Fetal Hemodynamic Adaptive Changes Related to Intrauterine Growth
The Generation R Study

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Background—It has been suggested that an adverse fetal environment increases susceptibility to hypertension and cardiovascular disease in adult life. This increased risk may result from suboptimal development of the heart and main arteries in utero and from adaptive cardiovascular changes in conditions of reduced fetal growth. The aim of the present study was to evaluate whether reduced fetal growth is associated with fetal circulatory changes and cardiac dysfunction.

Methods and Results—This study was embedded in a population-based, prospective cohort study starting in early fetal life. Fetal growth characteristics and fetal circulation variables were assessed with ultrasound and Doppler examinations in 1215 healthy women. The fetal circulation was examined in relation to estimated fetal weight. Higher placental resistance indices were strongly associated with decreased fetal growth. Cerebral resistance showed a gradual decline with reduced fetal growth. Cardiac output, peak systolic velocity of the outflow tracts, and cardiac compliance showed a gradual reduction with diminished fetal growth, whereas intraventricular pressure gradually increased.

Conclusions—Decreased fetal growth is associated with adaptive fetal cardiovascular changes. Cardiac remodeling and cardiac output changes are consistent with a gradual increase in afterload and compromised arterial compliance in conditions of decreased fetal growth. These changes have already begun to occur before the stage of clinically apparent fetal growth restriction and may contribute to the increased risk of cardiovascular disease in later life. (Circulation. 2008;117:649-659.)

Key Words: physiology ■ circulation, fetoplacental ■ fetal development ■ epidemiology ■ echocardiography ■ cardiovascular diseases

Epidemiological studies have demonstrated fetal growth restriction and low birth weight to be risk factors that contribute to cardiovascular disease and hypertension in adult life.1–3 This increased risk may result from suboptimal development of the fetal heart and main arteries in utero and from adaptive cardiovascular changes in fetal growth restriction.4 This hypothesis is supported by studies in fetal and postnatal life that found lower cardiac compliance and increased arterial stiffness in subjects with fetal growth restriction. These adaptations may predispose individuals to an increased risk of hypertension and ventricular hypertrophy in later life.5–9 Cardiovascular changes due to fetal growth restriction might already be present in fetal life. To the best of our knowledge, no population-based prospective studies exist that relate fetal growth characteristics to cardiovascular function in fetal life.

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Frequently, fetal growth restriction is a consequence of impaired placental perfusion or placental insufficiency.10 In response to general fetal malnutrition due to placental insufficiency or other factors such as smoking or maternal nutrient restriction, blood flow is preferential to the brain and heart, which deprives other organs of adequate oxygen and an adequate supply of nutrients. The increased blood flow to the brain is caused by vasodilation in the brain, which results in a lower peripheral resistance (“brain-sparing effect”).11 This is part of the phenomenon known as fetal redistribution. Evidence of redistribution or centralization of the arterial circulation with fetal cardiac output in favor of the left ventricle has been described in compromised, small-for-gestational-age fetuses.12,13 These hemodynamic changes are quantifiable by Doppler measurements of the fetal and
placental circulation and are associated with increased perinatal mortality, low birth weight, and hypoxia.\textsuperscript{14–16} Therefore, Doppler surveillance of the fetal circulation represents an important tool for management of the growth-restricted fetus and provides information about fetal circulation characteristics.\textsuperscript{17,18}

Traditionally, a fetus is considered growth restricted when fetal abdominal circumference or estimated fetal weight is below the 10th percentile; however, this state of overt fetal growth restriction is preceded by a period of diminished fetal growth within the normal estimated fetal weight range. Not much is known about adaptive hemodynamic mechanisms during this stage of reduced fetal growth. Knowledge of changes that occur in the fetal circulation before overt fetal growth restriction may improve our understanding of compensatory adaptive fetal mechanisms in response to an adverse fetal environment. Furthermore, adaptations of the fetal circulation that precede fetal growth restriction could elucidate the pathophysiological pathways responsible for the increased susceptibility of subjects with fetal growth restriction to hypertension and cardiovascular disease in adult life. The aim of the present study was to evaluate whether reduced fetal growth is associated with adaptive fetal cardiovascular changes.

**Methods**

**Design**

This study was embedded in the Generation R Study, a population-based, prospective cohort study from fetal life until young adulthood. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development, and health from fetal life until young adulthood and has been described previously in detail.\textsuperscript{19,20} Briefly, the cohort includes 9778 mothers and their children of different ethnicities living in Rotterdam, the Netherlands. Enrollment was aimed for early pregnancy (gestational age <18 weeks) but was allowed until the birth of the child. Mothers were informed about the study by routine healthcare workers in pregnancy (midwives and obstetricians) and were enrolled in the study at their routine prenatal ultrasound examination. A vast majority of mothers (69%) were enrolled early in their pregnancies.\textsuperscript{20} Assessments during pregnancy included physical examinations, fetal ultrasounds, biological samples, and questionnaires and were planned in early (gestational age <18 weeks), mid (gestational age 18 to 25 weeks), and late (gestational age >25 weeks) pregnancy to collect information about fetal growth and its main determinants. Maternal smoking habits were assessed by questionnaire in early, mid, and late pregnancy. We categorized smoking habits during pregnancy as “nonsmoking” and “smoking.” Mothers who never smoked during pregnancy or who quit smoking immediately after they knew they were pregnant were classified as nonsmoking. Mothers who reported smoking in early, mid, and/or late pregnancy were categorized as smoking. The children were born between April 2002 and January 2006 and form a prenatally recruited birth cohort that is currently being followed up until young adulthood. In total, 65% of all eligible children in the study area participated at birth. Additionally, more detailed assessments of fetal growth and development were conducted in a subgroup of 1232 Dutch mothers and children, referred to as the Generation R Focus Study. Of all women approached for participation, 80% were enrolled in this subgroup in late pregnancy. This subgroup is ethnically homogeneous to exclude possible confounding or effect modification by ethnicity. For the present study, fetal circulation variables were assessed in this subset between 28 and 34 weeks of gestation. Written informed consent was obtained from all participants. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam.

**Population for Analysis**

In total, 1232 women were enrolled in the Generation R Focus Study in late pregnancy. All of these women were already participating in the Generation R Study from early pregnancy. Twin pregnancies (n=15) and pregnancies that led to perinatal death (n=2) were excluded from the analysis. No major cardiac anomalies were present other than small ventricular septum defects (n=3). The present analysis was performed in a total of 1215 subjects.

**Ultrasound Measurements**

**Fetal Biometry**

Routine ultrasound examinations were performed in the entire Generation R cohort in a research setting at a regional health facility in the center of Rotterdam in early, mid, and late pregnancy. These fetal ultrasound procedures were used both to establish gestational age and to assess fetal growth characteristics.\textsuperscript{21} Estimated fetal weight was calculated with the formula by Hadlock et al,\textsuperscript{22} which used head circumference, abdominal circumference, and femur length. For the present study, only late-pregnancy measurements were used in the analysis.

**Fetal Circulation**

Fetal circulation variables were assessed by pulsed-wave Doppler between 28 and 34 weeks’ gestation in the Generation R Focus Group, obtained once in each participant. For all Doppler measurements, color imaging was used to optimize placement of the pulsed-wave Doppler gate. The insonation angle was kept as close to 0° as possible and always below 20°. The sample volume was adjusted to cover the entire vessel. For each measurement, 3 consecutive uniform waveforms were recorded by pulsed Doppler ultrasound, during fetal apnea and without fetal movement. The mean of 3 measurements was used for further analysis. Three experienced sonographers performed all measurements.

To entirely appreciate all aspects of the fetal circulation, one should integrate Doppler measurement in different vascular beds.\textsuperscript{18} Placental vascular resistance was evaluated with recorded flow-velocity waveforms from the umbilical and uterine arteries. A raised umbilical artery pulsatility index (PI) and uterine artery resistance index (RI) indicate increased placental resistance.\textsuperscript{20} Umbilical artery PI was measured in a free-floating loop of the umbilical cord. Uterine artery RI was measured in the uterine arteries near the crossover with the external iliac artery. Umbilical vein diameter was derived from a cross section of a free-floating loop of the umbilical cord, with the mean of 3 tracings of the inner edge of the vessel. Volume flow was determined online with the inner diameter and by placing the sample volume over the entire venous vessel, parallel to the ultrasound beam with maximal time-averaged velocity.\textsuperscript{18} Umbilical vein volume flow (in milliliters per minute) was used for the analysis, and the volume flow per kilogram of fetal weight was calculated as well.

The redistribution of blood flow in favor of the fetal brain was quantified by the middle and anterior cerebral artery PI. Reductions in middle and anterior cerebral artery PI are valid indicators of the brain-sparing effect and fetal redistribution.\textsuperscript{11,12,24} Middle and anterior cerebral artery Doppler measurements were performed with color Doppler visualization of the circle of Willis in the fetal brain, and flow-velocity waveforms were obtained in the proximal part of the cerebral arteries.

Cardiac flow-velocity waveforms at the level of the mitral and tricuspid valves were recorded from the apical 4-chamber view of the fetal heart, with the sample volume placed just below the atrioventricular valves. Color Doppler visualization of the blood flow allowed us to align the Doppler beam in the direction of the blood flow. Peak velocities of the E wave, which represents early passive ventricular filling, and the A wave, which represents active atrial contraction filling, were recorded. The E/A ratio, which is an index for ventricular diastolic function and expresses both cardiac compliance and preload conditions, was calculated. Cardiac outflow flow-velocity waveforms from the aorta and pulmonary artery were recorded from the 5-chamber view and the short-axis view of the
fetal heart just above the semilunar valves, respectively. Peak systolic velocity (PSV), time-velocity integral, fetal heart rate, and the inner diameter during systole of both arteries were recorded. Left- and right-sided cardiac output were calculated in milliliters per minute by multiplying the vessel area by the time-velocity integral by fetal heart rate. Combined cardiac output was calculated by summing the left and right ventricular output. Weight-adjusted cardiac output was determined (cardiac output/estimated fetal weight).

Flow assessment at the level of the ductus venosus was performed in either a transversal or a parasagittal oblique scanning plane of the fetal abdomen immediately after the origin of the ductus from the umbilical vein. The venous pulsatility index (PIV) was used to assess atrial contraction and preload conditions. To assess reproducibility of ultrasound measurements, the intraclass correlation coefficient and coefficient of variation between and among observers were calculated in 12 subjects for various Doppler measurements. One observer performed the measurements; subsequently, the other observer did the same, after which the first examiner repeated the process. The sonographers left the ultrasound room during each other’s assessment and were blinded to the measurements on the screen and printouts. The intraclass correlation coefficient measures the strength of the agreement between the 2 sets of measurements, and the coefficient of variation is the ratio of the SD to the mean. Table 1 shows results of the intraobserver and interobserver variability analysis. The results show high intraclass correlation coefficient values (>0.80) with corresponding low coefficient of variation values (<10%), which indicates adequate reproducibility for all Doppler measurements. All ultrasound examinations were performed with an ATL-Philips model HDI 5000 (Seattle, Wash) equipped with a 5.0-MHz high-frequency, curved-array transducer.

Statistical Analysis
Characteristics of boys and girls were compared by use of the independent-samples t test if the measurement was normally distributed. If it was skewed, the Mann–Whitney U test was used. Left-versus right-heart performance and measurements were compared with the paired-samples t test.

Gestational age–adjusted SD scores, which are equivalent to a z score, were developed for estimated fetal weight. Fetal weight was categorized in 10 groups according to deciles of SDs of estimated fetal weight that indicated fetuses that were small (group 1) to large (group 10) for gestational age. The means for fetal circulation measurements of these groups were plotted to visualize differences over the range of fetuses from small to large for gestational age. We compared the distribution of the characteristics of gestational age, fetal gender, and maternal smoking across deciles of fetal weight using tests for trend.

Table 1. Intraobserver and Interobserver Intraclass Correlation Coefficients and Coefficients of Variation

<table>
<thead>
<tr>
<th>Table 1. Intraobserver and Interobserver Intraclass Correlation Coefficients and Coefficients of Variation</th>
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<tr>
<td>Doppler Measurement</td>
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<td></td>
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<tr>
<td>Uterine artery</td>
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<td>Umbilical artery</td>
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<tr>
<td>Middle cerebral artery</td>
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<tr>
<td>Aorta ascendens</td>
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<tr>
<td>Mitral valve</td>
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<tr>
<td>Pulmonary artery</td>
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<tr>
<td>Ductus venosus</td>
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</table>

ICC indicates intraclass correlation coefficient; CV, coefficient of variation.

Results
Characteristics of the study population are presented in Table 2. The percentage of boys was 51%. The mean gestational age at the time of the measurements was 30.4 weeks. Estimated fetal weight and birth weight were higher in boys than in girls. Umbilical artery PI, pulmonary artery PSV, and fetal heart rate were lower in boys than in girls, whereas umbilical vein diameter, aortic diameter, and ductus venosus PIV were larger in boys.

Table 3 presents cardiac measurements for the left and right ventricle and outflow tracts. Pulmonary diameter, right cardiac output, and E-wave and A-wave velocities of the right ventricle were larger than on the left side of the heart. PSV and time-velocity integral were larger in the aorta than in the pulmonary artery. E/A ratio was the same in the left and right ventricles. Right-heart dominance existed, with a right/left cardiac output ratio of 1.38.

Figures 1 through 4 show the means of the fetal circulation Doppler measurements depicted per SD decile of estimated fetal weight, ranging from small (group 1) to large (group 10) for gestational age. Gestational age and fetal gender were evenly distributed among the groups; however, maternal smoking was more common in the small-for-gestational-age groups. The values of the mean circulation measurements per decile of estimated fetal weight did not change materially after adjustment for smoking. Probability values in the figures represent the
probability values for the regression coefficients given in Table 4, adjusted for fetal gender and maternal smoking.

Figure 1 depicts placental resistance and venous return measurements in relation to estimated fetal weight. Placental resistance increased with decreasing fetal weight, with lower umbilical vein volume flow in smaller fetuses. Ductus venous PIV did not change with increasing estimated fetal weight.

Figure 2 shows the cerebral circulation variables. Middle cerebral artery PSV and anterior cerebral artery PI gradually decreased with diminished fetal growth. Middle cerebral artery PI showed no association with estimated fetal weight, although the group with the smallest fetuses for gestational age displayed a significantly lower PI than the other fetuses.

In Figure 3A and 3B, cardiac performance measurements are illustrated. Both left and right cardiac outflow PSV, time-velocity integral, and cardiac output decreased with reduced fetal growth, as did combined cardiac output. The right cardiac output/left cardiac output ratio remained constant. Transmural E-wave velocity decreased with diminished fetal growth. A-wave velocity was reduced with decreased fetal growth for both atrioventricular valves. E/A ratio was constant for both atrioventricular valves.

The main finding of this study is that fetal hemodynamic patterns have already begun to change in the presence of reduced fetal growth while the fetus is still within the normal estimated fetal weight range. Placental resistance indices, including PSV of the outflow tracts, were positively associated with estimated fetal weight. Similarly, umbilical vein volume flow, anterior cerebral artery PI, and middle cerebral artery PSV were positively associated with estimated fetal weight.

In the present study population, 162 mothers (13.3%) smoked during pregnancy. Smoking during pregnancy significantly reduced estimated fetal weight at the time of the measurements by an average of 76 g (95% CI 33 to 120 g) and reduced birth weight by an average of 192 g (95% CI 102 to 283 g). Smoking resulted in mean increases of the umbilical artery PI and middle cerebral artery PI of 0.03 (95% CI 0.01 to 0.06) and 0.07 (95% CI 0.02 to 0.13), respectively.

Formulas for the relationship between gestational age (28 to 34 weeks) and fetal circulation measurements are presented in Table I of the Appendix in the online-only Data Supplement. Scatterplots of individual measurements for fetal circulation variables against gestational age, with 5th and 95th percentiles, are shown in Figure IA through ID in the Appendix in the online-only Data Supplement.

Discussion

The main finding of this study is that fetal hemodynamic patterns have already begun to change in the presence of reduced fetal growth while the fetus is still within the normal estimated fetal weight range. Placental resistance indices were increased and cerebral resistance was decreased in smaller fetuses. Cardiac output and cardiac performance measurements were consistent with higher afterload and

Table 3. Descriptive Statistics of Cardiac Measurements, Left Versus Right Heart

<table>
<thead>
<tr>
<th>Cardiac Measurement</th>
<th>Aorta Ascendens/Mitral Valve</th>
<th>Pulmonary Artery/Tricuspid Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter outflow tract, cm</td>
<td>0.64 (0.07)</td>
<td>0.79 (0.08)*</td>
</tr>
<tr>
<td>PSV outflow, cm/s</td>
<td>91.3 (12.4)</td>
<td>73.6 (9.5)*</td>
</tr>
<tr>
<td>TVI outflow</td>
<td>13.3 (2.0)</td>
<td>12.1 (1.8)*</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>606 (175)</td>
<td>837 (248)*</td>
</tr>
<tr>
<td>% of Total cardiac output</td>
<td>42 (0.06)</td>
<td>58 (0.06)*</td>
</tr>
<tr>
<td>E wave, cm/s</td>
<td>40.0 (6.3)</td>
<td>43.0 (5.8)*</td>
</tr>
<tr>
<td>A wave, cm/s</td>
<td>51.6 (8.0)</td>
<td>55.8 (7.9)*</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.78 (0.10)</td>
<td>0.78 (0.08)</td>
</tr>
</tbody>
</table>

Values are mean (SD). Differences between left and right sides of the heart were compared with the paired samples t test. TVI indicates time-velocity integral.

*P<0.01.
decreased vascular compliance in diminished fetal growth. Reduced cardiac compliance was found mainly on the left side of the heart with decreased fetal growth. Higher end-diastolic ventricular filling pressure was present in reduced fetal growth.

The main strength of the present study is the prospective design from early fetal life within a large population-based cohort. Of all mothers of the Generation R Study who were approached for the detailed subgroup, 80% participated in the focus study. Nonparticipation was mainly due to lack of time. No differences in offspring birth weight and maternal characteristics were found between mothers participating and not participating in the present study. To the best of our knowledge, this is the largest population-based cohort study in which fetal circulation variables in late pregnancy were established. The population-based setting enabled us to assess fetal circulation physiology in an unbiased manner over the entire range of estimated fetal weight, rather than only in fetuses with growth restriction or other complications.

Placental Circulation
Inadequate placental perfusion is an important cause of fetal growth restriction, with a higher risk of adverse fetal outcome. The present results support the notion that increased placental impedance is highly associated with decreased fetal growth and reduced umbilical vein volume flow. Reduced umbilical venous volume flow is associated with and might precede fetal growth restriction and the occurrence of adverse Doppler measurements in other parts of the fetal circulation.

Cerebral Circulation
The presence of blood flow redistribution can be detected by demonstrating the brain-sparing phenomenon. This has been described to precede fetal deterioration and hypoxemia. However, the present study provides evidence that this is an adaptive process that may already exist in conditions of suboptimal fetal growth. Anterior cerebral artery PI gradually decreased, which suggests that continuous remodeling takes place for the anterior cerebral artery that results in optimized cerebral perfusion in diminished
fetal growth. We found a decrease in middle cerebral artery PI in the smallest fetuses only. This might indicate that it is a late sign of cerebral redistribution that could predict fetal compromise. Middle cerebral artery PI has been described to be a poor prognostic factor alone and performs better in combination with the umbilical artery PI, the cerebroumbilical ratio.29 The present study suggests that the anterior cerebral artery PI might perform better to describe the brain-sparing effect. The finding of a lower PSV in the middle cerebral artery with declining fetal growth may directly reflect the lower PSV in the cardiac outflow tracts in smaller fetuses. Alternatively, it may be caused by decreased vascular compliance at the level of the cerebral arteries.

Cardiac Circulation

Increased right ventricular afterload resulting from high impedance to flow in the fetoplacental vascular bed and decreased left ventricular afterload resulting from cerebral vasodilation are suggested to cause redistribution of cardiac output in favor of the left ventricle.12,13 In the present study, however, we did not see any change in the cardiac output ratio with decreasing fetal growth. A consequence of the existence of the parallel disposition of the 2 ventricles with shunts is that they share the same systemic ejection pressure. The function of the aortic isthmus as a watershed and a regulator between the cerebral and placental circulation has already been highlighted.30 With the shunts in operation, the fetal heart appears to be a very adaptive organ that plays a crucial role in stabilizing cardiac output in the normally developing fetus. Thus, changes in cardiac distribution did not appear to take place in conditions of suboptimal fetal growth in the present study, despite increased placental impedance and decreased cerebral resistance.

PSVs in the cardiac outflow tracts showed a gradual decrease with declining fetal growth. Lower PSVs of the cardiac outflow tracts may indicate reduced cardiac function or raised afterload. A progressive decrease of PSV in the cardiac outflow tracts has been observed in growth-restricted fetuses.31,32 Lower PSVs do not necessarily reflect poor ventricular function but may reflect a physiological adapta-
Figure 3. A, Mean cardiac performance measurements at the level of the outflow tracts with estimated fetal weight ranging from small (group 1) to large (group 10) for gestational age. B, Mean cardiac performance measurements at the level of the atrioventricular valves with estimated fetal weight ranging from small (group 1) to large (group 10) for gestational age.
tion to a higher afterload or decreased vascular compliance. This is supported by findings of lower PSVs in the outflow tracts in the presence of increased afterload.33

Decreased total cardiac output is described in other studies to suggest deterioration of cardiac function in compromised fetuses.31,34 Cardiac output declined with decreasing fetal growth in the present study. This is consistent with increasing afterload or decreased contractility. The gradual decline in left and right cardiac output in reduced fetal growth within the normal range supports the hypothesis that this is due to increased afterload. A deterioration of cardiac function is unlikely and not supported by our finding of normal preload conditions.

Figure 4. Mean cardiac output and umbilical vein volume flow per kilogram of estimated fetal weight, with estimated fetal weight ranging from small (group 1) to large (group 10) for gestational age.

Table 4. Regression Coefficients of Estimated Fetal Weight With Circulation Variables

<table>
<thead>
<tr>
<th>No. (%) of Total</th>
<th>Regression Coefficient (95% CI)</th>
<th>Standardized β-Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doppler measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine artery RI</td>
<td>1155 (95)</td>
<td>-0.008 (-0.013, -0.004)†</td>
</tr>
<tr>
<td>Umbilical artery RI</td>
<td>1191 (98)</td>
<td>-0.02 (-0.029, -0.010)†</td>
</tr>
<tr>
<td>Umbilical vein volume flow</td>
<td>1052 (95)</td>
<td>13.6 [9.8, 17.4]†</td>
</tr>
<tr>
<td>Middle cerebral artery RI</td>
<td>1165 (96)</td>
<td>0.019 (-0.001, 0.039)</td>
</tr>
<tr>
<td>Middle cerebral artery PSV</td>
<td>1166 (96)</td>
<td>0.87 (0.39, 1.35)†</td>
</tr>
<tr>
<td>Anterior cerebral artery RI</td>
<td>1061 (87)</td>
<td>0.02 (0.000, 0.037)*</td>
</tr>
<tr>
<td>Ductus venosus PV</td>
<td>1087 (89)</td>
<td>-0.001 (-0.012, 0.010)</td>
</tr>
<tr>
<td>Cardiac measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta ascendens PSV</td>
<td>1062 (87)</td>
<td>1.35 (0.56, 2.13)†</td>
</tr>
<tr>
<td>Left cardiac output, mL/min</td>
<td>1038 (85)</td>
<td>33.4 (22.4, 44.3)†</td>
</tr>
<tr>
<td>Pulmonary artery PSV</td>
<td>1046 (86)</td>
<td>1.07 (0.46, 1.67)†</td>
</tr>
<tr>
<td>Right cardiac output, mL/min</td>
<td>1017 (83)</td>
<td>46.9 (31.3, 62.6)†</td>
</tr>
<tr>
<td>Combined cardiac output, mL/min</td>
<td>985 (81)</td>
<td>82.3 (58.0, 106.6)†</td>
</tr>
<tr>
<td>Ratio left/right cardiac output</td>
<td>975 (80)</td>
<td>0.002 (-0.010, 0.014)</td>
</tr>
<tr>
<td>Mitral valve E wave</td>
<td>1152 (95)</td>
<td>0.75 (0.38, 1.12)†</td>
</tr>
<tr>
<td>Mitral valve A wave</td>
<td>1152 (95)</td>
<td>1.10 (0.63, 1.57)†</td>
</tr>
<tr>
<td>Mitral valve E/A ratio</td>
<td>1165 (96)</td>
<td>-0.003 (-0.009, 0.003)</td>
</tr>
<tr>
<td>Tricuspid valve E wave</td>
<td>1126 (93)</td>
<td>0.29 (-0.06, 0.64)</td>
</tr>
<tr>
<td>Tricuspid valve A wave</td>
<td>1126 (93)</td>
<td>0.58 (0.11, 1.06)*</td>
</tr>
<tr>
<td>Tricuspid valve E/A ratio</td>
<td>1135 (93)</td>
<td>-0.003 (-0.008, 0.002)</td>
</tr>
</tbody>
</table>

Values are regression coefficients (95% CI) or standardized β-coefficients and reflect the difference in cardiovascular measurement per unit increase in gestational age-adjusted SDs of estimated fetal weight. Models additionally adjusted for fetal gender and maternal smoking.

*P<0.05, †P<0.01.
Pulse-wave velocity has been studied in small-for-gestational-age fetuses. They appear to have a lower pulse-wave velocity, possibly caused by stiffer arteries with decreased vessel-wall pulsations. The pulse-wave velocity correlates with mean blood pressure and is associated with the PSVs of the cardiac outflow tracts. The present finding that cardiac output and PSV are reduced in fetuses with suboptimal fetal growth is consistent with decreased pulse-wave velocity in small fetuses and suggests increased afterload with raised mean arterial pressure.

Diastolic left ventricular performance in reduced fetal growth was characterized by lower transmural E-wave velocities, which suggests decreased ventricular compliance. This was not observed, however, at the level of the tricuspid valve. This could indicate that maturational changes of the diastolic filling properties of the fetal heart are less efficient in reduced fetal growth, resulting in decreased left ventricular compliance.

A-wave velocities for both atrioventricular valves decreased with declining fetal growth. This implies a gradual increase in ventricular end-diastolic pressure with decreasing fetal growth. Cardiac diastolic function differs in smaller fetuses, which suggests the existence of intracardiac hemodynamic changes. This is a gradual process, seen throughout the entire range of fetal growth. It has been proposed that the leading cause of ventricular remodeling in small-for-gestational-age fetuses is increased afterload, mainly due to increased placental vascular resistance.

Apart from modifications in afterload and ventricular compliance, cardiac hemodynamics are also altered by changes in preload. Diastolic dysfunction and filling properties at the level of the atrioventricular valves are illustrated by a lower E/A ratio in fetal growth restriction. Another study, however, described this to be constant in fetal compromise. In the present study, E/A ratios were constant over the estimated fetal weight ranges, which indicates no cardiac dysfunction in smaller fetuses and suggests that preload conditions had not changed. Even though venous return may be reduced in smaller fetuses, as shown by decreased umbilical vein volume flow, no effects were seen in ductus venosus PIV. We therefore presume the preload to be constant in these fetuses, with unaffected shunting through the ductus venosus, which supports the assumption that blood flow in the ductus venosus is maintained within normal ranges as long as possible.

Relative cardiac output and umbilical vein volume flow, which is the flow per unit of fetal weight, appeared to be increased in smaller fetuses. This tendency has been described previously and implies that cardiac output and umbilical vein volume flow in fetuses with decreased growth are reduced with regard to absolute values but increased relative to fetal size. This suggests some type of adaptation to a suboptimal environment in reduced fetal growth with a relative increase in cardiac output and umbilical vein volume flow to ensure adequate oxygen supply. Possible errors in fetal weight estimates can be larger in small or large fetuses because of a change in the volumetric proportion between head and abdomen. Volume flow indices per unit of estimated fetal weight should therefore be interpreted with caution.

It has been hypothesized that an adverse fetal environment and subsequent reduced fetal growth result in fetal blood flow redistribution and permanent fetal cardiovascular changes, such as increased arterial wall stiffness and left ventricular dysfunction. Studies in infants and adults have shown an association between small size at birth and increased arterial wall stiffness. Arterial compliance in fetal life may be influenced by a decrease in elastin deposition, a major determinant of stiffness, caused by changing hemodynamic conditions or abnormal pressure. Human elastin synthesis is at its maximum in the last weeks of pregnancy and decreases thereafter. Blood flow is an important hemodynamic stimulus for arterial wall development, and the finding of increased afterload and increased ventricular filling pressure may indicate that these phenomena may be involved in the association between reduced fetal growth and increased arterial wall stiffness. Arterial wall stiffness in adults is related to high blood pressure and has been recognized as an early marker of cardiovascular disease.

Furthermore, increased afterload and left ventricular dysfunction in fetuses with impaired growth could lead to permanent physiological and morphological changes of the left ventricle and predispose individuals to left ventricular hypertrophy. Fetuses with increased afterload have been described as showing signs of myocardial damage. Ventricular hypertrophy in children and adults is a known independent predictor of cardiovascular mortality.

Multiple stimuli have been identified as being capable of inducing fetal cardiac programming, including nutrient restriction, chronic hypoxia, and smoking. Smoking creates a state of chronic hypoxia due to carbon dioxide in the maternal bloodstream crossing the placenta and due to the vasoactive effects of nicotine. Increased umbilical and middle cerebral artery pulsatility indices indicate that smoking causes increased resistance in the vascular beds of the brain and the placenta. The latter may explain the reduction in estimated fetal weight. The effect of smoking might interfere with the brain-sparing effect in fetal growth restriction, because it increases peripheral resistance in the brain, whereas in the physiological situation, fetal growth restriction causes increased blood flow to the brain. This finding could indicate potential harm to brain development and merits further investigation. The smoking-related reduction in fetal cardiac output was mainly explained by differences in estimated fetal weight; thus, smoking during pregnancy did not appear to cause significant effects to cardiac function itself or to arterial compliance in the present study.

Cardiovascular performance in reduced fetal growth is consistent with an increase in afterload and increased end-diastolic ventricular filling pressure. Furthermore, cardiac and arterial compliance are compromised in diminished fetal growth. These adaptive fetal hemodynamic changes take place even before the stage of clinically apparent fetal growth restriction. These fetal circulation alterations may be part of the underlying associations between low birth weight and hypertension in adult life. Follow-up studies in the children in the present study are currently being performed to examine...
whether and to what extent changes in fetal circulation hemodynamics persist during childhood and whether they are related to cardiac function and blood pressure development in postnatal life.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

It has been suggested that an adverse human fetal environment increases susceptibility to hypertension and cardiovascular disease in adult life. This increased risk may result from suboptimal development of the heart and main arteries in utero and to adaptive cardiovascular changes in reduced fetal growth. In this population-based study, we found that cardiovascular performance in reduced fetal growth is consistent with an increase in afterload and increased end-diastolic ventricular filling pressure. Furthermore, cardiac and arterial compliance are compromised with diminished fetal growth. These adaptive fetal hemodynamic changes occur before the stage of clinically apparent fetal growth restriction. These fetal circulation alterations may contribute to intrauterine programming for adult cardiovascular disease. Follow-up studies in children in the present study are currently being performed to examine whether and to what extent changes in fetal circulation hemodynamics persist during childhood and whether they are related to cardiac function and blood pressure in later life. This may provide more insight into the origins of cardiovascular disease, perhaps allowing for the development of screening tests and customized fetal interventions.
Fetal Hemodynamic Adaptive Changes Related to Intrauterine Growth: The Generation R Study
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