Blood Pressure and Retinal Microvascular Characteristics During Pregnancy
Growing Up in Singapore Towards Healthy Outcomes (GUSTO) Study

Ling-Jun Li, Carol Yim-Lui Cheung, M. Kamran Ikram, Peter Gluckman, Michael J. Meaney, Yap-Seng Chong, Kenneth Kwek, Tien-Yin Wong, Seang-Mei Saw

Abstract—Changes in maternal blood pressure during pregnancy are associated with poor maternal and neonatal outcomes. We investigated whether maternal blood pressure during midpregnancy has an impact on the retinal microcirculation among pregnant Asian women. A total of 665 pregnant women aged 18 to 46 years were recruited from the Growing Up in Singapore Towards Healthy Outcomes Study. Blood pressure and retinal vascular parameters were both measured at 26 weeks’ gestation following a standardized protocol. Blood pressure was measured by a digital automatic blood pressure monitor (Omron HEM 705 LP). Quantitative retinal vascular parameters were assessed by a semiautomated computer-based program (Singapore I Vessel Assessment, version 3.0). In multiple linear regression models, every 10-mm Hg increase in mean arterial blood pressure was associated with a 1.9-μm (P<0.001) reduction in retinal arteriolar caliber, a 0.9° (P=0.05) reduction in retinal arteriolar branching angle, and a 0.07 (P<0.01) reduction in retinal arteriolar fractal dimension, respectively. Patients classified into a high-risk group in developing preeclampsia (mean arterial blood pressure ≥90 mm Hg) were twice as likely (odds ratio 2.1 [95% CI, 1.0–4.4]) to have generalized retinal arteriolar narrowing compared with those classified into a low-risk group (mean arterial blood pressure <90 mm Hg). Retinal venular caliber and vascular tortuosity were not associated with blood pressure measures. Elevated blood pressure is associated with a range of retinal arteriolar changes in pregnant women, providing evidence for an impact of blood pressure on the microcirculation during pregnancy. (Hypertension. 2012;60:223-230.)

Key Words: blood pressure ■ hypertension ■ microcirculation ■ vascular biology ■ retinal blood vessels ■ retinal vascular caliber ■ preeclampsia/pregnancy ■ pregnant women

The maternal cardiovascular system undergoes profound changes during pregnancy with hemodynamic adaptation, such as increases in cardiac output and stroke volume, and reductions in blood pressure and peripheral vascular resistance. In uncomplicated pregnancy, blood pressure decreases physiologically toward midpregnancy and rises to preconception values at term, which lowers vascular resistance, enhances placental function, and leads to improved pregnancy outcomes. In contrast, abnormally elevated maternal blood pressure in the second or third trimester is associated with poor maternal and neonatal outcomes, including preeclampsia, preterm delivery, and low birth weight. Recent evidence points to microvascular mechanisms, such as endothelial dysfunction, as contributory factors to the development of these poor outcomes. It has been reported that endothelium-dependent vasodilation is increased in women who have preeclampsia to levels over and above those seen in normal pregnancy. Nonetheless, whether maternal blood pressure is associated with microvascular changes that may lead to poor maternal and neonatal outcomes is uncertain because of a lack of means to visualize and assess the microcirculation directly.

Over the last decade, the retinal microcirculation has been established as a “biological model” to study the human microcirculation in vivo. Substantial epidemiological studies in general middle-aged and elderly populations have already demonstrated that changes in retinal microvasculature (eg, narrower retinal arteriolar diameter and decreased fractal dimension) are associated not only with hypertension but also with clinical cardiovascular outcomes (eg, stroke and cardiovascular mortality) and markers of subclinical vascular dis-

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ease (eg, intima-media thickness, flow-mediated vasodilation, carotid plaques, and coronary calcifications).13–19 Whether maternal blood pressure is associated with retinal microvascular characteristics during pregnancy has not yet been examined.

In this study, we investigated the relationship between maternal blood pressure and a spectrum of retinal vascular parameters in a cohort of Asian pregnant women to assess the impact of blood pressure on the microcirculation during pregnancy.

Methods

Study Population

We analyzed data from an ongoing cohort study, the Growing Up in Singapore Towards Healthy Outcomes birth cohort (naturally conceived) and the add-on In-Vitro Fertilization cohort study (conceived through assisted reproductive techniques). Except for differences in conception, both cohorts shared the same inclusion criteria, which were Singapore citizens or Singapore permanent residents of age ≥18 year, attending the first trimester antenatal clinic at the 2 major public maternity units of the KK Women’s and Children’s Hospital and the National University Hospital, intending to eventually deliver in the above-named hospitals and to reside in Singapore for the next 5 years.

Retinal photographs were only taken in participants who attended KK Women’s and Children’s Hospital clinic (952 of 1248 Growing Up in Singapore Towards Healthy Outcomes participants, 76.3%) because of logistic constraints. Of the 665 participants (response rate, 70.0%) with gradable retinal photographs, blood pressure and other measurements taken at the 26-week visit were included in our study. The study was approved by both Singhealth Centralized Institutional Review Board and the National Health Group’s Domain Specific Review Board. It was conducted according to the tenets of the Declaration of Helsinki. Informed written consent was obtained from every participant before any testing.

Blood Pressure Measurements

Upper arm blood pressure was measured using the automatic Omron sphygmomanometer (Omron HEM 705 LP, Omron Healthcare Inc) after 3 minutes of rest, according to standard protocols.20 All of the participants were seated in an upright position with back support. A cuff was placed around the nondominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation.21 The average of 3 separate measurements was taken. We calculated mean arterial blood pressure (MBP) as two-thirds diastolic blood pressure (DBP) plus one-third systolic blood pressure (SBP).

Retinal Photography and Measurements of Retinal Vascular Parameters

Digital retinal photographs were taken from participants without pharmacological pupil dilation using a 45° nonmydriatic retinal camera (Canon CR-1, 40D SLR digital retinal camera backing; Canon Inc). Right eye photographs centered on the optic disc were used for the measurement of retinal vascular parameters according to standardized protocols, as described previously in the general population.16,21,22 Retinal photographs were assessed by trained graders using a semiautomated computer-based program (Singapore I Vessel Assessment, version 3.0) that measures a spectrum of retinal vascular parameters quantitatively from 0.5 to 2.0 disc diameters (zone C) away from the optic disc margin (Figure). These retinal vascular parameters include the following: (1) retinal vascular caliber, represented as central retinal arteriolar equivalent and central retinal venular equivalent; (2) retinal vascular branching angle, defined as the first angle subtended between 2 daughter vessels at each bifurcation; (3) retinal vascular fractal dimension, which quantifies the complexity of the branching pattern of the retinal vascular tree and defined as the gradient of logarithms of the number of boxes and the size of the boxes; and (4) retinal vascular tortuosity, defined as the integral of the curvature square along the path of the vessel, normalized by the total path length, which takes into account the bowing and points of inflection.

Intragrader reliability was assessed in 90 randomly selected retinal photographs from the Growing Up in Singapore Toward Healthy Outcomes cohort, and the intraclass correlation coefficient was 0.94 for retinal arteriolar caliber, 0.97 for retinal venular caliber, 0.82 for retinal vessel branching angle, 0.92 for retinal vessel fractal dimension, 0.95 for retinal arteriolar tortuosity, and 0.87 for retinal venular tortuosity.

Other Measurements and Covariates

Standing height was measured by SECA model 213 (Seca, Hamburg, Germany) whereas weight was measured by SECA model 803 (Seca) according to standard protocols.5,10–12 Both measurements were separately taken 2 times with bare feet. If the first 2 measurements differed by 1 cm or 200 g for height or weight, a third measurement was taken for the average calculation. Body mass index (BMI) was...
calculated as weight divided by the height squared (kilograms per meter squared).

Autorefraction was performed using a Canon Autorefractor RK-F1 (Canon, Tokyo, Japan), where the average from 5 consecutive readings of sphere and cylinder were obtained. Readings were considered acceptable if the difference between the lowest and highest reading was <0.25 diopters. Spherical equivalent was calculated as the sphere plus half negative cylinder.

Questions on sociodemographic information were completed by participants in English, Chinese, Malay, or Tamil questionnaires. Household income was classified into 5 categories as follows: (1) Singapore dollar (SGD) 0 to 999 per month; (2) SGD 1000 to 1999 per month; (3) SGD 2000 to 3999 per month; (4) SGD 4000 to 5999 per month; and (5) More than or equal to SGD 6000 per month. Pregnancy outcome history was classified into 2 categories, no previous live birth and ≥1 previous live birth. Ethnicity; lifestyle, such as alcohol intake and cigarette smoking; and past medical history, such as hypertension, diabetes mellitus, and depression were obtained from the clinic interview.

Definitions and Statistical Analysis

A recent meta-analysis has reported that MBP in the second trimester is a better predictor of preeclampsia than SBP or DBP, with a predictive strength of MBP ≥90 mm Hg as moderate (area under the receiver operating characteristic curve, 0.76). We, therefore, defined pregnant women in our study who had MBP ≥90 mm Hg as “high” risk in developing incident preeclampsia and those with MBP <90 mm Hg as “low” risk.

All of the variables were normally distributed. Student t test and χ2 test (2-sided) were used for comparison of all of the baseline characteristics between participants with and without retinal photography. Blood pressure measurements (SBP, DBP, and MBP) were all analyzed continuously and categorized into quartiles. The test of trend was determined by treating quartiles of blood pressures as continuous ordinal variables. In addition, the lowest 20th percentile in central retinal arteriolar equivalent and the highest 20th percentile in central retinal venular equivalent were classified into generalized retinal arteriolar narrowing and retinal venular widening, respectively.

Multiple linear and logistic regression models were performed to examine the associations between blood pressure measurements and retinal vascular parameters. Retinal vascular caliber was analyzed as dependent variables in 2 models, model 1, age and ethnicity-adjusted, and model 2, multivariate-adjusted including variables in model 1, as well as for household income, pregnancy outcome, hypertension, diabetes mellitus cigarette smoking, BMI, spherical equivalent, Postnatal Edinburg Depression Score, and fellow vessel caliber (model 2), every 10-mm Hg increase in SBP, DBP, and MBP, statistically significant reductions of 0.9 μm (95% CI, −1.5 to −0.4 μm), 1.7 μm (95% CI, −2.5 to −1.1 μm), and 1.9 μm (95% CI, −2.86 to −1.3 μm) were observed in retinal arteriolar caliber, respectively. Similar inverse associations of higher SBP (P=0.02), higher DBP (P<0.001), and higher MBP (P<0.001) with smaller arteriole-to-venule ratio (AVR) were observed. Furthermore, there was a significant decreasing trend (all P values <0.001) in retinal arteriolar caliber from the lowest quartile to highest quartile in SBP, DBP, and MBP.

We also examined the associations between blood pressure with generalized retinal arteriolar narrowing and retinal venular widening. Compared with the lowest quartile, pregnant women in the highest quartile of SBP were 2.4 times (odds ratio, 2.4 [95% CI, 1.1–5.2]) more likely to have generalized retinal arteriolar narrowing. For DBP and MBP, the corresponding odds ratios were 2.8 (95% CI, 1.3–6.1) and 2.5 (95% CI, 1.1–5.6), respectively.

Table 3 shows the relationships between different blood pressure measures and retinal vascular branching angle and retinal vascular fractal dimension. There were consistent associations of higher SBP, higher DBP, and higher MBP with smaller retinal arteriolar branching angle and small retinal arteriolar fractal dimension. Similarly, there were significant descending trends in retinal arteriolar branching angle and retinal arteriolar fractal dimension when we compared the highest quartiles of blood pressure measures with the lowest quartiles.

We then categorized the participants as low- and high-risk groups for preeclampsia by MBP. Compared with participants in the low-risk group (MBP, <90 mm Hg), participants in the high-risk group (MBP, ≥90 mm Hg) had narrower retinal arteriolar caliber (122.7 versus 125.1 μm; P<0.01) and higher odds (odds ratio, 2.1 [95% CI, 1.0–4.4]) to have generalized retinal arteriolar narrowing (Tables 2 and 3).

In a supplementary analysis, we excluded participants who had been diagnosed previously with hypertension before pregnancy (n=12). There were no differences in associations of blood pressure and retinal vascular parameters among the 653 remaining participants. Both retinal arteriolar and venular tortuosity were not significantly associated with any blood pressure measures. Moreover, there were no potential effect modifiers on the relationship between blood pressure and retinal vascular parameters (data not shown).

**Discussion**

In this present study, we showed that elevated blood pressure during midpregnancy is associated with retinal microvascular characteristics, including narrower retinal arterioles and arte-
riolar branching angles and reduced arteriolar fractal dimension. Blood pressure was not associated with retinal venular characteristics. These data provide evidence that blood pressure has a significant effect on the arteriolar microcirculation during pregnancy.

The relationship between blood pressure and retinal vascular caliber has been widely documented by epidemiological studies in a general population.27–30 Peripherally measured blood pressure values (SBP, DBP, and MBP) have been associated with retinal arteriolar narrowing among children and adults of a wide range of ages, sex, and ethnicity.13,14,25–28 The pathophysiolog-
ical changes in retina in response to blood pressure elevation are widely hypothesized as hypertensive retinopathy.29,30 In hypertension, elevated blood pressure either directly or indi-
rectly leads to a series of morphological changes, including vasoconstriction of peripheral arterioles, growth and apoptosis of smooth muscle cells of peripheral arterial wall, and vascular fibrosis by means of vasoactive peptides.31–33 Subsequently, changes in small arterial structure among hypertensive patients can be categorized into either inward eutrophic remodeling or outward hypertrophic remodeling.31 Arteriolar narrowing and remodeling are described as initial steps of retinal and peripheral changes in hypertension, and, thus, retinal arterioles may undergo remodeling similar to that seen in arterioles of the subcutaneous tissues.33,34 More recent studies have further shown that examining the geometric branching pattern of the retinal vascular tree, which may capture the “optimal state” of the retinal microcirculation, is

Table 1. Comparison of Baseline Characteristics Between Subjects With and Without Retinal Photographs, Growing Up in Singapore Towards Healthy Outcomes Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>With Retinal Photography (N=665)</th>
<th>Without Retinal Photography (N=287)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>N 665 Mean or % 30.6 SD 5.4</td>
<td>N 287 Mean or % 30.4 SD 5.5</td>
<td>0.56</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Chinese 345 Mean or % 51.3 SD . .</td>
<td>Malay 192 Mean or % 28.9 SD . .</td>
<td>0.31</td>
</tr>
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<td>In Vitro Fertilization</td>
<td>Yes 54 Mean or % 8.1 SD . .</td>
<td>No 611 Mean or % 91.9 SD . .</td>
<td>0.80</td>
</tr>
<tr>
<td>Pregnancy outcome history</td>
<td>No live birth 324 Mean or % 48.7 SD . .</td>
<td>≥1 live birth 313 Mean or % 47.1 SD . .</td>
<td>0.96</td>
</tr>
<tr>
<td>Household income</td>
<td>SGD 0–999 per mo 18 Mean or % 2.7 SD . .</td>
<td>SGD 1000–1999 per mo 83 Mean or % 12.5 SD . .</td>
<td>0.56</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>665 Mean or % 111.1 SD 12.4</td>
<td>15 Mean or % 109.1 SD 13.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>665 Mean or % 81.7 SD 9.2</td>
<td>15 Mean or % 82.4 SD 8.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>648 Mean or % 26.4 SD 4.7</td>
<td>228 Mean or % 26.2 SD 5.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Edinburgh Postnatal Depression Score</td>
<td>640 Mean or % 8.0 SD 4.5</td>
<td>226 Mean or % 8.0 SD 4.6</td>
<td>0.98</td>
</tr>
</tbody>
</table>

SGD indicates Singapore dollar.

*Data show Student t test or χ² test (2 sided).
also influenced by blood pressure. Narrower retinal arteriolar branch angle and reduced fractal dimension have been reported to be associated with higher levels of blood pressure, and suboptimal fractal dimension has also been linked to acute lacunar stroke, chronic kidney disease, and coronary heart disease mortality.

To our best knowledge, this is the first comprehensive study to examine the relationship between maternal blood pressure and retinal microvasculature in pregnant women. The maternal cardiovascular system undergoes profound changes during pregnancy, as well as in women with complicated pregnancies. In our study, elevated blood pressure was associated with retinal arteriolar narrowing, narrower retinal arteriolar branch angle, and smaller retinal arteriolar fractal dimension. These changes may reflect a range of possible mechanisms, including vasospasm, decrease in NO release, endothelial dysfunction, impairment of perfusion, or oxygenation in retinal microvasculature. The human circulatory system is believed to conform an “optimum design” based on Murray’s principle of minimum work, deviations or alterations from the optimal retinal vascular architecture are associated with impaired microcirculatory transport and reduced efficiency and can be a marker of increased cardiovascular risk and poorer pregnancy outcomes. Further studies are required to explore the hemodynamics of the retinal microcirculation in response to elevated blood pressure.

During normal pregnancy, it has been shown that MBP is a better predictor of pre-eclampsia than SBP or DBP, with positive and negative likelihood ratios of MBP of 3.50 and 0.46, respectively. In the current study, we demonstrated that pregnant women with MBP...
90 mm Hg had significantly narrower retinal arteriolar caliber than those with MBP < 90 mm Hg, suggesting that retinal vascular caliber changes might provide new insights into hypertensive disorders, such as preeclampsia. Therefore, predictive value of retinal arteriolar caliber on the development of preeclampsia/eclampsia is warranted to further investigate.

The strengths of our study include standardized blood pressure and clinical measurements, quantitative assessment of retinal microvascular characteristics, and detailed information on a range of potential confounders. However, there are some potential limitations. First, the cross-sectional nature at 26 weeks’ gestation limits our interpretation of the temporal sequence of blood pressure and retinal vascular parameters. Second, there is some selection bias, because only pregnant women recruited from 1 site (KK Women’s and Children’s Hospital clinic) were

<table>
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<th>Table 3. Multivariate Linear Regression Analysis of Blood Pressure With Retinal Vascular Tortuosity and Fractal Dimension</th>
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<tbody>
<tr>
<td>Retinal Vascular Branching Angle, Degree</td>
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<tr>
<td>Arteriolar</td>
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<td>Model 1*</td>
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<tr>
<td>Systolic blood pressure (per 10 mm Hg increase)</td>
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<tr>
<td>P value</td>
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<tr>
<td>Systolic blood pressure in quartiles</td>
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<tr>
<td>First quartile, ≤102.5</td>
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<tr>
<td>Second quartile, 102.6–110.4</td>
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<tr>
<td>Third quartile, 110.5–119.3</td>
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<td>Fourth quartile, &gt;119.3</td>
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<tr>
<td>P for trend</td>
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<tr>
<td>Diastolic blood pressure (per 10-mm Hg increase)</td>
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<tr>
<td>P value</td>
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<tr>
<td>Diastolic blood pressure in quartiles</td>
</tr>
<tr>
<td>First quartile, ≤60.4</td>
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<tr>
<td>Second quartile, 60.5–67.7</td>
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<tr>
<td>Third quartile, 67.8–73.2</td>
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<tr>
<td>Fourth quartile, &gt;73.2</td>
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<td>P for trend</td>
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<tr>
<td>Mean arterial blood pressure (per 10-mm Hg increase)</td>
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<td>P value</td>
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<tr>
<td>Mean arterial blood pressure in quartiles</td>
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<tr>
<td>First quartile, ≤75.4</td>
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<tr>
<td>Second quartile, 75.5–80.6</td>
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<tr>
<td>Third quartile, 80.7–87.8</td>
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<tr>
<td>Fourth quartile, &gt;87.8</td>
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<td>P for trend</td>
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<th>Preeclampsia risk group‡</th>
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<tr>
<td>Low risk</td>
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<tr>
<td>High risk</td>
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<tr>
<td>P for trend</td>
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</table>

*Data were adjusted for age and ethnicity.
†Data were adjusted for age, ethnicity, pregnancy outcome, household income, hypertension, diabetes mellitus, cigarette smoking, body mass index, and spherical equivalent.
‡Data were defined by mean arterial blood pressure (MBP). Low-risk MBP was <90 mm Hg; high-risk MBP was ≥90 mm Hg.5

≥90 mm Hg had significantly narrower retinal arteriolar caliber than those with MBP <90 mm Hg, suggesting that retinal vascular caliber changes might provide new insights into hypertensive disorders, such as preeclampsia. Therefore, predictive value of retinal arteriolar caliber on the development of preeclampsia/eclampsia is warranted to further investigate.

The strengths of our study include standardized blood pressure and clinical measurements, quantitative assessment of retinal microvascular characteristics, and detailed information on a range of potential confounders. However, there are some potential limitations. First, the cross-sectional nature at 26 weeks’ gestation limits our interpretation of the temporal sequence of blood pressure and retinal vascular parameters. Second, there is some selection bias, because only pregnant women recruited from 1 site (KK Women’s and Children’s Hospital clinic) were
analyzed. However, such a bias is not expected to be differential in nature.

Perspectives
In conclusion, our study shows that elevated blood pressure is possibly associated with a range of adverse retinal arteriolar parameters, providing evidence of an impact of blood pressure on the microcirculation during pregnancy and further insights into physiological and hemodynamic changes during pregnancy. Our further prospective studies will look at the relationships between retinal microcirculation and gestational complications among Growing Up in Singapore Towards Healthy Outcomes participants who develop preeclampsia or eclampsia to determine whether retinal photography may allow for the prediction of major gestational complications.

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Disclosures
None.

References
Novelty and Significance

What Is New?
● To our best knowledge, this is the first comprehensive study to examine the relationship between maternal blood pressure and retinal microvasculature in pregnant women.

What Is Relevant?
● In our study, elevated blood pressure was associated with a range of adverse retinal microvascular signs, which have been suggested to be present in patients with hypertension. Thus, retinal microcirculation during pregnancy might carry the predictive value for future occurrence of gestational hypertensive disorders.

Summary
Our study shows that elevated blood pressure is associated with a range of adverse retinal arteriolar parameters, providing evidence of a physiological impact of blood pressure on the microcirculation during pregnancy.
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