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Early Predictors of Hypertension in Prematurely Born Adolescents

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Abstract

Objective—To assess the blood pressure of former preterm and term matched adolescent controls, and identify risk factors associated with blood pressure at 16 years.

Design—Observational cohort study. Secondary analysis of a randomized clinical trial.

Setting—Three academic centers participating in the Multicenter Indomethacin IVH Prevention Trial.

Participants—296 children born in 1989–1992 with birth weights 600- <1250g who participated in the Multicenter Indomethacin IVH Prevention Trial and 95 term controls were evaluated at 16 years.

Main Outcome Measures—Blood pressure and predictors of blood pressure.

Results—The adjusted mean difference in blood pressure for preterm adolescents was 5.1 mm Hg; p=0.002 for systolic and 2.1 mm Hg; p=0.027 for diastolic blood pressure. Among preterms, the primary predictors of increased systolic blood pressure were weight gain velocity between birth and 36 months (b=8.54, p<.001), preeclampsia (b=5.67, p=0.020), non-white race (b=3.77, p=0.04) and male gender (b=5.09). Predictors of diastolic blood pressure were weight gain velocity between birth and 36 months, (b=4.69, p=0.001, brain injury (b=6.51, p=0.002 and male gender (b=−2.4, p=0.02).

Conclusions—Early programming secondary to increased early weight gain velocity, intrauterine stress and neonatal brain injury may all contribute to risk of increased blood pressure among former preterm adolescents.

Keywords

brain injury; hypertension; preterm; weight gain velocity

BACKGROUND

Although very low birth weight (VLBW) infants represent ~ 1.5% of live births in the United States today, (1) there have been few longitudinal investigations of VLBW infants to

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evaluate the association of prematurity with the risk of hypertension in adolescence or in young adulthood.(2–8) Most outcome studies of preterm infants have shown that they are shorter and weigh less than term controls.(9–11) Furthermore, although increased systolic BP has been attributed to changes in body mass index (BMI) in preterm subjects, (2–7) there has been no evaluation of the effects of early maternal and neonatal factors on risk of hypertension during adolescence in former preterm infants.

Higher BP in children and adults who were term or near term has been attributed to growth restriction in utero.(12–13) Barker(13–14) first proposed the “fetal origins” of adult disease hypothesis, that alterations in fetal nutrition causing intrauterine growth restriction result in developmental adaptations that permanently change structure, physiology, and metabolism predisposing the child to subsequent cardiovascular, metabolic, and endocrine disease in adult life. This concept has been expanded to concerns regarding “rapid catch-up growth” of premature infants predisposing them to subsequent cardiovascular risk and obesity.

The primary objective of this study was to determine the incidence of pre-hypertension and hypertension among a cohort of former preterm infants at 16 years of age compared to gender- and age-matched term controls. Secondary objectives were to examine the effects of maternal and neonatal risk factors and early catch-up growth on the risk of hypertension. The hypotheses were that former preterm infants have higher rates of hypertension compared to term controls and that hypertension at 16 years among preterms is associated with increased early weight gain catch-up growth.

METHODS

Between 09/05/1989 and 08/31/1992, 505 infants with a birth weight of 600 to 1250 g admitted by 6 hours of age to 3 tertiary care centers, Women and Infants’ Hospital (Providence, RI), Maine Medical Center (Portland, ME), and Yale New Haven Hospital (New Haven, CT) were enrolled after parental consent to a prospective randomized trial on early administration of low-dose indomethacin to prevent IVH. (15–17) All infants enrolled in the study were examined using cranial echoencephalography (ECHO) between 5 and 11 hours. Of the 505 enrolled infants, 431 did not have IVH @ 6 hours and were randomized to the primary IVH prevention trial, and 62 had grades 1 and 2 IVH and were randomized to the secondary prevention trial; Infants with congenital abnormalities or syndromes were excluded. Twelve infants who were diagnosed with grades 3 and 4 IVH at 6 postnatal hours were also enrolled and followed. All infants were enrolled for long term neurodevelopmental and growth assessments at 3, 4 ½, 6, 8, 12, and 16 years. Sixty-eight of these 505 infants died before 16 years. Complete anthropometric measures and BP were obtained on 296/ 437 (68%) preterm survivors at 16 years.

Prenatal and neonatal data were retrieved from the study database. Maternal pre-eclampsia was defined as hypertension, chronic or pregnancy induced, with or without edema and albuminuria recorded in the mother’s chart, or maternal BP above 140 systolic or 90 diastolic starting prior to or during present pregnancy. Bronchopulmonary dysplasia (BPD) was defined as an oxygen requirement and abnormal chest x-ray at 28 days of life.(18) Severe brain injury was defined as the presence of either grade 3–4 intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), or severe ventriculomegaly. (16)

The cohort of term control children was added when the study patients reached age 8 years to provide comparison data from typically-developing children. They were recruited from the local community or randomly selected from a telemarketing list of 10,000 families. Term

controls were frequency-matched on zip-code, age, gender, and race. At age 16, 95/102 (93%) controls had weight, height and BP obtained.

Weight and length /height were obtained at 3, 4 ½, 6, 8, 12 and 16 years. Weight was obtained using a horizontal scale until 18 months and an upright scale after 18 months. Standard procedures were used.(19) Upright stature was measured with a permanently affixed stadiometer or upright scale. Two measurements were taken and the mean calculated. Weight gain velocity was calculated as weight in grams at time two minus weight in grams at time one divided by the number of interval months between visits. Body mass index (BMI) (weight (kg/ht m^2) was calculated at 16 years. Overweight was defined as a BMI>85th% and obesity as a BMI>95th %.

BP measurements were obtained at the 16 year visit using standard techniques (20) Subjects sat in a quiet room with the right arm fully exposed and resting on a supportive surface at the heart level. A vital signs monitor (Welch Allyn 420 Series, Skaneateles Falls, NY, USA), commonly utilized in epidemiologic studies of BP in children was used.(5) The appropriate-sized cuff to cover approximately 75% of the upper arm between the top of the shoulder and the olecranon was used. The mean of two measurements was used and reported as normal (average systolic and diastolic BP both below the 90th percentile for gender, age and height), prehypertension (average systolic BP or diastolic BP values ≥ 90th % and <95th% for gender, age and height) and hypertension (average systolic BP or diastolic BP values ≥ 95th % for gender, age and height) were used.(20)

A standard neurological examination was completed. An abnormal neurologic exam was defined as the presence of any of the following: cerebral palsy, a seizure disorder, hearing aids with bilateral hearing loss, or bilateral vision impairment with utilization of Services for the Blind. Updated sociodemographic information was provided by the primary caretaker. The Achenbach Child Behavior Checklist (21) was administered and the activities score was analyzed as a marker of physical activity. The study received institutional review board approval, and informed consents were obtained from parents of all children. Assent was obtained at age 16.

Statistical analysis

BP values, growth parameters, and 16 year BMI were compared between preterm and term subjects using Wilcoxon rank sum and chi square analyses. Two sets of multiple linear regression models were run. The first set was run on the total cohort to confirm the independent effects of preterm birth adjusted for gender, age, BMI and height. The second set of multiple linear regression analyses was used to identify factors that predicted BP among the preterm subjects. Independent variables known to be associated with cardiovascular sequelae were selected. Effects of minority, maternal pre-eclampsia,, maternal diabetes, gender, birth weight, gestational age, small for gestation and weight gain velocities of intervals between birth and 36 months were examined. Since weight gain velocity between birth and 36 months was the strongest predictor of BP it was entered into the final models. Because of the characteristics of this sample the effects of indomethacin and the presence of brain injury (grade 3–4 IVH, PVL or ventriculomegaly at term) were also explored. The final models included gestational age as a marker of immaturity and predictor variables that were significant or approached clinical significance in bivariate analyses. Analyses were conducted with SAS 9.1. P values ≤ 0.05 were considered for statistical significance.

RESULTS

Maternal and child characteristics are shown in Table 1. Among the mothers, 25.3% belonged to a minority, 10.8% had pre-eclampsia, and 35.8% received antenatal steroids. Among the 296 preterm children seen at 16 years, 10.8% were small for gestation and 8.8% had neonatal brain injury. There were no differences between preterm children seen and not seen at 16 years in maternal preeclampsia, gender, growth restriction, gestational age, bronchopulmonary dysplasia, or brain injury. Children seen were more likely to be Caucasian (75% versus 61%, p=0.0035) and their mothers were more likely to have received antenatal steroids (36% versus 26%; p=0.05).

A comparison of preterm and term characteristics at 16 years is shown in Table 2. Preterm had mean higher systolic BP (114±13 versus 110±10, p=0.003) compared to term adolescents. Rates of systolic prehypertension and hypertension were higher for preterms than terms (p=0.005). Mean diastolic BP trended higher for preterm than term adolescents (66.1±8 versus 64.2± 7, p=051). In addition, preterms were shorter, weighed less, and had similar rates of BMI< 85th%.

Table 3 shows the characteristics of the preterm children with systolic or diastolic BP ≥ 90th% (prehypertension or hypertension) adjusted for age, gender and height. Older maternal age, maternal preeclampsia, weight gain velocity 0–36 months, and 16 year BMI were associated with systolic BP ≥ 90th%. For diastolic BP, in addition to the maternal factors and 16 year BMI ≥ 95th%, shorter stature was associated with BP ≥ 90th%. The only significant neonatal characteristic associated with diastolic BP ≥ 90th% was neonatal brain injury (26% versus 8%, p=0.017).

Linear regression models to predict BP for the total cohort and for the preterm adolescents are shown in Table 4. For the total cohort, preterm birth was significant in the models for both systolic and diastolic BP after adjusting for gender, age, and BMI. The models accounted for 15 percent of the variance for systolic and 5 percent of the variance for diastolic BP. When the models (data not shown) were run with height substituted for BMI, preterm birth remained significant for both systolic (b=5.85, p=0.001) and diastolic BP (b=2.32, p=0.02).

In the preterm models we adjusted for gender, gestational age and non-white race. Male gender was associated with increased systolic BP (+5.1 mm Hg) and decreased diastolic BP (−2.4 mm Hg) compared to females and non-white race was associated with increased systolic BP (3.8 mm Hg). Increased weight gain velocity from birth to 36 months was associated with both systolic and diastolic BP. Every additional 100 grams of weight gain per month was associated with an increase of 8.5 mm Hg of systolic BP and 4.7 mmHg diastolic BP. In addition, we tested for effects of catch-up growth in the first 6 months and 6–18 months; these effects were not significant. Birth to 36 months provided the strongest contribution to our regression models. Preeclampsia had a positive association with higher systolic BP (+5.7 mm Hg). Finally, neonatal brain injury was associated with a 6.26 mm Hg increase in diastolic BP. The final models accounted for almost 18 percent of the variance for systolic BP and 14 percent of the variance for diastolic BP. In addition, we ran the models adding indomethacin, which was not significant for either systolic (b = 1.27 p = 0.406) or diastolic BP (b = 0.13 p = 0.896).

DISCUSSION

Former preterm 16 year old adolescents in this cohort have higher systolic BP and higher rates of systolic pre-hypertension and hypertension compared to term controls. Despite the fact that the former preterm subjects were shorter and weighed less than the term controls at

16 years of age, they had rates of overweight and obesity similar to the matched term controls.

Among the preterm subjects, linear regression modeling confirmed that weight gain velocity between birth and 36 months was significantly associated with both higher systolic and diastolic BP. Weight gain velocity was also independently associated with systolic BP ≥ 90^{th} % among the preterm subjects after adjusting for confounders in logistic regression. . Early weight gain catch-up between birth and 2 years in term infants has previously been shown to be associated with subsequent obesity.(22) A lag time for a critical window during which weight gain catch-up impacts subsequent obesity and BP in prematurely-born adolescents may well be related to the early post-natal extra-uterine growth restriction observed in preterm infants cared for in newborn intensive care units.(23) This delay in the time line of effects of catch-up in growth may also reflect a variant of the Barker Hypothesis(13–14) and raises worrisome concerns regarding early catch-up growth, hypertension, overweight, and potential increased risk for adult cardiovascular disease in prematurely-born neonates. (22,24)

Overweight and obesity were more common among the former preterm adolescents with elevated systolic and diastolic BP, but the association was stronger for systolic BP ≥ 90^{th}%. Approximately 50 % of former preterms with BP ≥ 90^{th} % had a BMI ≥ 85^{th}%. Obesity is well known to be associated with systolic hypertension. Although an association of overweight and obesity with BP ≥ 90^{th}% was identified in our preterm cohort, we propose that this association is reflective of a causal pathway beginning with early increased weight-gain velocity between birth and 36 months among preterm infants.

The association between preterm brain injury and diastolic hypertension at age 16 is a new and potentially important finding since there is increasing evidence suggesting that the brain may be implicated in the etiology of hypertension.(24) Pyhala et al (25) recently reported that former preterm young adults had higher diastolic BP during a structured social stress test and higher diastolic reactivity to the social stress after adjustment for confounders compared to controls. The authors speculated that this reactivity may be associated with alterations in the regulation of the hypothalamic-pituitary-adrenal axis. The central nervous system regulates multiple systems which may potentially contribute to hypertension including sympathetic nervous system activity. BP is modulated by functional circuitry linking the hypothalamus, nucleus tractus solitarius, and the rostral ventrolateral medulla, (26) and several specific potential CNS mechanisms relative to hypertension have been explored. Hypothalamic action via the parventricular nucleus in response to information about blood volume and osmolality influences the kidney via sympathetic efferents.(26) In addition, angiotensin, recognized as a centrally active peptide, has been shown to be produced in the brain in addition to other sites.(27) Angiotensin has been shown to directly excite the primary brainstem area known to project to sympathetic efferents, the rostral venterolateral medulla.

MRI studies also suggest that brain changes may play a role in the etiology of hypertension. Hayley(28) found differences in the blood-oxygen level dependent (BOLD) signal of young adults at risk of hypertension. Those at risk showed less activation in the posterior cingulate cortex, the right inferior parietal lobule and the right inferior temporal gyrus. These findings suggest that cerebral changes may precede the clinical appearance of hypertension.

Although we tested for effects of birth weight, gestational age, and small for gestation in our regression models for the preterm infants, these infant characteristics did not reach significance. This is consistent with the findings of Keijzer-Veen et al(5) in a preterm cohort evaluated at 19 years of age. In addition, while preterms have higher BP than terms, our data

also suggest that factors other than degree of prematurity or degree of low birth weight predispose the former preterm to changes in BP.

Finally, linear regression modeling also identified a relationship between preeclampsia and systolic BP. A relationship between preeclampsia and hypertension in former preterm adolescents has been reported by a number of investigators.(2) Hovi et al (8) identified an association between maternal hypertension but not maternal preeclampsia with a 24 hour recording of systolic BP in a cohort of former preterm adults. Our study definition of preeclampsia differed in that it included all mothers with hypertension in pregnancy. These associations between maternal and offspring BP may reflect either a genetic predisposition to hypertension or a response to stress imposed in-utero or a combination of these factors.

Strengths of our study are that it includes a large longitudinal cohort of former preterms with maternal, neonatal, follow-up and neuro-imaging data. Limitations include the fact that we obtained BP readings only at the 16 year visit, an oscillimetric method rather than an auscultatory method was used, and there may be a bias in our dataset secondary to the enrollment protocol which was based on birth weight. This was common during the years of birth of the study cohort (1989–1992). Although gestational age in our cohort ranged from 23 to 34 weeks and 10.8% were SGA, the higher birth weight infants were more likely SGA, making it difficult, both because of the method of enrollment and because of the sample size to clearly differentiate effects of SGA from being preterm versus low birth weight among our subjects.(29) Additional risk factors for risk of hypertension including family history of cardiovascular disease, smoking and renal disease were not available.

These findings and speculations may be relevant to the association of hypertension and preterm birth. Brain injury is common among preterm infants, and the MRI findings of the indomethacin preterm cohort at 8 to 16 years of age provide evidence of structural abnormalities and alternative neural circuitry.(30–31) Our novel findings of an association between neonatal brain injury and diastolic BP in former preterm subjects at age 16 years support the concept of central nervous system dysregulation. In view of the associations of brain injury, maternal pre-eclampsia and early weight gain velocity with 16 year BP in former preterm adolescents, further investigation of these associations, and possible interventions to prevent hypertension, are warranted. Careful longitudinal monitoring of the BP of former preterm infants is indicated.

Our findings are novel and hypothesis generating. Early programming secondary to increased early weight gain velocity, intrauterine stress and neonatal brain injury may all play a role in the development of hypertension among former preterm infants as they approach young adulthood.

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Abbreviations

BMI	body mass index

BP	Blood pressure
IVH	intraventricular hemorrhage
PVL	periventricular hemorrhage
VLBW	very low birth weight

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Table 1

Maternal and Child Characteristics of Preterm Cohort

Characteristic	Preterm Group
N	296
Maternal Age years	28±6
Race White n (%)	221 (74.7%)
Black n (%) not Hispanic	46 (15.5%)
Hispanic (%)	24 (8.1%)
Other	5 (1.7%)
All Minority	75 (25.3%)
Maternal years of education	13.6±2
Education < High school n (%)	31 (10.7%)
C-section n (%)	153 (51.7%)
Pre-eclampsia n (%)	32 (10.8%)
Diabetes n (%)	8/284 (2.8%)
Antenatal Steroids n (%)	106 (35.8%)
Birth weight grams	968±172
Gestation weeks	27.9±2
Small for gestation n (%)	32 (10.8%)
Gender	160 (54.1%)
Indomethacin	146 (49.3%)
Brain injury total n (%)*	26 (8.8%)
Sepsis ≥1 episode n (%)	61 (21.2%)
NEC n (%)	25 (8.4%)
BPD-oxygen at 28 days n (%)	134 (45.4%)
Days of hospitalization Median	75

*The presence of at least one of the following: Grade 3–4 IVH, severe ventriculomegaly or cystic PVL.

Table 2

Characteristics of Preterm and Term Children at 16 Years

Characteristic	Preterm	Term	p
N	296	95	
Visit Age years	16.1±0.2	16.2±0.3	0.073
Male Gender n (%)	160 (54%)	48 (51%)	0.549
Indomethacin	146 (49%)		
Systolic blood pressure	114±13	110±10	0.003
<90th %	244 (82%)	90 (94.7%)	
Prehypertension ≥ 90th%< 95th%	12 (4.0 %)	1 (1.1%)	0.005^
Hypertension ≥ 95th%	40 (13.5%)	4 (4.2%)	
Girls systolic blood pressure	111±12	109±11	0.156
Boys systolic blood pressure	117±13	111±10	0.002
Diastolic blood pressure	66.1±8	64.2±7	0.051
<90th%	277 (93.6%)	93 (97.9%)	
Prehypertension ≥ 90th%<95th%	11 (3.7%)	1 (1.1%)	0.140^
Hypertension ≥ 95th%	8 (2.7%)	1 (1.1%)	
Girls diastolic blood pressure	67±9	65±7	0.191
Boys diastolic blood pressure	65±8	63±7	0.085
Combined outcome of Systolic or Diastolic prehypertension or Hypertension	56(18.9%)	5(5.3%)	0.001
Heart Rate	70.6±13	69.1±13	0.328
Weight kg	63.4±17	68.7±17	0.010
Height cm	164.2± 9	168.4±10	0.002
BMI	23.4±6	24.1±5	0.301
BMI < 85th percentile n (%)	203 (69%)	60 (63%)	
BMI ≥ 85th <95th percentile n (%)	45 (15%)	15 (16%)	0.261^
BMI ≥ 95th percentile n (%)	48 (16%)	20 (21%)	
21Child Behavior Checklist Activities T score	N=224 44.3±10	N=72 46.3±9	0.136
Abnormal Neurologic Examination	39/295 (13.2%)	1/68 (1.5%)	0.002*

*Fishers exact test

^Mantel-Haenszel chi square 1 degree of freedom

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Table 3

Maternal and Infants Characteristics of Preterm Infants with and without Systolic or Diastolic Prehypertension or Hypertension

Characteristic	Systolic Prehypertension or Hypertension		p	Diastolic Prehypertension or Hypertension		p
Group	≥ 90th%	<90th%		≥ 90th%	<90th%	
N	52(18%)	244 (82%)		19 (6%)	277 (94%)	
Maternal Age	29.8±5.8	27.6±6.3	0.019	30.9±6	27.8±6	0.044
Black Race	9 (17%)	37 (15%)		4 (21%)	42 (15%)	
Caucasian	38 (73%)	183 (75%)	0.971	13 (68%)	208 (75%)	0.911
Hispanic	4 (8%)	20 (8%)		2 (11%)	22 (8%)	
Other	1 (1.9%)	4 (1.6%)		0	5 (1.8%)	
Minority	14 (27%)	61 (25%)	0.772	6 (32%)	69 (25%)	0.586
Preeclampsia	10 (19%)	22 (9%)	0.031	5 (26%)	27 (10%)	0.041*
Diabetes	1/51 (2%)	7/233(3%)	1.000*	0	8/265 (3%)	1.000*
Birth weight	952±187	972±169	0.437	938±144	970±174	0.366
SGA	6 (12%)	26 (11%)	0.852	3 (16%)	29 (10%)	0.444*
Gender male	28 (54%)	132 (54%)	0.974	7 (37%)	153 (55%)	0.120
Female	24 (46%)	112 (46%		12 (63%	124 (45%)	0.119
Indomethacin	26 (50%)	120 (49%)	0.915	13 (68%)	133 (48%)	0.085
Brain Injury	7 (13%)	19 (8%)	0.185*	5 (26%)	21 (8%)	0.017*
BPD	23 (44%)	111 (46%)	0.849	9 (47%)	125 (45%)	0.860
Wt gain velocity 0–36m	334±44	317±46	0.015	335±61	319±45	0.518
16 year Weight kg	70.5±21	61.9±16	0.007	66.4±24	63.2±17	0.730
Height cm	164.5±8	164.1±10	0.784	159.6±8	164.5±9	0.027
BMI	26.0±7	22.9±6	0.006	25.7±8	23.3±6	0.203
< 85th %	28 (54%)	175 (72%)		9 (47%)	194 (70%)	
≥ 85th <95th%	6 (12%)	39 (16%)	0.001^	3 (16%)	42 (15%)	0.013^
≥ 95th %	18 (35%)	30 (12%)		7 (37%)	41 (15%)	

Characteristic	Systolic Prehypertension or Hypertension		p	Diastolic Prehypertension or Hypertension		p
CBCL Activities T score	45.5±10	43.9±10	0.254	42.6±10	44.4±10	0.517
Abnormal Neurologic Exam	9 (17%)	30 (12%)	0.338	2 (11%)	37 (13%)	1.000*

*Fishers two tail test

^Mantel-Haenszel chi square 1 degree of freedom

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Table 4

Regression Models to Assess Factors Associated with Systolic or Diastolic Blood Pressure

Total Cohort					
Systolic Blood Pressure (mm Hg)			**Diastolic Blood Pressure(mm Hg)**		
Independent Variables	beta	P value	Independent Variables	beta	P value
Male Gender	5.10	0.001	Male Gender	−1.7	0.035
Age (years)	−0.11	0.960	age (years)	0.26	0.870
BMI	0.60	0.001	BMI	0.22	0.002
Preterm	5.06	0.002	Preterm	2.09	0.027
R-Square= 14.8 P value= 0.0001			R-Square= 4.7 P value=0.0009		
Preterm Subjects					
Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
Independent Variables	beta	P value	Independent Variables	beta	P value
Weight Gain Velocity 0–36m Unit=100g	8.54	0.001	Weight Gain Velocity 0–36m Unit= 100 g	4.69	0.0001
Preeclampsia	5.67	0.02	Preeclampsia	2.69	0.11
Brain Injury	0.180	0.95	Brain Injury	6.51	.0002
Male Gender	5.09	0.0001	Male Gender	−2.4	0.02
Gestational age (week)	−.55	0.18	Gestational age (week)	0.12	0.65
Non White	3.77	0.04	Non White	1.98	0.09
R-Square= 17.7 P value= 0.0001			R-Square= 13.9 P value=0.001		