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Prenatal and perinatal predictors of blood pressure at school age in former preterm, low birth weight infants

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Abstract

Objective—To investigate prenatal and perinatal determinants of school age blood pressure (BP) in former preterm, low birth weight infants

Study Design—We studied 694 participants in the Infant Health and Development Program, an 8-center longitudinal study of children born ≤37 weeks and ≤2500 grams. We obtained information about prenatal and perinatal factors by interview and medical record review and measured BP 3 times at age 6.5 years.

Result—Adjusting for sex, age, sociodemographic variables, and height z-score, for each z-score birth weight for gestational age – which represents fetal growth – systolic BP at 6.5 years was 0.7 mmHg higher (95% CI −0.1, 1.6). Maternal age, pre-pregnancy weight, gestational weight gain, smoking, preeclampsia, gestational diabetes; and child gestational age and neonatal complications were also not associated with BP.

Conclusion—In contrast to full term infants, slower fetal growth was not associated with higher BP in former preterm, low birth weight infants.

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CONFLICT OF INTEREST
None

INTRODUCTION

Compared with infants born full term, former preterm infants have higher blood pressure in adolescence and adulthood, with studies reporting systolic blood pressure 2.4 to 13 mmHg higher in former preterm infants compared with term born controls[1, 2, 3, 4, 5, 6, 7, 8, 9]. Identifying the determinants of higher blood pressure in this population may allow clinicians to identify which former preterm children and adults are at highest risk for developing hypertension and its sequelae later in life, and would also help elucidate the underlying mechanisms of fetal blood pressure programming.

In animal models of fetal growth restriction, growth restricted offspring develop sustained blood pressure elevation after birth[10], consistent with the biological phenomenon of developmental programming. In human populations born at or near term, investigators have found associations of fetal growth restriction – as represented by lower birth weight – with later blood pressure elevation[11], and have identified other prenatal determinants of higher blood pressure, including preeclampsia[12, 13, 14, 15, 16], other hypertensive disorders of pregnancy[17], and maternal smoking[18]. Little information exists regarding the extent to which these and other prenatal and perinatal factors influence later blood pressure in preterm populations.

The objective of our study was to examine associations of maternal and child prenatal and perinatal factors with systolic blood pressure at school age in a large sample of preterm, low birth weight infants.

MATERIALS/SUBJECTS AND METHODS

Study Design and Participants

We performed a secondary analysis of data from the Infant Health and Development Program (IHDP), an 8-center longitudinal study of 1080 infants born at ≤37 completed weeks gestation and ≤2500g that began in 1984 as a randomized trial of a post-discharge early child development intervention. Participants were enrolled in IHDP at the time of their newborn hospitalization. The methods of IHDP have been described elsewhere in detail[19]. The trial's primary outcomes related to cognitive development, behavior, and health status have been reported through 18 years of age[20, 21, 22]. Institutional review boards for all participating centers approved the study, and caregivers provided written informed consent.

Participants were eligible for this analysis if they were from one of the 7 IHDP study sites that conducted a clinical exam including blood pressure at age 6.5 years. Of the 931 eligible participants, 809 (87%) completed any part of the age 6.5 year exam and of these, 694 (86%) had any blood pressure data recorded. The main reason for missing blood pressure data was that the study visit was completed at a location other than the IHDP clinical site, such as by telephone or in the mother's home. All 694 participants had data for at least one predictor variable, so were included in the final sample for analysis.

Measurements

At the time of enrollment, study staff collected data regarding maternal and child health from the medical record including birth weight, gestational age, birth order, maternal age, and pregnancy and neonatal complications. Pregnancy complications including preeclampsia and other hypertensive disorders were recorded if they were noted in the medical record. Bronchopulmonary dysplasia was defined as requiring supplemental oxygen for >30 consecutive days or requiring ventilator therapy with chest x-ray findings consistent with the diagnosis. Mothers were interviewed regarding their weight (pre-conception and at delivery), smoking and alcohol intake during pregnancy, and socio-demographic factors.

When children were 6.5 years old, study staff followed a standardized protocol to measure resting blood pressure 3 times in the right arm by auscultation (n=164) or Dinamap automated oscillometric device (n=530). The correct cuff size was chosen based on the measured mid-arm circumference. Staff also recorded the participants' behavioral state at the time of blood pressure measurement as 'fully cooperative' or 'somewhat cooperative and fussy' and did not attempt to measure blood pressure if the participant or parent refused (n=2).

Analysis

Our primary outcome was the mean systolic blood pressure at age 6.5 years. Although systolic blood pressure predicts later outcomes better than diastolic blood pressure[23], we also examined mean diastolic blood pressure as a secondary outcome. Continuous predictors were maternal age, pre-pregnancy weight, and gestational weight gain; and child birth weight, gestational age, birth order, and fetal growth as represented by birth weight for gestational age z-score based on a national reference[24]. Categorical predictors were pregnancy and neonatal complications including preeclampsia and other hypertensive disorders, gestational diabetes, and bronchopulmonary dysplasia; fetal growth status, with small for gestational age (SGA) defined as birth weight for gestational age <10th percentile; and smoking and alcohol intake in pregnancy. We considered confounding by socio-demographic variables including maternal race/ethnicity, attained education level, and annual household income, all assessed at the time of study enrollment.

We used multivariable linear regression to examine associations of predictor variables with the mean systolic and diastolic blood pressure in mmHg at 6.5 years, adjusting all analyses for the exact age in days at the time of blood pressure measurement, measurement method (auscultation vs. automated), and the child's behavioral state at the time of measurement. In examining the effect of gestational weight gain on blood pressure, we additionally adjusted for gestational age at birth. We also adjusted estimates for sociodemographic variables and for height z-score at age 6.5 years, based on the Centers for Disease Control growth reference[25], because height is an important determinant of blood pressure and may be affected by prenatal and perinatal factors. Because IHDP included children born at a wide range of gestational ages, and to facilitate comparison with other published studies[3, 5, 26] that included only very preterm infants, we stratified our fetal growth analyses by gestational age category (<32 weeks vs. ≥32 weeks). We used SAS version 9.2 (SAS Institute Inc., Cary, NC) for all analyses.

RESULTS

Characteristics of the 694 children included in this analysis and their mothers are shown in Table 1. Median (range) birth weight was 1.87 (0.54, 2.50) kg and median (range) gestational age was 34 (25, 37) weeks. The median birth weight for gestational age z-score, which reflects fetal growth, was −1.1, showing that on average, fetal growth for this cohort was approximately 1 standard deviation (SD) below the median for a contemporary national reference population[24]. Using the same reference population, 39% of this cohort was small for gestational age (SGA), defined as having a birth weight for gestational age percentile <10. These characteristics were similar for the original IHDP cohort of 1080 children (data not shown). In comparison to the original IHDP cohort, mothers of children included in this analysis were somewhat more likely to be black (59% vs. 53%) and less likely to have a college degree (28% vs. 33%).

Table 2 shows associations of maternal and child variables with systolic blood pressure at 6.5 years. In model 1, estimates were adjusted for child age, sex, blood pressure measurement conditions, and sociodemographic variables. For each z-score increment in birth weight for gestational age, systolic blood pressure at age 6.5 years was 1.0 mmHg higher [95% confidence interval (CI) 0.2, 1.9]. Additional adjustment for height z-score at 7 years (model 2) attenuated this estimate (0.7 mmHg, 95% CI −0.1, 0.2). Children born SGA had systolic blood pressure 0.7 mmHg lower (95% CI −2.0, 0.6) than children born appropriate for gestational age (AGA). The presence of maternal hypertensive disorder was associated with higher systolic blood pressure in the child (3.5 mmHg, 95% CI 0.0, 7.0), but additional adjustment for maternal hypertensive disorder in the fetal growth models did not change the effect estimates, nor did adjustment for body mass index at 6.5 years (data not shown). None of the other maternal or child predictor variables was substantially associated with child systolic blood pressure (Table 2), nor was any predictor variable associated with diastolic blood pressure (data not shown). In analyses stratified by blood pressure method (auscultation or automated device), no statistically significant association of birth weight for gestational age z-score with child systolic blood pressure was identified for either method [for auscultation, 0.4 mmHg per z-score (95% CI −1.2, 1.9) and for automated device, 0.1 mmHg per z-score (95% CI −0.9, 1.1)]. Results were also similar between methods for other predictor variables.

Consistent with findings in the overall sample, in analyses stratified by gestational age category (<32 weeks vs. >=32 weeks), greater fetal growth was associated with somewhat higher systolic blood pressure in both gestational age categories (Table 3), though results did not reach statistical significance.

DISCUSSION

In full term populations, numerous authors have reported that lower birth weight is associated with higher blood pressure later in life[11], but the majority of those studies did not consider separate effects of gestational length and fetal growth – both determinants of birth weight – on later blood pressure. Studies in full term children suggest that SGA status at birth is a risk factor for later hypertension[27]. In contrast, our study, which included only children born preterm and low birth weight, found that fetal growth restriction was not associated with higher blood pressure. In fact, we found that poorer fetal growth was associated with slightly *lower* systolic blood pressure at school age, although the result was not statistically significant after adjustment for attained height.

A large study[26] of Dutch infants born at <32 weeks gestation and/or <1500 grams (very low birth weight, VLBW) also examined the association of fetal growth with later blood pressure. That population based study found no association of birth weight standard deviation score, a measure of fetal growth, with systolic blood pressure at age 19 years; our point estimate of 1.0 mmHg per z-score falls within that study's 95% confidence interval of −0.7 to 1.7. Studies led by Hack[3] in the United States and Doyle[5] in Australia also failed to find an association of poorer fetal growth with higher blood pressure later in life. Our study extends the findings of those studies, demonstrating that in heavier and more mature preterm infants, as well as in VLBW infants, fetal growth restriction does not appear to be a risk factor for later hypertension.

Additionally, in contrast to studies in full term children[12, 13, 14], we did not find that maternal preeclampsia was associated with higher school age blood pressure. We also did not find an association of maternal smoking with offspring blood pressure, in contrast to one study in a full term cohort[18], but consistent with the results of another[28]. A possible explanation for the discrepant findings between full term and preterm populations relates to the timing of prenatal exposures. The developmental origins of health and disease paradigm rests on the hypothesis that exposures during critical periods of development, particularly fetal life and early infancy, can program long-term health[29]. It is possible that fetal growth restriction, preeclampsia, and/or maternal smoking late in the 3rd trimester influence blood pressure, whereas the same exposures earlier in gestation, as experienced by infants born preterm, do not.

Studies[11, 30] in children born full term have found that more rapid weight gain in infancy is associated with higher blood pressure later in life. However, the extent to which more rapid early weight gain leads to higher blood pressure in preterm populations is unclear. In this cohort, faster weight gain in the first year of life was associated with only slightly higher (1.1 mmHg per z-score weight gain) systolic blood pressure at age 6.5 years, only for children born at ≥32 weeks gestation[31]. Weight gain later in childhood may also be an important determinant of later blood pressure in children born preterm[15].

Our study is limited by the fact that children in IHDP were born in the 1980′s when clinical care of preterm, low birth weight infants differed from current practices. Additionally, obesity – an important determinant of blood pressure – has become substantially more prevalent since that time. A majority of IHDP mothers were poor, black, and had attained low levels of education, possibly limiting generalizability, although participants were enrolled at 8 centers across the country. Additionally, when compared with a contemporary reference population[24], 39% of our cohort was considered SGA. Thus, despite overall poorer fetal growth in our study population compared with a contemporary cohort, we still did not find an association of fetal growth restriction with higher blood pressure. Blood pressure was measured by auscultation in some centers and oscillometric device in others, but associations of fetal growth and other predictor variables with blood pressure were similar regardless of blood pressure measurement method.

In summary, we found that, in former preterm low birth weight infants, slower fetal growth was not associated with higher blood pressure later in life. Fetal growth restriction does not appear to be a risk factor for later hypertension in this population.

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Table 1

Characteristics of 694 Infant Health and Development Program participants

Maternal characteristics	***Mean (SD) or number (%)***
Age (years)	24.6 (6.0)
Pre-pregnancy weight (kg)	60.2 (13.4)
Gestational weight gain (kg)	10.8 (6.2)
Gestational diabetes	7(1%)
Preeclampsia or eclampsia	112 (16%)
Hypertensive disorder	22 (3%)
Any smoking during pregnancy	227 (33%)
Any alcohol use during pregnancy	73 (10%)
Education attained at study enrollment	
<12th grade	291 (42%)
High school graduate	206 (30%)
College or more	197 (28%)
Race/ethnicity	
Black	407 (59%)
White	193 (28%)
Asian	94 (13%)
Annual household income at enrollment	
<$15,000	196 (28)
$15,000 to < $35,000	225 (32)
>$35,000	176 (26)
Do not know/refused/missing	97 (14)
Fetal and infant characteristics	*Median (range) or number (%)*
Birth weight (kg)	1.87 (0.54, 2.50)
Gestational age (weeks)	34.0 (25, 37)
Birth weight for gestational age z-score*	−1.1 (−2.6, 1.7)
Small for gestational age†	269 (39%)
Birth order	
1	277 (40%)
2	219 (31%)
≥3	198 (29%)
Bronchopulmonary dysplasia	34 (5%)
Male	333 (48%)
School age characteristics	Mean (SD)
Systolic blood pressure (mmHg)	104.2 (8.4)
Diastolic blood pressure (mmHg)	59.7 (8.2)
Height z-score‡	−0.1 (1.0)

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Maternal characteristics	*Mean (SD) or number (%)*
Body mass index z-score[‡]	−0.0 (1.2)

[*]Based on a national reference[24]

[†]Birth weight for gestational age percentile <10

[‡]Based on the Center for Disease Control growth reference[25]

Table 2

Associations of maternal, fetal, and infant factors with systolic blood pressure at age 6.5 years in 694 Infant Health and Development Program participants

Maternal factors	**Model 1***	**Model 2†**
Age (per 5 years)	0.4 (−0.2, 1.0)	0.4 (−0.2, 1.0)
Pre-pregnancy weight (per 5 kg)	0.1 (−0.1, 0.4)	−0.1 (−0.2, 0.0)
Gestational weight gain (per kg)‡	−0.1 (−0.2, 0.0)	−0.1 (−0.2, 0.0)
Gestational diabetes	1.4 (−4.8, 7.6)	1.2 (−4.9, 7.4)
Preeclampsia	−0.7 (−2.4, 1.0)	−0.7 (−2.4, 1.0)
Hypertensive disorder	3.3 (−0.3, 6.8)	3.5 (0.0, 7.0)
Smoking (any compared with none)	0.6 (−0.7, 2.1)	0.6 (−0.7, 2.0)
Alcohol (any compared with none)	−1.3 (−3.4, 0.7)	−1.1 (−3.1, 0.9)
Fetal and infant factors		
Birth weight (kg)	0.6 (−0.8, 2.0)	0.6 (−0.8, 2.0)
Gestational age (weeks)	−0.1 (−0.3, 0.1)	−0.1 (−0.3, 0.2)
Birth weight for gestational age z-score	1.0 (0.2, 1.9)	0.7 (−0.1, 1.6)
SGA (compared with AGA)	−1.1 (−2.4, −0.2)	−0.7 (−2.0, 0.6)
Birth order (compared with 1)		
2	0.4 (−1.3, 2.1)	0.4 (−1.3 2.1)
3	1.1 (−0.7, 3.0)	1.1 (−0.8, 2.9)
Bronchopulmonary dysplasia	1.0 (−1.9, 3.9)	1.0 (−1.9, 3.9)

Numbers in the table represent blood pressure differences in mmHg (95% confidence intervals).

[*] Model 1 is adjusted for age, sex, blood pressure measurement method and child behavioral state, and sociodemographic variables at enrollment (maternal age, education attained, race/ethnicity, and annual household income)

[†] Model 2 is adjusted for all variables in model 1 plus height z-score at 6.5 years

[‡] Estimates additionally adjusted for gestational age at birth

Table 3

Associations of fetal growth with blood pressure at 6.5 years stratified by gestational age category

Gestational age category	Systolic blood pressure (mmHg)
<32 weeks (n=186)	1.4 (−0.4, 3.4)
≥ 32 weeks (n=501)	1.0 (−0.2, 2.3)

Numbers in the table represent blood pressure differences in mmHg per z-score of birth weight for gestational age (95% confidence interval), adjusted for child age, sex, blood pressure measurement method and child behavioral state, maternal age, education attained, race/ethnicity, annual household income at enrollment, and height z-score at 6.5 years