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Renal function and blood pressure are altered in adolescents born preterm

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Abstract

Background: Preterm birth increases the risk of hypertension and kidney disease. However, it is unclear when changes in blood pressure (BP) and renal function become apparent and what role obesity and sex play. We hypothesized adolescents born preterm have higher BP and worse kidney function compared to term in an obesity- and sex-dependent manner.

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Compliance with ethical standards

The Wake Forest School of Medicine and Forsyth Medical Center Institutional Review Boards approved the study. Parents or legal guardians provided written informed consent, and participants provided assent.

Conflict of Interest: The authors declare that they have no conflict of interest.

Data Availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Methods: Cross-sectional analysis of 14-year-olds born preterm with very low birth weight ($n=96$) compared to term ($n=43$). We used generalized linear models to estimate the associations among preterm birth and BP, estimated glomerular filtration rate (eGFR), and ln(x) urinary albumin-to-creatinine ratio (ACR), stratified by overweight/obesity (OWO, body mass index (BMI) $\geq 85^{\text{th}}$ percentile) and sex.

Results: Compared to term, preterm-born adolescents had higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) (adjusted β ($a\beta$): 3.5 mmHg, 95% CI -0.1 to 7.2 and 3.6 mmHg, 95% CI 0.1 to 7.0), lower eGFR (β : -8.2 mL/min/1.73 m², 95% CI -15.9 to -0.4), and higher ACR ($a\beta$: 0.34, 95% CI -0.04 to 0.72). OWO modified the preterm-term difference in DBP (BMI $<85^{\text{th}}$ percentile $a\beta$: 5.0 mmHg, 95% CI 0.7 to 9.2 vs. OWO 0.2 mmHg, 95% CI -5.3 to 5.6) and ACR (OWO $a\beta$: 0.72, 95% CI 0.15 to 1.29 vs. BMI $<85^{\text{th}}$ percentile 0.17, 95% CI -0.31 to 0.65). Sex modified the preterm-term ACR difference (female $a\beta$: 0.52, 95% CI 0.001 to 1.04 vs. male 0.18, 95% CI -0.36 to 0.72).

Conclusions: Prematurity was associated with higher BP and reduced renal function that were detectable in adolescence. OWO and sex may modify the strength of these relationships.

Keywords

Chronic Kidney Disease; Hypertension; Obesity; Programming; Sex Differences; Very Low Birth Weight

Introduction

Improved clinical care has resulted in a significant increase in childhood survival of infants born prematurely. However, individuals born preterm exhibit an increased risk of adverse health outcomes including hypertension and renal disease, though when these abnormalities are detectable is incompletely known [1–4]. Reduced nephron endowment and neonatal acute kidney injury contribute to the development of hypertension and kidney disease [5, 6]. Antecedents of preterm birth including preeclampsia and low socioeconomic status have also been implicated [7, 8]. Obesity and male sex generally have a negative influence on renal function and the development of hypertension, but their role in preterm birth-related disease is unclear [6, 9–11]. Therefore the objective of this study was to compare blood pressure (BP) and renal function in 14-year-olds born preterm with very low birth weight (VLBW, <1500 g) to their term-born peers and evaluate whether obesity and sex modify these relationships. We hypothesized that adolescents born preterm have higher BP, lower glomerular filtration rate (GFR), and higher albumin-to-creatinine ratio (ACR) as compared to their term-born adolescent peers in an obesity- and sex-dependent manner.

Methods

Study Design

Study participants were recruited from a larger birth cohort of 479 patients born preterm with VLBW between January 1st, 1992 and June 30th, 1996 at a regional perinatal center (Forsyth Medical Center, Winston Salem, NC). Inclusion criteria included singleton birth, follow-up data through at least 1 year corrected age, and successful contact at 14 years of

age. Term peers were recruited via newspaper advertisement and word of mouth at age 14 years from those born at the same medical center via singleton birth, if birth weight was >2500 g, gestational age ≥ 37 weeks, and no antenatal steroid exposure ($N = 52$). Exclusion criteria for both groups included being a ward of the state or having a major congenital anomaly or genetic syndrome. Subjects were compensated for completing all study visits, and parents/guardians were compensated to cover travel expenses.

Data collection

We collected perinatal clinical information from subjects' medical records and research databases, including birth via cesarean section, antenatal corticosteroid exposure, maternal smoking during pregnancy, and maternal hypertension during pregnancy. Birth characteristics were recorded and included sex, gestational age, and birth weight. We calculated birth weight z-scores and categorized subjects as small-for-gestational age if birth weight was <10th percentile for gestational age [12, 13]. We collected demographic information at age 14 years, including parental-reported race (black vs. non-black), patient smoking status, and current Medicaid use. We measured height, weight, and waist circumference and calculated BMI and waist-to-height ratio. We categorized subjects as having overweight/obesity (OWO) if BMI ≥ 85th percentile for age and sex according to established pediatric guidelines [14]. Subjects privately reported their sexual maturity rating via questionnaire (scale of 1 to 5), and we reported the percent of subjects with a score of 5 in either of the two secondary sexual characteristics (pubic hair plus breast development in females and external genitalia development in males) [15].

We measured BP according to established guidelines [16]. Subjects were quietly seated and at rest for a minimum of five minutes with the arm fully supported. Trained personnel measured BP with a mercury manometer and an appropriately sized BP cuff. We recorded the average of three measurements (taken 1 minute apart) and calculated BP z-scores according to age-, sex-, and height-specific normative values [17]. We defined high BP as systolic BP (SBP) or diastolic BP (DBP) ≥ 120/80 and further classified stages of hypertension as i) elevated BP if SBP 120 to 129 mmHg but DBP <80 mmHg; ii) stage 1 hypertension if SBP 130 to 139 mmHg or DBP 80 to 89 mmHg; and iii) stage 2 hypertension if SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, according to established pediatric guidelines [18].

Blood was collected with subjects in the seated position. We measured serum creatinine and calculated the estimated GFR (eGFR, mL/min/1.73 m²) by the Schwartz equation ($k \times \text{height (cm)} / \text{serum creatinine (mg/dL)}$), with $k = 0.55$ for females and $k = 0.7$ for males [19]. We measured urinary albumin and creatinine on first-morning urine samples, calculated the ACR (mg/g), and defined albuminuria as ACR >30 mg/g [20]. A modified Jaffe assay was used to analyze creatinine; the assay was updated during the study period so a correction factor of 1.06 was applied to initial values ($n = 20$, all preterm).

Statistical analysis

We assessed frequencies and measures of central tendency and dispersion for descriptive statistics, including mean with standard deviation or median with interquartile range for

continuous variables, and employed Chi-square test, Fisher's exact test, t-test, and Wilcoxon Rank-Sum test for between-group comparisons. Correlations were analyzed by bivariate generalized linear models. A two-sided alpha level of less than 0.05 was considered statistically significant.

We employed generalized linear models to estimate the associations between preterm birth and BP, eGFR, and ln (x) ACR. We assessed for potential modification of the associations by OWO and sex via inclusion of an interaction term and generated stratified models if the interaction term suggested an interactive effect ($p < 0.2$), in order to minimize type II errors. We applied directed acyclic graphs to determine potentially confounding factors *a priori* and identified maternal hypertensive pregnancy and Medicaid use at age 14 years (a marker of socioeconomic status) in our minimally sufficient set of confounders for inclusion in the models [7, 8, 21]. We used SAS Enterprise Guide software for Windows for all analyses (Version 7.11, SAS Institute Inc., Cary, NC).

Results

Perinatal and adolescent characteristics

We enrolled 62% ($N = 193$) of subjects successfully contacted (Figure 1). Within the preterm cohort, 188 subjects were evaluated at age 14 years (five subjects were excluded: two subjects were twins, one had polycystic kidney disease, one had a chromosomal abnormality, and one had severe cerebral palsy). We report the data collected at the third study visit; 11 were further excluded (missing study visit). Of the remaining subjects, we included those who provided blood samples and first-morning urine samples ($N = 96$). Within the term cohort, we included in the current analysis those subjects who provided blood samples and first-morning urine samples ($N = 43$).

There were no significant preterm-term birth differences in sex or race (Table 1). Within the perinatal period, the preterm birth cohort had significantly higher rates of maternal hypertensive pregnancy, maternal smoking during pregnancy, and Cesarean section. Subjects born preterm had a mean gestational age of 27.8 weeks and a mean birth weight of 1048 g compared to 39.7 weeks and 3458 g in those born term. The two groups did not differ in the proportions that were small for gestational age. At 14 years of age, the preterm birth group was shorter but there were no differences in weight, BMI, or rates of OWO. Adolescents born preterm had a greater rate of current Medicaid use.

Blood pressure

As compared to those born term, adolescents born preterm had significantly higher mean SBP, DBP, SBP z-score and DBP z-score (Table 2). The preterm birth cohort also had a significantly greater rate of high BP. The preterm-term birth difference in BP persisted after adjusting for maternal hypertensive pregnancy and current Medicaid use (Table 3): SBP (adjusted β : 3.5 mmHg, 95% CI -0.1 to 7.2), DBP (adjusted β : 3.6 mmHg, 95% CI 0.1 to 7.0), SBP z-score (adjusted β : 0.48, 95% CI 0.15 to 0.81), and DBP z-score (adjusted β : 0.45, 95% CI 0.13 to 0.78) were all higher in adolescents born preterm as compared to those born term.

Evaluation for an interaction between OWO and preterm birth indicated potential modification of the preterm birth relationship with both DBP and DBP z-score, though these relationships approached statistical significance (interaction terms $p = 0.1$ and $p = 0.13$, respectively) (Figure 2). The preterm-term birth difference in DBP was slightly greater in subjects with BMI <85th percentile (adjusted β : 5.0 mmHg, 95% CI 0.7 to 9.2) as compared to those with OWO (adjusted β : 0.2 mmHg, 95% CI -5.3 to 5.6) (Table 4). The preterm-term birth difference in DBP z-score was slightly greater in subjects with BMI <85th percentile (adjusted β : 0.57, 95% CI 0.18 to 0.97) as compared to those with OWO (adjusted β : 0.15, 95% CI -0.37 to 0.66). Sex did not modify the preterm birth-BP relationships.

Renal function

While there were no differences in blood urea nitrogen or creatinine, adolescents born preterm had a significantly lower mean eGFR as compared to those born term (Table 2). The preterm birth group had a higher ACR but this did not achieve statistical significance ($p = 0.08$); there was no difference in rates of albuminuria. In crude analyses, preterm birth was associated with lower eGFR (Table 3). Adjusting for maternal hypertensive pregnancy and current Medicaid use attenuated this relationship (adjusted β : -6.3 mL/min/1.73 m², 95% CI -15.0 to 2.4). After adjustment, preterm birth demonstrated a trend towards higher ACR (adjusted β : 0.34, 95% CI -0.04 to 0.72).

There was potential modification of the preterm birth-ACR relationship according to OWO, though this approached statistical significance (interaction term $p = 0.17$) (Figure 3a). The preterm-term birth difference in ACR was slightly greater in subjects with OWO (adjusted β : 0.72, 95% CI 0.15 to 1.29) as compared to those with BMI <85th percentile (adjusted β : 0.17, 95% CI -0.31 to 0.65) (Table 4). Sex also potentially modified the preterm birth-ACR relationship, though this approached statistical significance (interaction term $p = 0.18$, Figure 3b): the preterm-term difference in ACR was slightly greater in females (β : 0.52, 95% CI 0.001 to 1.04) as compared to males (β : 0.18, 95% CI -0.36 to 0.72) (Table 4).

Discussion

We found that increased BP, a greater rate of high BP, and reduced renal function are detectable during adolescence in healthy individuals born preterm with VLBW as compared to their term-born peers. Moreover, these relationships tended to be greater according to OWO status and sex. Amongst adolescents with BMI <85th percentile, the preterm-term difference in BP was modestly increased and amongst adolescents with OWO as well as in female adolescents, the preterm-term difference in ACR was modestly increased, though these interactions approached statistical significance. The preterm-term BP difference persisted after controlling for height by analyzing BP z-scores, which is notable given that our preterm birth cohort was shorter than their term-born peers, and shorter height in children and adolescents is associated with lower BP [18].

The age at which preterm-term differences in BP are apparent is variable. Differences in BP have been described by 6 years of age [22]. While BP differences have been described in individuals into their 30's, most studies do not consistently demonstrate when hypertension itself develops [23]. Several explanations for the increased risk of hypertension have been

proposed, including alterations in renal structure and function, vascular changes, and salt sensitivity of BP [24]. Additional factors include elevated uric acid, alterations in the renin-angiotensin system, suppressed klotho, blunted pressure natriuresis, and aberrant autonomic function, all of which we have previously described in our preterm birth cohort [25–29]. Our study revealed a novel effect of obesity on BP: the preterm-term difference in DBP was modestly greater among individuals with a BMI <85th percentile compared to those with OWO, though this interaction approached statistical significance. Obesity generally increases the risk of hypertension in children and adolescents as well as adults, but there is a dearth of evidence about obesity's role in the development of hypertension in preterm-born individuals [22, 30, 31]. A possible interpretation of our analysis is that prematurity may induce adverse cardiovascular changes akin to those ascribed to obesity alone. Larger prospective studies are needed to better evaluate the influence of obesity on BP in individuals born preterm.

The reduced renal function observed in the preterm birth group may contribute to their higher BP. As these individuals reach young adulthood, it is likely the differences in renal function will become more apparent. The timing of when changes in renal function are apparent is unclear, with some studies detecting differences during childhood and others showing no differences even into early adulthood [2, 22, 32, 33]. Our study provides evidence of a divergence in renal function that was detected at 14 years of age, though it should be noted that the original Schwartz equation we used may overestimate GFR when in the normal range. The exact mechanisms underlying these alterations in renal function are incompletely described but may be due in part to reductions in nephron number and maturity, poor growth, and alterations in uric acid and the renin-angiotensin system [27, 28, 34, 35].

We found that OWO and sex may influence the relationship between preterm birth and higher ACR, as the preterm-term difference in ACR was modestly greater in subjects with OWO and in adolescent females, though these interactions approached statistical significance. Low birth weight is associated with the development of obesity as well as kidney disease, and obesity-induced renal pathology mirrors that of prematurity [36, 37]. The reasons for this are not fully understood but may be due to a predisposition to obesity and increased sensitivity to the renal and cardiovascular effects of obesity. This suggests that the development of obesity during adolescence may compound the risk of developing renal disease in preterm-born individuals. Our results suggest that females born preterm could be at higher risk than males in developing kidney disease, which is a novel finding because in general males born preterm are thought to be at increased risk [10]. However, females born preterm have been shown to have a higher rate of diastolic hypertension compared to males, and females with a reduced number of glomeruli have been shown to lack compensatory glomerular hypertrophy compared to males [22, 38]. The reasons for this are unclear but may be due to hormonal effects on renal size and the renin-angiotensin system [28, 38]. Larger prospective studies are needed to fully evaluate the influence of obesity and sex on renal outcomes in individuals born preterm.

Strengths of our study include a large preterm birth cohort with a term-born control cohort for comparison with comprehensive renal, cardiac, and metabolic assessments. The study

had several limitations. The cross-sectional design limited our ability to directly determine when changes in BP are first apparent. Although our study included a large-sized preterm birth cohort, the smaller sample size in the term birth group likely limited our power to detect significant differences upon stratified analyses by OWO and sex. We did not have information available about which preterm birth participants had neonatal acute kidney injury, which influences future renal function [6]. We measured eGFR by the Schwartz equation, which is the standard clinical pediatric eGFR equation in children and adolescents with normal renal function [39, 40]. Not all of our subjects' creatinine measurements were analyzed via an assay traceable to isotope dilution mass spectrometry nor did any subject have documented chronic kidney disease, which precluded the use of the updated Schwartz (CKiD) eGFR equation according to established guidelines [41]. We did not measure GFR directly or measure cystatin C, which are more sensitive methods to assess GFR. Our study did not assess renal length or volume, both of which have been shown to be decreased in individuals born preterm [2]. Larger prospective studies with more comprehensive measures of renal function are warranted to more accurately assess renal function in individuals born preterm.

In summary, adolescents born preterm with VLBW had increased BP, a greater rate of high BP, and reduced renal function as compared to their term-born peers that were detectable at 14 years of age. Preterm-term birth differences in BP tended to be greater in individuals with BMI <85th percentile; however, differences in urinary albumin excretion tended to be greater in individuals with OWO and in females. Our results suggest that preterm birth-related alterations in the kidney are detectable during adolescence and provide further evidence that prematurity is associated with an increased risk of developing hypertension and chronic kidney disease.

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Fig. 1. Cohort Subject Recruitment Flow Diagram

Fig. 2. Diastolic Blood Pressure and Preterm Birth by Overweight/Obesity Preterm in red, term in blue. Body mass index (BMI) < 85th %ile: preterm $n = 63$, term $n = 30$; overweight/obesity: preterm $n = 33$, term $n = 13$. Filled circles indicate means, boxes include 25% to 75%, whiskers include 5% to 95%, and open circles indicate outliers. *Preterm-term difference $p = 0.01$ by t-test; overweight/obesity (OWO) * preterm birth interaction term $p = 0.1$.

Fig. 3. Urinary Albumin-to-Creatinine Ratio and Preterm Birth by Overweight/Obesity and Sex
 Preterm in red, term in blue. Diamonds indicate means, bars indicate medians, boxes include 25% to 75%, and open circles indicate data points; outliers not shown. a. Overweight/obesity (OWO): preterm $n = 33$, term $n = 13$; body mass index (BMI) $< 85^{\text{th}}$ %ile: preterm $n = 63$, term $n = 30$. *Preterm-term difference $p = 0.03$ by Wilcoxon Rank-Sum test; OWO * preterm birth interaction term $p = 0.17$. b. Female: preterm $n = 56$, term $n = 22$; Male: preterm $n = 40$, term $n = 21$. *Preterm-term difference $p = 0.06$ by Wilcoxon Rank-Sum test; sex * preterm birth interaction term $p = 0.18$.

Table 1

Clinical Characteristics of Adolescents Born Preterm Compared to Those Born Term

	Preterm <i>n</i> =96	Term <i>n</i> =43
<i>Perinatal</i>		
Male	40 (42%)	21 (49%)
Black	35 (36%)	17 (40%)
Maternal HTN	40 (42%) [*]	2 (5%)
Maternal Smoking	17 (18%) [*]	1 (2%)
Cesarean Section	48 (50%) [*]	8 (19%)
GA, weeks	27.8 (2.6) [*]	39.7 (1.1)
Birth Weight, g	1048 (276) [*]	3458 (451)
Small for GA	9 (9%)	3 (7%)
<i>Adolescent</i>		
Height, cm	162.2 (9.2) [*]	168.2 (7.2)
Weight, kg	58.7 [48.5, 69.0]	59.8 [55.1, 69.7]
Body Mass Index, kg/m ²	21.4 [19.0, 25.9]	21.2 [19.3, 24.0]
Overweight/Obesity	33 (34%)	13 (30%)
Waist-to-Height Ratio	0.46 [0.42, 0.54]	0.44 [0.42, 0.47]
Sexual Maturity Rating of 5	57 (60%)	26 (60%)
Medicaid	34 (36%) [*]	7 (16%)
Current Smoker	2 (2%)	1 (2%)

N(%), mean (*SD*), or median [IQR].^{*} *p*<0.05 for preterm vs term comparison by chi-square test or t-test. *GA* gestational age, *Maternal HTN* maternal hypertensive pregnancy.

Table 2

Blood Pressure and Renal Function in Adolescents Born Preterm Compared to Those Born Term

	Preterm <i>n</i> =96	Term <i>n</i> =43
SBP, mmHg	108.4 (10.0) *	103.8 (6.8)
DBP, mmHg	62.0 (8.9) *	58.6 (7.9)
SBP z-score	-0.09 (0.91) *	-0.67 (0.64)
DBP z-score	-0.2 (0.83) *	-0.62 (0.72)
High BP	14 (15%) *	1 (2%)
Elevated BP	10 (10%)	1 (2%)
Stage 1 Hypertension	3 (3%)	0 (0%)
Stage 2 Hypertension	1 (1%)	0 (0%)
Blood Urea Nitrogen, mg/dL	11.7 (3.2)	11.9 (3.1)
Creatinine, mg/dL	0.8 (0.13)	0.79 (0.11)
eGFR, mL/min/1.73 m ²	126.2 (21.9) *	134.3 (21.4)
ACR, mg/g	4.9 [3.0, 11.0]	4.0 [2.5, 10.9]
Albuminuria (ACR >30 mg/g)	7 (7%)	3 (7%)

N (%), mean (*SD*), or median [IQR].

* *p*<0.05 for preterm vs term comparison by t-test and Fisher's Exact test. *ACR* albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate, *BP* blood pressure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 3

Differences in Adolescent Blood Pressure and Renal Function by Preterm Birth

	Crude	Adjusted*
	Estimate 95% CI	Estimate 95% CI
SBP, mmHg	4.6 (1.3, 7.9)	3.5 (-0.1, 7.2)
DBP, mmHg	3.4 (0.4, 6.5)	3.6 (0.1, 7.0)
SBP z-score	0.58 (0.28, 0.88)	0.48 (0.15, 0.81)
DBP z-score	0.42 (0.14, 0.71)	0.45 (0.13, 0.78)
Blood Urea Nitrogen, mg/dL	-0.21 (-1.35, 0.93)	-0.25 (-1.53, 1.03)
Creatinine, mg/dL	0.01 (-0.03, 0.06)	-0.004 (-0.06, 0.05)
eGFR, mL/min/1.73 m ²	-8.2 (-15.9, -0.4)	-6.3 (-15.0, 2.4)
ACR ^a	0.21 (-0.13, 0.55)	0.34 (-0.04, 0.72)

Generalized linear models

* adjusted for maternal hypertensive pregnancy and Medicaid use at age 14 years

^a natural-log transformed. *ACR* albumin-to-creatinine ratio, *eGFR* estimated glomerular filtration rate, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Table 4

Differences in Adolescent Blood Pressure and Renal Function by Preterm Birth According to Overweight/Obesity and Sex

<u>Adjusted Models[*]</u>		<u>Stratified Models[*]</u>	
	Estimate (95% CI)		Estimate (95% CI)
DBP, mmHg	3.6 (0.1, 7.0)	BMI <85th percentile	5.0 (0.7, 9.2)
		Overweight/Obesity	0.2 (-5.3, 5.6)
DBP z-score	0.45 (0.13, 0.78)	BMI <85th percentile	0.57 (0.18, 0.97)
		Overweight/Obesity	0.15 (-0.37, 0.66)
ACR ^a	0.34 (-0.04, 0.72)	Overweight/Obesity	0.72 (0.15, 1.29)
		BMI <85th percentile	0.17 (-0.31, 0.65)
		Female	0.52 (0.001, 1.04)
		Male	0.18 (-0.36, 0.72)

Generalized linear models

^{*} adjusted for maternal hypertensive pregnancy and Medicaid use at age 14 years

^a natural-log transformed. *ACR* albumin-to-creatinine ratio, *DBP* diastolic blood pressure, *BMI* body mass index