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Original Contribution

Blood Pressure in Different Gestational Trimesters, Fetal Growth, and the Risk of Adverse Birth Outcomes

The Generation R Study

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Researchers have suggested that maternal hypertensive disorders during pregnancy affect fetal growth. The authors examined the associations between systolic and diastolic blood pressures in different trimesters of pregnancy and both repeatedly measured fetal growth characteristics and the risks of adverse birth outcomes. The present study (2001–2005) was performed in 8,623 women who were participating in a population-based prospective cohort study from fetal life onwards. Blood pressure and fetal growth characteristics were assessed in each trimester of pregnancy. Information on hypertensive complications and adverse birth outcomes was obtained from medical records. The results suggested that higher blood pressure was associated with smaller fetal head circumference and femur length, as well as lower fetal weight from the third trimester onward. An increase in blood pressure from the second trimester to the third trimester was associated with an increased risk of adverse birth outcomes. Compared with women who did not experience hypertension during pregnancy, women with preeclampsia had increased risks of having children who were preterm (odds ratio = 5.89, 95% confidence interval: 2.63, 13.14), had a low birth weight (odds ratio = 8.94, 95% confidence interval: 6.19, 12.90), or were small for their gestational age (odds ratio = 5.03, 95% confidence interval: 3.31, 7.62). The present results suggest that higher maternal blood pressure is associated with impaired fetal growth during the third trimester of pregnancy and increased risks of adverse birth outcomes.

blood pressure; fetal development; pregnancy; pregnancy outcome

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

Gestational hypertension and preeclampsia are the leading causes of maternal morbidity and adverse birth outcomes (1–3), and they occur in approximately 5%–6% of all pregnant women (4). The observed associations between preeclampsia and the risk of birth complications have been inconsistent. In some studies, researchers reported increased risks of delivering children who were preterm or small for their gestational age among women who developed gestational hypertension or preeclampsia (3, 5–7), whereas others reported increased risks of delivering children who were large for their gestational age among women with preeclampsia (8, 9).

Some have suggested that maternal blood pressure levels are associated with birth weight (10, 11). Waugh et al. (10) showed a significant inverse association between diastolic blood pressure in the third trimester and birth weight in women who had hypertension during pregnancy. Similar results were reported by Zhang et al. (11), who showed overall lower birth weight and increased risks of children with a birth weight less than 2,500 g and children who were small for their gestational age among pregnant women with diastolic blood pressure levels above 90 mm Hg. Furthermore, Steer et al. (12) found an inverse U-shaped association between diastolic blood pressure levels and birth weight in nonhypertensive pregnant women. Less is known about the associations between maternal blood pressure and fetal growth in different periods of pregnancy and the risk of adverse birth outcomes. This information might be important for identifying critical periods during pregnancy. Altered diastolic blood pressure levels, rather than systolic blood pressure levels, are believed to contribute to the development of preeclampsia (13). Also, systolic and diastolic blood pressures might reflect different cardiovascular adaptations and might affect fetal growth.

Therefore, in a population-based prospective cohort study of 8,623 pregnant women, we assessed the associations between systolic and diastolic blood pressures in different trimesters of pregnancy and both repeatedly measured fetal growth characteristics and the risks of adverse birth outcomes, including preterm birth, low birth weight, and small size for gestational age at birth. To identify critical periods of pregnancy during which blood pressure levels affect fetal growth and adverse birth outcomes, we performed analyses on the changes in blood pressure levels between trimesters of pregnancy. We also examined the associations between gestational hypertension and preeclampsia and differences in birth weight and the risks of adverse birth outcomes.

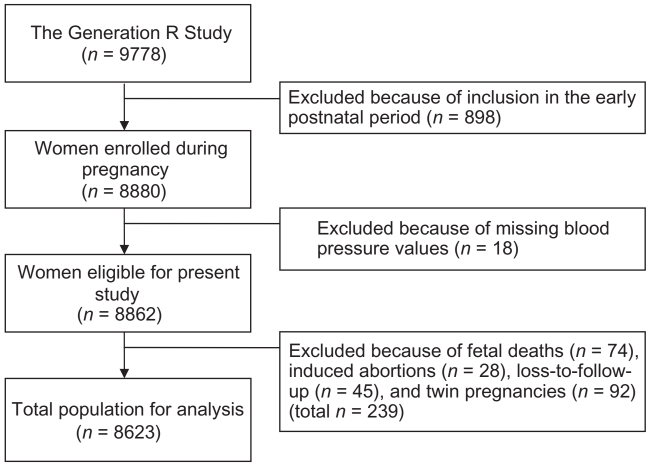

Figure 1. Flow chart of the population for analysis, the Generation R Study, 2001–2005.

MATERIALS AND METHODS

Study design

The present study was part of the Generation R Study, a population-based prospective cohort study from early pregnancy onwards in Rotterdam, the Netherlands (14, 15). The study has been approved by the medical ethical committee of the Erasmus Medical Center in Rotterdam. Written consent was obtained from all participating women. All pregnant women were enrolled during pregnancy between 2001 and 2005. Of all eligible children in the study area, 61% were enrolled in the study at birth (15). The Generation R Study is a prenatally recruited birth cohort study, and therefore the response percentage of the children at birth is reported. Assessments during pregnancy were planned in the first, second, and third trimesters. The individual timing of these assessments depended on the gestational age at enrollment. In total, 8,880 women were enrolled during pregnancy. In the present study, we excluded women for whom we did not have blood pressure measurements ($n = 18$), leaving 8,862 women. In addition, we excluded pregnancies that ended in fetal death ($n = 74$), induced abortions ($n = 28$), participants lost to follow-up ($n = 45$), and twin pregnancies ($n = 92$). Thus, the cohort for analysis comprised 8,623 women (Figure 1).

Blood pressure

Blood pressure was measured at our 2 dedicated research facilities using the Omron 907 automated digital oscillometric sphygmanometer (OMRON Healthcare Europe, Hoofddorp, the Netherlands), which has been validated for use in nonpregnant adults (16). All participants were seated in an upright position with back support and were asked to relax for 5 minutes. 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. For participants with upper arm circumferences exceeding 33 cm, a larger cuff (32–42 cm) was used. The mean value of 2 blood pressure readings over a 60-second interval was documented for each participant. In total, blood pressure was measured in 6,493 women in their first trimester of pregnancy (mean weeks of gestation = 13.2; range, 9.8–17.6), in 8,046 women in their second trimester (mean weeks of gestation = 20.4; range, 18.5–23.6), and in 8,119 women in their third trimester (mean weeks of gestation = 30.2; range, 28.4–32.9). There were 3, 2, and 1 blood pressure measurements available for 5,959, 2,120, and 544 women, respectively.

Gestational hypertensive complications

Information on gestational hypertensive complications was obtained from medical records. Data about women who were suspected of having hypertensive complications during pregnancy on the basis of these records were cross-checked with the original hospital charts (17). The women with no previous history of hypertension who had a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher were considered to have gestational hypertension. These criteria plus the presence of proteinuria (defined as 2 or more dipstick readings of 2 or greater, 1 catheter sample reading of 1 or greater, or a 24–hour urine collection containing at least 300 mg of protein) were used to identify women with preeclampsia (18).

Fetal growth

Fetal ultrasound examinations were carried out in 2 dedicated research centers in each trimester of pregnancy. We established gestational age by using data from the first-trimester fetal ultrasound examination (19). In the second and third trimesters of pregnancy, we measured parameters of fetal head circumference, abdominal circumference, and femur length to the nearest millimeter using standardized ultrasound procedures (20). Estimated fetal weight was subsequently calculated by using the formula of Hadlock et al. (21). Birth weight was obtained from medical records and hospital registries. Fetal growth measurements were available for 8,068 children in the second trimester and 8,235 children in the third trimester. Standard-deviation scores for all fetal growth characteristics were constructed from data from the study group (19).

Adverse birth outcomes

Information about offspring sex, gestational age, weight, length, and head circumference was obtained from medical records and hospital registries. Because head circumference and length at birth were not routinely measured, fewer measurements were available for these variables ($n = 4{,}538$ and $n = 5{,}361$, respectively). Gestational-age-adjusted standard-deviation scores for birth weight, length, and head circumference were constructed using growth standards defined by Niklasson et al. (22). Preterm birth was defined as a gestational age of less than 37 weeks at delivery. Because preterm delivery might be a treatment option for severe preeclampsia, analyses with preterm birth as the dependent variable were restricted to women who had had a spontaneous delivery. The term lower birth weight referred to a difference in absolute birth weight; low birth weight was defined as birth weight below 2,500 g. Small size for gestational age at birth was defined as a gestational-age-adjusted birth weight below the fifth percentile in the study cohort (less than 1.78 standard deviation (SD)).

Covariates

Information on maternal age (years), educational level (primary school, secondary school, or postsecondary education), ethnicity (European or non-European), parity (nulliparous or multiparous), and use of folic acid supplements (preconceptional use, first trimester use only, or no use) was obtained at enrollment. Information about smoking (none, first trimester only, or continued), alcohol consumption (none, first trimester only, or continued), and caffeine intake (none, <2 units/day, 2–5.9 units/day, or ≥ 6 units/day) was assessed by using questionnaires in each trimester. At enrollment, weight (kg) and height (cm) were measured when the women were without shoes and were wearing light clothing. Weight was repeatedly measured during subsequent visits at the research center. Maternal distress was measured by questionnaire at 20 weeks of gestation using the Brief Symptom Inventory (23). A higher index reflects a higher stress level.

Statistical analysis

First, the associations between maternal systolic and diastolic blood pressures in the second and third trimesters and fetal head circumference (second- and third-trimester head circumference and head circumference at birth), length (second- and third-trimester femur length and birth body length), and weight (second- and third-trimester estimated fetal weight and birth weight) were analyzed by using multiple linear regression models. Third-trimester blood pressure levels were used to assess the associations with growth measures at birth. To enable comparison of effect estimates, we used the standard-deviation scores of systolic and diastolic blood pressures as independent variables and the standard-deviation scores of each growth characteristic as dependent variables. We then assessed the associations between blood pressure change (first to second trimester, second to third trimester, and first to third trimester) and birth weight and the risks of adverse birth outcomes (preterm birth, low birth weight, and small size for gestational age at birth) by using multiple linear and logistic regression models. Both analyses were also performed with mean arterial pressure as the independent variable (24). Next, using similar models, we assessed the associations between maternal hypertensive disorders (gestational hypertension and preeclampsia) and birth weight and the risks of adverse birth outcomes. Models were adjusted for gestational age at blood pressure measurement, number of weeks between the measurements for analyses of blood pressure change between trimesters, maternal age, educational level, ethnicity, parity, folic acid supplement use, smoking habits, alcohol consumption, caffeine intake, weight, height, stress, and fetal sex. Finally, we analyzed the associations between the changes in blood pressure levels per trimester and between different trimesters and fetal growth characteristics using quartiles of blood pressure. The percentages of missing values within the population for analysis were lower than 15%, except for folic acid supplement use (26%) and maternal stress (24%). These higher percentages were due to the large number of women who only partially completed the questionnaire or who were not enrolled in their first trimester of pregnancy. We used multiple imputations for missing values in the covariates. Five imputed data sets were created and analyzed together. We included all covariates, plus gestational age at birth, gestational age at 20 weeks, gestational age at 30 weeks, and fetal sex in the imputation model. Furthermore, we added systolic and diastolic blood pressures in the first, second, and third trimesters and gestational hypertensive complication in the imputation model as prediction variables only; they were not imputed themselves. The pooled standard error was calculated using the average variance of the effect estimate between the imputed sets (variance of the 5 standard errors) and the variance of the imputed sets (variance of the 5 effect estimates) (25). The analyses were performed using the Statistical Package for the Social Sciences, version 17.0, for Windows (SPSS, Inc., Chicago, Illinois).

RESULTS

Tables 1 and 2 present the maternal and fetal characteristics of the participants included in the analyses. Of all pregnancies, 3.6% ($n = 311$) led to gestational hypertension and 2.0% ($n = 171$) led to preeclampsia. Of all children, 5.4% ($n = 433$) were born preterm and 4.8% ($n = 400$) were born with a low birth weight.

Figure 2 shows that maternal systolic and diastolic blood pressures were not associated with any second-trimester fetal-growth characteristics. Figure 2A shows that higher third-trimester systolic blood pressure and diastolic blood pressures were associated with smaller third-trimester fetal head circumference (SD, −0.03 (−0.39 mm), 95% confidence interval (CI): −0.06, −0.01, and SD, −0.03 (−0.39 mm), 95% CI: −0.05, 0, respectively, per 1-SD change in blood pressure) and that higher third-trimester diastolic blood

Table 1. Maternal Characteristics of Participants in the Generation R Study, 2001–2005 ($n = 8{,}623$)

Characteristic	Mean (SD)	%	Median (2.5th Percentile, 97.5th Percentile)
Age, years	29.6 (5.3)		
Height, cm	167.1 (7.4)		
Weight, kg	69.4 (13.2)		
Body mass index[a]	24.9 (4.5)		
Parity			
Nulliparous		57.1	
Multiparous		42.9	
Gestational age at intake, weeks			14.4 (10.4, 28.6)
Highest completed educational level			
Primary school		11.7	
Secondary school		46.4	
Postsecondary education		41.9	
Ethnicity			
European		57.5	
Non-European		42.5	
Maternal stress index			0.17 (0.00, 1.46)
Alcohol consumption			
None		49.8	
First trimester only		13.5	
Continued		36.7	
Smoking			
None		74.5	
First trimester only		8.3	
Continued		17.2	
Folic acid supplement use			
Preconceptional use		39.5	
Use in the first 10 weeks		31.1	
No use		29.4	

Table continues

pressure was associated with a smaller head circumference at birth (SD, −0.06 (−1.38 mm), 95% CI: −0.09, −0.02 per 1-SD change in diastolic blood pressure). Figure 2B shows that higher third-trimester diastolic blood pressure, but not systolic blood pressure, was associated with birth body length (SD, −0.04 (−1.12 mm), 95% CI: −0.08, 0 per 1-SD change in diastolic blood pressure). Figure 2C shows that higher third-trimester systolic blood pressure was not associated with a lower third-trimester estimated fetal weight but was associated with a lower birth weight (SD, −0.03 (−16.9 g), 95% CI: −0.06, 0 per 1-SD change in systolic blood pressure). Higher third-trimester diastolic blood pressure was associated with both a lower third-trimester estimated fetal weight and lower birth weight (SD, −0.03 (−8.0 g), 95% CI: −0.06, 0 and SD, −0.09 (−50.6 g), 95% CI: −0.12, −0.06, respectively, per 1-SD change in diastolic blood pressure).

For all fetal growth characteristics, we observed larger effect sizes for diastolic blood pressure than for systolic blood pressure. Also, the effect estimates for the associations between blood pressure and fetal growth characteristics tended to be larger at older gestational ages. Similar results were found for mean arterial pressure. (All effect estimates are given in Web Table 1, available at http://aje.oxfordjournals.org/.)

Table 3 shows that the first-to-second-trimester change in blood pressure was not associated with birth weight or the risk of adverse birth outcomes. A change in systolic blood pressure from the second trimester to the third trimester was associated with an increased risk of low birth weight (odds ratio (OR) = 1.25, 95% CI: 1.12, 1.40). Also, the change in diastolic blood pressure from the second trimester to the third trimester was associated with lower birth weight (SD, −11.24 g, 95% CI: −20.63, −1.86), increased risk of preterm delivery (OR = 1.26, 95% CI: 1.10, 1.44), low birth weight (OR = 1.49, 95% CI: 1.34, 1.67), and small size for gestational age at birth (OR = 1.12, 95% CI: 1.01, 1.24). For the change in mean arterial pressure from the second trimester to the third trimester, similar results were found for

Table 1. Continued

Characteristic	Mean (SD)	%	Median (2.5th Percentile, 97.5th Percentile)
Caffeine intake			
None		4.7	
<2 units/day		56.6	
2–5.9 units/day		37.3	
≥6 units/day		1.4	
First trimester			
Gestational age, weeks			13.2 (9.8, 17.6)
Systolic blood pressure, mm Hg	116 (12)		
Diastolic blood pressure, mm Hg	68 (10)		
Mean arterial pressure, mm Hg	84 (9)		
Second trimester			
Gestational age, weeks			20.4 (18.5, 23.6)
Systolic blood pressure, mm Hg	117 (12)		
Diastolic blood pressure, mm Hg	67 (9)		
Mean arterial pressure, mm Hg	84 (9)		
Third trimester			
Gestational age, weeks			30.2 (28.4, 32.9)
Systolic blood pressure, mm Hg	118 (12)		
Diastolic blood pressure, mm Hg	69 (9)		
Mean arterial pressure, mm Hg	85 (9)		
Gestational hypertension		3.6	
Preeclampsia		2.0	

[a] Weight (kg)/height (m)^2.

Table 2. Characteristics of Participants' Fetuses in the Generation R Study, 2001–2005 ($n = 8,623$)

Characteristic	Mean (SD)	%	Median (2.5th Percentile, 97.5th Percentile)
Second trimester			
Gestational age, weeks			20.4 (18.5, 23.6)
Head circumference, mm	180 (15)		
Femur length, mm	34 (4)		
Estimated fetal weight, g	382 (96)		
Third trimester			
Gestational age, weeks			30.2 (28.4, 32.9)
Head circumference, mm	285 (13)		
Femur length, mm	57 (3)		
Estimated fetal weight, g	1,616 (266)		
Birth			
Gestational age, weeks			40.1 (35.4, 42.3)
Head circumference, mm	350 (23)		
Length, mm	509 (28)		
Weight, g	3,411 (562)		
Male sex		50.3	
Preterm birth		5.4	
Low birth weight		4.8	

Abbreviation: SD, standard deviation.

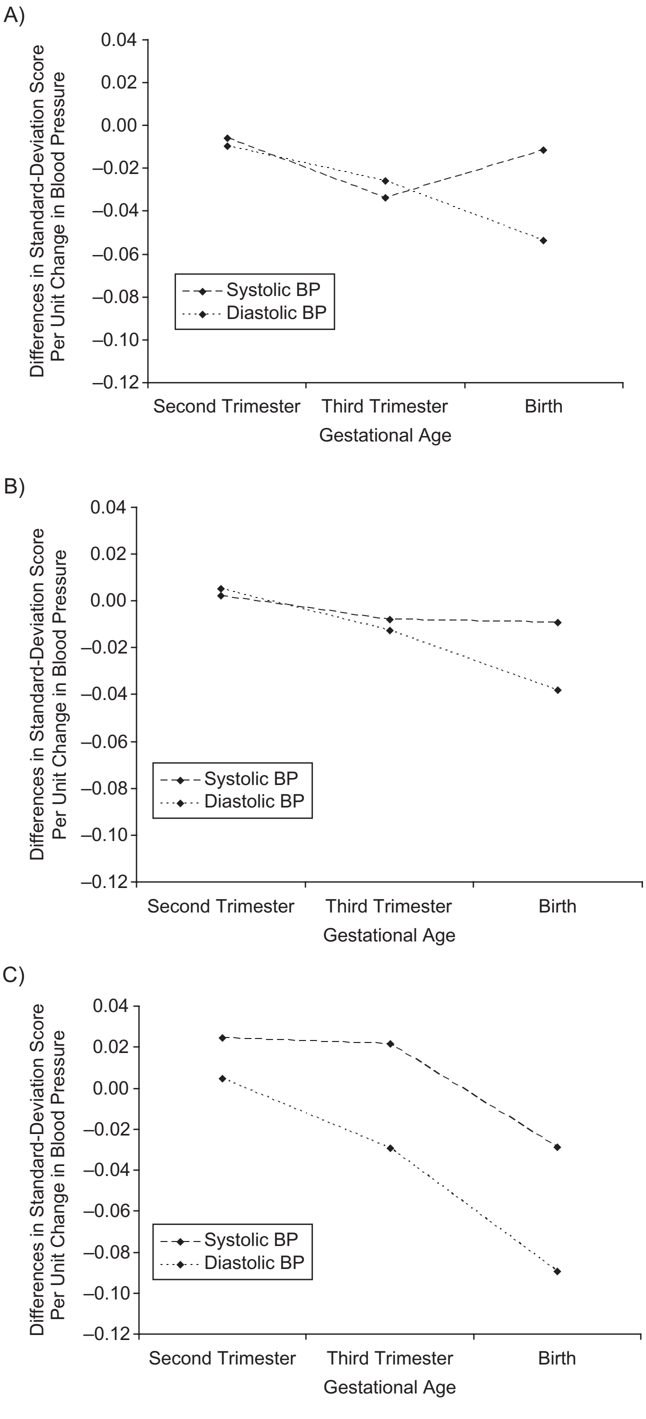

Figure 2. Associations of a 1-unit change in blood pressure (BP) with a longitudinally measured standard-deviation score for A) head circumference, B) length, and C) weight in the Generation R Study, 2001–2005. All results were adjusted for maternal age, gestational age at the visit, height, weight, ethnicity, educational level, parity, alcohol consumption, smoking habits, caffeine intake, folic acid supplement use, stress, and fetal sex. The reference value was a standard-deviation score of 0. Estimates are from multiply imputed data. The total number of measurements for head circumference was 7,880 in the second trimester, 7,998 in the third trimester, and 4,364 at birth. The total number of measurements for length was 7,903 in the second trimester, 8,066 in the third trimester, and 5,116 at birth. The total number of measurements for weight was 7,863 in the second trimester, 8,036 in the third trimester, and 8,070 at birth. A 1-standard-deviation change in systolic blood pressure from the first trimester to the second trimester, from the second trimester to the third trimester, and from the first trimester to the third trimester corresponds to change of 12 mm Hg. A 1-standard-deviation change in diastolic blood pressure from the first trimester to the second trimester and from the second trimester to the third trimester corresponds to a change of 9 mm Hg; from the first trimester to the third trimester, the change was 10 mm Hg. The effect estimates for fetal growth characteristics are given in Web Table 1.

preterm birth and low birth weight but not for small size for gestational age (Web Table 2).

Table 4 shows that, compared with women who did not develop hypertension while pregnant, women with gestational hypertension or preeclampsia delivered children with lower birth weights (−89 absolute grams, 95% CI: −137, −41 and −220 absolute grams, 95% CI: −294, −165, respectively). Accordingly, among pregnant women who developed preeclampsia, we observed increased risks of preterm delivery (OR = 5.89, 95% CI: 2.63, 13.14), having children with a low birth weight (OR = 8.94, 95% CI: 6.19, 12.90), and having children who were small for their gestational age at birth (OR = 5.03, 95% CI: 3.31, 7.62). Smaller increased risks of adverse birth outcomes were found in women who developed gestational hypertension; however, no differences in the risk of preterm delivery were found in comparison with nonhypertensive pregnancies.

Web Tables 3–6 give the results for the associations between change in blood pressure levels during pregnancy and fetal growth characteristics by quartile of blood pressure. The results showed only some marginal differences; however, the directions of the effect estimates were similar and therefore justified the linear approach used in our analyses.

DISCUSSION

We observed associations between higher maternal blood pressure and smaller fetal growth characteristics in the third trimester and at birth. Overall, stronger associations were observed for higher diastolic blood pressure levels and at older gestational ages. The change in blood pressure level from the second trimester to the third trimester was associated with an increased risk of adverse birth outcomes. Compared with women who did not become hypertensive during their pregnancies, women with either gestational hypertension or preeclampsia had increased risks of adverse birth outcomes.

Methodological considerations

One of the strengths of the present study was the prospective data collection, which started in early pregnancy. In addition, we had a large sample size of 8,623 participants with 22,658 blood pressure measurements. A wide range of potentially confounding factors was available. A potential limitation might be the response rate of 61% in this study. Pregnant women who participated were more highly educated, healthier, and more frequently of Dutch origin than

Table 3. Association Between Change in Blood Pressure Level During Pregnancy, Birth Weight, and the Risk of Adverse Birth Outcomes, the Generation R Study, 2001–2005[a,b]

Change in Blood Pressure[f]	Difference in Birth Weight, g[c]			Preterm Birth[d,e]				Low Birth Weight[d]				Small Size for Gestational Age[d]			
	No. of Participants[g]	β	95% CI	No. of Participants[g]	No. of Cases	OR	95% CI	No. of Participants[g]	No. of Cases	OR	95% CI	No. of Participants[g]	No. of Cases	OR	95% CI
Systolic blood pressure															
First–second trimester	6,160	6.75	−3.74, 17.25	3,993	185	1.04	0.90, 1.21	6,160	297	0.91	0.81, 1.02	6,151	318	0.95	0.85, 1.06
Second–third trimester	7,612	−1.18	−10.55, 8.19	4,983	214	1.09	0.95, 1.25	7,612	317	1.25**	1.12, 1.40	7,603	380	1.00	0.90, 1.11
First–third trimester	6,134	4.74	−5.74, 15.22	3,999	158	1.12	0.96, 1.32	6,134	254	1.13	0.99, 1.28	6,126	309	0.95	0.84, 1.06
Diastolic blood pressure															
First–second trimester	6,160	3.07	−7.44, 13.58	3,993	185	1.05	0.90, 1.22	6,160	297	0.91	0.81, 1.02	6,151	318	1.02	0.91, 1.14
Second–third trimester	7,612	−11.24*	−20.63, −1.86	4,983	214	1.26**	1.10, 1.44	7,612	317	1.49**	1.34, 1.67	7,603	380	1.12*	1.01, 1.24
First–third trimester	6,134	−11.13*	−21.64, −0.63	3,999	158	1.25**	1.06, 1.46	6,134	254	1.33**	1.18, 1.51	6,126	309	1.13*	1.01, 1.27

Abbreviations: CI, confidence interval; OR, odds ratio.

* $P < 0.05$; ** $P < 0.01$.

[a] Estimates were from multiply imputed data.

[b] Results were adjusted for gestational age at birth (only in birth-weight analyses), number of weeks between measurements, maternal age, educational level, ethnicity, parity, folic acid supplement use, smoking habits, alcohol consumption, caffeine intake, weight, height, stress, and fetal sex.

[c] Difference in birth weight per 1-standard-deviation change in blood pressure within the trimesters.

[d] Odds ratios for the risk of adverse birth outcomes per 1-standard-deviation change in blood pressure within the trimesters.

[e] Analyses of the risk of preterm birth were performed in a selection of participants who had spontaneous delivery.

[f] A 1-standard-deviation change in systolic blood pressure from the first trimester to the second trimester, the second trimester to the third trimester, and the first trimester to the third trimester corresponded to a change of 12 mm Hg. A 1-standard-deviation change in diastolic blood pressure from the first trimester to the second trimester and the second trimester to the third trimester corresponded to a change of 9 mm Hg; from the first trimester to the third trimester, the change was 10 mm Hg.

[g] Number of participants with available data.

Table 4. Association Between Maternal Hypertensive Disorders, Birth Weight, and the Risk of Adverse Birth Outcomes, Generation R Study, 2001–2005[a,b]

Blood Pressure Group	No. of Participants With Available Data	Difference in Birth Weight, g (n = 8,334)[c]		Preterm Birth (n = 5,499; n_{Cases} = 274)[d,e]			Low Birth Weight (n = 8,334; n_{Cases} = 400)[d]			Small Size for Gestational Age (n = 8,324; n_{Cases} = 424)[d]		
		β	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI	No. of Cases	OR	95% CI
Nonhypertensive women (n = 7,889)	7,857	Referent		255	Referent		330	Referent		364	Referent	
Women with gestational hypertension (n = 311)	310	−89**	−137, −41	10	1.42	0.72, 2.77	21	1.85*	1.15, 2.97	27	2.58**	1.67, 3.96
Women with preeclampsia (n = 171)	167	−220**	−294, −165	9	5.89**	2.63, 13.14	49	8.94**	6.19, 12.90	33	5.03**	3.31, 7.62

Abbreviations: CI, confidence interval; OR, odds ratio.

* $P < 0.05$; ** $P < 0.01$.

[a] Estimates are from multiply imputed data.

[b] Models were adjusted for gestational age at birth (only in birth weight analyses), maternal age, educational level, ethnicity, parity, folic acid supplement use, smoking habits, alcohol consumption, caffeine intake, weight, height, stress, and fetal sex.

[c] Differences in birth weight in different blood-pressure groups compared with the reference group of nonhypertensive pregnant women.

[d] Odds ratios that reflect the difference in risks of adverse birth outcomes in different blood-pressure groups compared with the reference group of nonhypertensive pregnant women.

[e] Analyses of the risk of preterm birth were performed in a selection of participants who had spontaneous delivery.

were those who did not participate (15). This might have led to selective participation. Selection bias occurs if participation depends on both the exposure (maternal blood pressure) and the outcomes (fetal growth and birth complications) (26). However, selection bias in follow-up studies primarily arises from loss to follow-up rather than from nonresponse at baseline because of the prospective nature of the study (27).

We aimed to take third-trimester blood pressure measurements around week 30 of gestation; therefore, few measurements were available in late pregnancy. Several different outcomes were studied: fetal growth characteristics, birth weight, preterm delivery, low birth weight, and small size for gestational age at birth. Because our results are not independent outcomes, we did not perform adjustment for multiple testing.

Blood pressure, gestational hypertensive complications, and fetal growth

To our knowledge, no previous studies have been performed to analyze blood pressure levels during pregnancy and fetal growth characteristics in different trimesters of pregnancy. Our results are comparable to those of the studies by Waugh et al. (10), Zhang et al. (11), and Churchill et al. (28). Furthermore, Steer et al. (12) showed that both diastolic blood pressure levels that were higher than average and diastolic blood pressure levels that were lower than average were associated with smaller offspring.

A change in diastolic blood pressure level, but not systolic blood pressure level, from the first trimester to the third trimester was associated with lower birth weight and increased risk of adverse birth outcomes. Among women who had systolic blood pressure levels that increased from the second trimester to the third trimester, we found an increased risk of having children with a low birth weight, whereas previous studies found associations with diastolic blood pressure levels only. After exclusion of women who were treated with medication for high blood pressure during pregnancy, only marginal differences in the effect estimates were found.

Although we have studied fetal growth and neonatal outcomes, a review by Cnossen et al. (29) suggested that mean arterial pressure is a better predictor of preeclampsia than are systolic and diastolic blood pressures in the first or second trimester and the change in blood pressure from the first trimester to the second trimester. This may also be the case for fetal growth outcomes. Therefore, we repeated our analyses with mean arterial pressure as the independent variable. Similar results were found for fetal growth and the risk of adverse birth outcomes.

A high diastolic blood pressure level (as opposed to systolic blood pressure level) is believed to be the main contributor to the development of preeclampsia (13). Our finding seems to be in line with this hypothesis. The increase in diastolic blood pressure from the first trimester to the third trimester was much smaller than the increase in systolic blood pressure, which is due to the midpregnancy fall in diastolic blood pressure. In nonhypertensive pregnant women, blood pressure, most notably diastolic blood pressure, falls steadily until the middle of gestation and then rises again until delivery (30). In women who develop preeclampsia, this midpregnancy fall in blood pressure does not occur; instead, blood pressure tends to remain stable during the first half of pregnancy and then rise continuously until delivery (30). Results from an observational study suggested that treatment of hypertensive disorders during early pregnancy may lower both the risks of severe maternal hypertensive complications later in pregnancy and the risk of preterm birth (31). However, the risk of fetal growth restriction may increase because of inadequate adjustment of therapy in response to changes in cardiac output or peripheral vascular resistance. On the other hand, Abalos et al. (32) reported less clear evidence of adverse associations of treatment of hypertension during pregnancy. Currently, the treatment of hypertensive complications should be managed carefully.

Most previous studies that focused on the associations of maternal hypertensive disorders during pregnancy with the risk of preterm birth did not restrict their analyses to spontaneous deliveries. In the present study, we did made this restriction, as the only effective cure for hypertensive disorders during pregnancy is delivery of the fetus. We observed increased risks of all adverse neonatal outcomes among women with hypertensive complications during pregnancy as compared with women in the nonhypertensive range. Similar results were found in previous studies (33–35).

Underlying mechanisms

The mechanisms by which maternal blood pressure levels can affect fetal growth are not yet clear. Higher blood pressure levels and intrauterine growth restriction may both be the result of placental dysfunction or adverse maternal cardiovascular adaptations to pregnancy. Tranquilli et al. (36) proposed that increased maternal blood pressure might be a consequence, rather than the cause, of fetal growth restriction. According to the authors, increased blood pressure levels during pregnancy could possibly compensate for inadequate placental perfusion. In nonhypertensive pregnant women with intrauterine growth restriction, significantly higher systolic and diastolic blood pressure levels were found. Increased blood pressure levels might affect the development of the placental villous tree and lead to reduced functional capacity of the placenta, which could lead to a reduction in fetal growth and thus lower birth weight (37). Our results do not explain the causal mechanisms between blood pressure levels and fetal growth. It might be that both blood pressure and fetal growth variation are markers of placental dysfunction.

Conclusions

Our results suggested that higher maternal blood pressure levels were associated with impaired fetal growth from the third trimester onward and increased risks of adverse birth outcomes. Gestational hypertension and preeclampsia were associated with strongly increased risks of preterm birth, low birth weight, and small size for gestational age at birth. The underlying mechanisms for these associations need to be identified.

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