is proportional to the severity of the hypertensive condition being most severe in pregnancies that result in premature delivery. We have now found a 30% reduction in endothelial function in adult preterm offspring of hypertensive pregnancy. We believe the findings are biologically plausible and hypothesize that endothelial dysfunction may also occur in the fetus in response to the same placenta-related factors that affect the mother. Thus, our finding is likely to reflect either persistent endothelial dysfunction after the pregnancy or relate to a heritable predisposition to endothelial dysfunction in both mother and child. The clinical history leading to preterm birth in each group may also differ, for example, mode of delivery, and this may be relevant to the mechanism of long-term programming of the vasculature. Impaired endothelial function is an important feature of established hypertension and may predate the development of clinical disease. Indeed, studies have shown that reduced NO availability and increased endothelial derived constrictor factors secondary to endothelial dysfunction or raised endogenous inhibitors of NO synthase play a role in the pathogenesis of hypertension even in children.

Carotid intima-media thickness is a well-established, independent predictor of future cardiovascular risk in asymptomatic adults. In a meta-analysis, Lorenz et al reported that an absolute difference in intima-media thickness of 0.1 mm was associated with a relative risk of myocardial infarction and stroke of 1.15 and 1.18, respectively, in adults over the age of 40 years. Carotid wall thickening has been demonstrated previously in children and adults with cardiovascular risk factors, such as smoking and hypercholesterolemia. We were, therefore, interested to know whether, similar to the
variation in vascular function, there was variation in carotid wall thickness that was determined by background maternal pathology. We found preterm offspring of hypertensive pregnancies had, on average, a 0.15-mm greater carotid wall thickness compared with term controls. The levels of thickness in our term controls were equivalent to those previously reported in healthy young adults, and the differences may in part be determined by the prematurity and higher levels of cardiovascular risk factors, such as blood pressure and lipids, which are well known to relate to carotid intima-media thickness in young adult life. However, there was also an approximately 0.05-mm difference between normotensive and hypertensive preterm offspring in whom levels of risk factors were equivalent. This observation is novel, and the increase in carotid wall thickness is equivalent to that reported in young adults with a family history of cardiovascular disease and 4 times that observed in young adult smokers. The difference may be accounted for by the independent association between endothelial dysfunction and progression of carotid wall thickness. Alternatively, the findings may be a manifestation of the developmental in utero vascular changes or the vascular phenotype associated with a family history of hypertensive pregnancy.

There was a significantly higher proportion of reported smoking in women who had a premature delivery with a normotensive pregnancy than those with a hypertensive pregnancy. This difference is consistent with increased prematurity in smoking mothers and generally lower rates of smoking in mothers with preeclampsia. However, maternal smoking was not associated with vascular parameters in our cohort and did not account for the differences in measures between groups. Because cardiovascular complications in offspring of hypertensive pregnancy appear to be graded, it will be of interest to study a group of offspring born to milder forms of hypertensive pregnancy, such as those born at term to mothers with hypertensive pregnancy. This will help establish whether there is a similar graded difference in severity of vascular dysfunction and the relevance of our findings to the broader population. Furthermore, because of the limited numbers it was not possible to determine whether the strength of the association differed between males and females.

We conclude that premature offspring have significantly higher levels of blood pressure in early adult life. We go on to demonstrate differences in vascular biology that might explain the elevated blood pressure and, furthermore, that the offspring vascular phenotype varies with the underlying maternal pathology. In preterm offspring whose mothers were normotensive there may be benefit from studying changes in arterial structural development to understand their predisposition to hypertension. In contrast, offspring of hypertensive pregnancies have significantly increased carotid intima-media thickness and lower endothelial responses. Novel primary prevention strategies for cardiovascular disease and risk factor development after pregnancies complicated by hypertension may be best targeted at reversal of endothelial dysfunction.

**Perspectives**

Preeclampsia and gestational hypertension are common conditions affecting 5% to 7% of all pregnancies and are associated with significant fetal morbidity, particularly premature delivery. It has emerged recently that offspring of hypertensive pregnancies have higher blood pressure in childhood and are at greater risk of stroke in later life. This study demonstrated that subjects born to a hypertensive pregnancy have significantly higher blood pressure in young adult life that equates to a 20% increase in age-adjusted risk of cardiovascular events. We have also shown that the effect of hypertension in pregnancy on the offspring vascular phenotype goes beyond that of prematurity with evidence of impaired endothelial responses and greater subclinical atherosclerosis. Therefore, through a better understanding of the variation in underlying vascular pathophysiology, which precedes development of cardiovascular risk factors, novel primary prevention strategies may be best targeted at early reversal of offspring endothelial dysfunction after pregnancies complicated by hypertension.

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**Disclosures**

None.

**References**

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