

Fetal Origin of Childhood Disease

Intrauterine Growth Restriction in Term Infants and Risk for Hypertension at 6 Years of Age

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Objective: To examine the association between intrauterine growth restriction (IUGR) status at birth among full-term infants, exposure to substance use during pregnancy, and risk of hypertension at 6 years of age.

Design: Prospective evaluation of high-risk children.

Setting: Four centers of the National Institute of Child Health and Human Development Neonatal Research Network.

Participants: One thousand three hundred eighty-eight infants (600 cocaine exposed, 781 nonexposed, and 7 indeterminate, matched by gestational age, race, and sex), were enrolled at these sites. Nine hundred fifty children (415 exposed, 535 nonexposed) were followed up for 6 years.

Intervention: Right arm blood pressure was measured using the Dinamap portable adult/pediatric monitor with appropriate cuff size.

Main Outcome Measure: Blood pressure levels. Hypertension was defined as either systolic or diastolic blood pressure higher than the 95th percentile for sex, age, and height.

Results: Eight hundred ninety-one children had blood pressure data at 6 years of age: 516 were born at full term; 144 (28%) of the 516 children had a diagnosis of IUGR at birth. At 6 years of age, 93 (19%) of 516 children had hypertension. Of 144 children with IUGR, 35 (24%) had hypertension as compared with 58 (16%) of 372 children without IUGR ($P < .05$). Twenty percent of cocaine-exposed children had hypertension as compared with 16% of nonexposed children ($P = .20$). Intrauterine growth restriction status at birth was significantly associated with hypertension (relative risk, 1.8 [95% confidence interval, 1.2-2.7]) when multivariable Poisson regression analysis was performed adjusting for site; maternal race, education, and tobacco, marijuana, alcohol, and cocaine use during pregnancy; and child's current body mass index (calculated as weight in kilograms divided by height in meters squared).

Conclusion: In term infants, IUGR is linked to risk of hypertension in early childhood, which may be a marker for adult cardiovascular disease.

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ADLTS WHO WERE NOTED at birth to have low birth weight have been found to have hypertension in retrospective analysis of the relationship between current blood pressure (BP) and birth weight.¹ A prospective study (Perinatal Collaborative Project) studied 137 black Americans and found BP and birth weight are not correlated at age 28 years.² Hinchliffe et al³ proposed a potential pathogenesis for the linkage between low birth weight and hypertension in adulthood: the undernourished, growth-retarded fetus becomes a low-birth-weight newborn whose kidneys have a reduced number of nephrons. To our knowledge, the risk of hypertension in early childhood among infants who were

of normal gestation but growth restricted at birth has not been examined in a prospective manner.

Prenatal cocaine exposure is associated with growth restriction at birth in both full-term and preterm pregnancies.⁴⁻⁶ The deleterious effect of prenatal cocaine exposure may be greater in full-term compared with preterm pregnancies,⁷ with growth deceleration in cocaine-exposed infants evident after 32 weeks' gestation.⁴

The association between prenatal cocaine exposure and BP in early childhood appears to be unclear. In the study by Horn,⁸ high BP was noted among cocaine-exposed infants ($n = 12$), while the study by Needlman et al⁹ evaluating BP in 32 cocaine-exposed and 23 nonexposed infants found no differences in BP between groups.

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Table 1. Baseline Characteristics of 6-Year-Old, Full-Term Children

Characteristic	Children Born at Term and Evaluated at Age 6 Years (n = 516)	Children Born at Term and Not Evaluated at Age 6 Years (n = 295)
Maternal characteristic, No. (%)		
Prenatal care	483 (93.60)	270 (91.53)
Race*		
White	83 (16.09)	63 (21.36)
Black	399 (77.33)	210 (71.19)
Other	34 (6.59)	22 (7.46)
Smoking during pregnancy	271 (52.52)	163 (55.25)
Alcohol during pregnancy	320 (62.02)	180 (61.02)
Marijuana during pregnancy	112 (21.71)	72 (24.49)
Cocaine during pregnancy	220 (42.64)	121 (41.02)
Opiates during pregnancy	39 (7.56)	33 (11.19)
Maternal education, y		
<12	204 (39.53)	106 (36.18)
12	205 (39.73)	117 (39.93)
>12	107 (20.74)	70 (23.89)
Socioeconomic status: Hollingshead Index of Social Status ¹⁸ score, mean (SD)†	27.98 (10.46)	29.78 (10.47)
Neonatal characteristic, No. (%)		
Neonatal birth weight, g, mean (SD)	3100.94 (535.99)	3141.9 (490.97)
IUGR status	144 (27.91)	66 (22.37)
Sex of infant		
M	275 (53.29)	174 (58.98)
F	241 (46.71)	121 (41.02)
Length of hospital stay, d, mean (SD)	4.24 (4.82)	4.62 (5.99)

Abbreviation: IUGR, intrauterine growth restriction.

*Race was identified by mother.

†Statistically significant difference ($P < .05$) between term children whose cases were evaluated and not evaluated at age 6 years.

The objective of this study was to examine the association between intrauterine growth restriction (IUGR) status at birth among full-term infants, substance use during pregnancy, and risk for hypertension at 6 years of age in a multisite, prospective, longitudinal study.

METHODS

This analysis is part of the ongoing Maternal Life Style study, evaluating the impact of maternal lifestyle during pregnancy on childhood outcome. The study is performed at Brown University, University of Miami, University of Tennessee (Memphis), and Wayne State University. The 4 clinical sites are participating centers of the National Institute of Child Health and Human Development Neonatal Research Network. The study was approved by the institutional review board at each site and informed consent was obtained from the parents prior to participation.

Infants were prospectively recruited into the study between May 1993 and May 1995. Infants born to women who used cocaine during pregnancy (exposed group) were matched to non-cocaine exposed (comparison group) infants by gestational age, race, and sex within the same institution during the same recruitment year. Inclusion criteria were maternal age 18 years or older, inborn birth, singleton birth, and gestational age of 43 weeks or less. Exclusion criteria were maternal psychiatric disorders or developmental delay and language barriers to informed consent. Co-

caine and opiate exposure were determined by maternal admission of use during pregnancy and/or a positive screen for meconium metabolites confirmed with gas chromatography/mass spectroscopy. Prenatal exposure to alcohol, tobacco, and marijuana existed in both cocaine-exposed and non-cocaine exposed groups.¹⁰ Gestational age was assessed by the Ballard examination.¹¹ The children were categorized at birth to have a normal birth weight for gestational age or IUGR if birth weight was lower than the 10th percentile.¹² Only full-term infants were participants in the present study, since prematurity is a risk factor for elevated BP in adolescents and adulthood.^{13,14} Infants were prospectively followed up at each site with annual visits. At the 6-year visit to each clinical center, BP was measured as the average of 3 measurements of the right arm BP using the Dinamap portable adult/pediatric monitor (Critikon, Tampa, Fla) with the appropriate cuff size for the upper arm, with the width of the cuff bladder that was 40% of mid upper arm circumference. The child was seated during the measurements. The child's height was obtained using a stadiometer and weight, with the pediatric digital scale. The child's body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was noted on the growth charts established by the National Center for Health Statistics in collaboration with the Centers for Disease Control and Prevention.¹⁵ Hypertension was defined as systolic BP or diastolic BP in the 95th percentile or higher for sex, age, and height based on the National High Blood Pressure Education Working Group on High Blood Pressure in Children and Adolescents.¹⁶ The growth measurements and BP measurements were obtained by the study research nurse at each clinical center. Prior to each annual clinic visit, the study center primary investigator and research nurse reviewed the manual of operations developed, and each center's research nurse was certified to obtain BP measurements.

Poisson regression with robust standard errors¹⁷ was used to examine the effect of IUGR status at birth and BP at 6 years of age, adjusting for (1) clinical center, maternal race and education, and preeclampsia, and (2) use of tobacco, marijuana, alcohol, and cocaine during pregnancy and child's BMI at 6 years of age. Maternal BP levels were not obtained at the child's 6-year visit to the clinic.

RESULTS

Of the 19 079 women screened, 11 811 consented to participate in the acute phase of the study evaluating neonatal effects of cocaine exposure during pregnancy.⁶ For the longitudinal phase of the study, 1388 infants were enrolled at 1 month; there were 600 infants in the cocaine-exposed group, 781 in the comparison group, and 7 infants with indeterminate cocaine exposure who were subsequently excluded from this analysis. There were 811 full-term infants with a gestational age of more than 36 weeks enrolled at 1 month. Infants were examined at 4 and 8 months and annually thereafter until 6 years of age. The children were evaluated for the 6-year visit between November 1999 and November 2001. Of the children enrolled at the onset of the longitudinal study, 891 had BP and growth parameters at 6 years of age. Among these 891 children, 516 were born at full-term gestation. These 516 children are the subject of this report. Intrauterine growth restriction status at birth was noted in 144 (27.91%) of the 516 children. The clinical and demographic characteristics of the full-term children evaluated at 6 years of age and those not examined (lost to follow-up) are noted in **Table 1**. Only socioeconomic status was different between the children whose cases were evaluated at 6 years of age and those not evaluated.

Table 2. Clinical Characteristics of Children With and Without IUGR

Characteristic	With IUGR (n = 144)	Without IUGR (n = 372)
Maternal characteristic, No. (%)		
Race		
White	15 (10.42)	68 (18.28)
Black	121 (84.03)	278 (74.73)
Other	8 (5.56)	26 (6.99)
Maternal age, y, mean (SD)*	29.10 (6.08)	27.96 (5.76)
Marital status		
Married	20 (13.89)	77 (20.75)
Single	117 (81.25)	282 (76.01)
Divorced	7 (4.86)	8 (2.16)
Widowed	0	4 (1.08)
Insurance		
Private health insurance	6 (4.17)	28 (7.53)
Medical assistance or Medicaid	121 (84.03)	296 (79.57)
Prepaid HMO	8 (5.56)	28 (7.53)
Self-pay	8 (5.56)	16 (4.30)
Unknown	1 (0.69)	4 (1.08)
Maternal education, y		
<12	58 (40.28)	146 (39.25)
12	62 (43.06)	143 (38.44)
>12	24 (16.67)	83 (22.31)
Prenatal care	130 (90.28)	353 (94.89)
Substance use		
Alcohol	96 (66.67)	224 (60.22)
Tobacco*	97 (67.36)	174 (46.77)
Cocaine*	79 (54.86)	141 (37.90)
Marijuana	36 (25.00)	76 (20.43)
Other	3 (2.08)	4 (1.08)
Chronic hypertension	5 (3.47)	7 (1.88)
Preeclampsia	7 (4.86)	14 (3.76)
Oligohydramnios	10 (6.94)	13 (3.49)
Polyhydramnios	0	2 (0.54)
Prolonged rupture of membranes	3 (2.08)	5 (1.34)
Treated for chorioamnionitis	4 (2.78)	11 (2.96)
Cesarean section delivery	32 (22.22)	56 (15.05)
Neonatal characteristic		
Birth weight, g, mean (SD)*	2472.94 (241.65)	3344.03 (404.91)
Gestational age, wk, mean (SD)	38.75 (1.34)	38.99 (1.33)
Major congenital anomaly, No. (%)	0	0
Proven in utero infections, No. (%)	8 (5.56)	15 (4.03)

Abbreviations: HMO, health maintenance organization; IUGR, intrauterine growth restriction.

*Statistically significant difference ($P < .05$) between children with and without IUGR.

The clinical and demographic characteristics of the children born with IUGR and those without IUGR status are presented in **Table 2**. Maternal age was higher and tobacco and cocaine use during pregnancy were higher among the women with infants who had IUGR at birth as compared with those infants who did not have growth restriction at birth. The average weight of the infants who had IUGR at birth was 871 g less than those who did not have IUGR at birth.

MEASUREMENTS AT 6 YEARS OF AGE

A systolic BP in the 95th percentile or higher was noted among 90 (17.4%) of 516 children born full term. A dia-

Table 3. Risk for Hypertension at Age 6 Years

	No. (%)		Unadjusted Relative Risk (95% Confidence Interval)*
	Hypertension (n = 93)	No Hypertension (n = 423)	
Site			
A (n = 187)	26 (14)	161 (86)	2.5 (1.4-3.3)
B (n = 13)	34 (26)	99 (74)	1.2 (0.8-2.0)
C (n = 97)	30 (31)	67 (69)	5.0 (2.0-10.0)
D (n = 99)	7 (7)	92 (93)	1.0
Sex			
M (n = 275)	45 (16)	229 (84)	0.8 (0.6-1.2)
F (n = 241)	48 (20)	193 (80)	1.0
Race			
Black (n = 399)	76 (19)	323 (81)	1.4 (0.8-2.6)
Other (n = 34)	6 (18)	28 (82)	1.3 (0.5-3.3)
White (n = 83)	11 (13)	71 (87)	1.0
Maternal education, y			
<12 (n = 204)	31 (15)	173 (85)	0.9 (0.5-1.4)
12 (n = 205)	43 (21)	161 (79)	1.2 (0.7-1.9)
>12 (n = 107)	19 (18)	88 (82)	1.0
Substance use during pregnancy			
Smoking			
Yes (n = 271)	54 (20)	216 (80)	1.3 (0.9-1.8)
No (n = 245)	39 (16)	206 (84)	1.0
Alcohol			
Yes (n = 320)	51 (16)	269 (84)	0.7 (0.5-1.1)
No (n = 196)	42 (22)	153 (78)	1.0
Marijuana			
Yes (n = 112)	21 (19)	91 (81)	1.0 (0.7-1.6)
No (n = 404)	72 (18)	331 (82)	1.0
Cocaine			
Yes (n = 220)	45 (20)	175 (80)	1.3 (0.9-1.8)
No (n = 295)	48 (16)	247 (84)	1.0
Opiates			
Yes (n = 38)	7 (18)	31 (82)	1.1 (0.5-2.2)
No (n = 421)	70 (17)	351 (83)	1.0
Preeclampsia			
Yes (n = 21)	4 (19)	17 (81)	1.1 (0.4-2.6)
No (n = 494)	89 (18)	405 (82)	1.0
IUGR status at birth			
Yes (n = 144)	35 (24)	109 (76)	1.6 (1.1-2.3)
No (n = 372)	58 (16)	313 (84)	1.0
BMI at age 6 y, mean (SD)	17.8 (3.9)	16.2 (2.2)	1.6 (1.0-2.1)*

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IUGR, intrauterine growth restriction.

*Value is expressed as mean difference (95% confidence interval).

stolic BP in the 95th percentile or higher was recorded among 14 (2.7%) of 516 children born full term. A systolic BP in the 95th percentile or higher was seen among 93 (18.0%) of 516 children. These measurements were the mean of 3 readings. The first reading was the highest of 3 systolic BP readings in 44% of the children, while the first reading was the highest of 3 diastolic BP readings in 36% of the children.

The characteristics of the children with and without hypertension are presented in **Table 3**. The rate of hypertension at 6 years of age was greater among children who had IUGR at birth as compared with those who were of normal weight. Center differences in the rate of hypertension were also noted. The rate of hypertension did not differ among children exposed to maternal use of to-

Table 4. Adjusted Relative Risk of Hypertension at Age 6 Years

Risk Factor	Adjusted Relative Risk* (95% Confidence Interval)
Site	
A vs D	0.2 (0.1-0.5)
B vs D	0.5 (0.3-0.8)
C vs D	0.8 (0.5-1.2)
Race	
Black vs white	1.0 (0.5-2.0)
Other vs white	1.2 (0.5-3.1)
Sex	
F vs M	1.0 (0.7-1.5)
Maternal education, y	
<12 vs >12	0.8 (0.5-1.3)
12 vs >12	1.0 (0.6-1.5)
Maternal preeclampsia	0.7 (0.3-1.7)
BMI at age 6 y, per unit increase	1.1 (1.1-1.2)
IUGR	1.8 (1.2-2.7)
Tobacco exposure	1.4 (0.8-2.4)
Alcohol exposure	0.8 (0.5-1.1)
Marijuana exposure	0.9 (0.5-1.4)
Cocaine exposure	1.2 (0.7-1.8)

Abbreviations: See Table 3.

*Adjusted relative risks are obtained from Poisson regression modeling risk of hypertension at 6 years of age, adjusting for all the factors presented in Table 4.

bacco, alcohol, marijuana, cocaine, and opiates during pregnancy as compared with those not exposed to these substances. Maternal educational status did not influence rate of hypertension.

The mean (SD) BMI at 6 years of age among children who had IUGR at birth was 15.3 (2.0) as compared with those who did not have growth restriction at birth (16.9 [2.8]) ($P<.001$).

The multivariable logistic regression analyses evaluating model of risk for hypertension show that IUGR status at birth (relative risk, 1.8 [95% confidence interval, 1.2-2.7]) and BMI (per unit increase, relative risk, 1.1 [95% CI, 1.1-1.2]) increase risk for hypertension (**Table 4**). Again, center differences were noted in the risk for hypertension at 6 years of age.

COMMENT

In this report, we have demonstrated that in full-term infants, IUGR status at birth appears to be linked to risk for hypertension in childhood after adjusting for potential confounders. These results suggest that IUGR status at birth may result in lifelong consequences because hypertension is a marker for adult cardiovascular disease.

We excluded preterm infants in this study because preterm birth has effects on the vascular system that persist to adult life. Kistner et al¹³ have demonstrated that preterm birth affects the retinal vascular system, both functionally and structurally, resulting in a lower threshold for the development of vascular disease. Another reason for excluding children who were born preterm was that BP has been found to be significantly higher in very low-birth-weight subjects in late adolescence as compared with normal-birth-weight subjects.¹⁴

Blood pressure was measured in our study by the portable Dinamap monitor, an oscillometric device, and compared with normative data obtained by the sphygmomanometer auscultatory method.¹⁶ Relationships between BP measurements using the Dinamap monitor and the sphygmomanometer method have been debated. Earlier reports by investigators have noted the accuracy of BP measurements by the Dinamap monitor in infants and children.^{19,20} Most recent data, however, have shown that higher readings are obtained by the Dinamap monitor as compared with the sphygmomanometer.²¹ However, the Dinamap monitor is the most common instrument used in current clinical practice. The BP cuffs used in this study were based on the recommendations established by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.¹⁶ By doing so, we believe we have avoided the pitfalls of inappropriate cuff selection.²²

In this study, an association between increases in BMI and elevation in BP was noted. The systolic BP of children, adolescents, and adults is affected by BMI measured at corresponding ages.²³⁻²⁶ Although overweight and obesity status were not seen in the 6-year-old children in this report, we anticipate the frequency of these conditions to increase as the children continue to be evaluated at older ages,^{27,28} when it is anticipated a greater association of BMI with hypertension can be demonstrated.

Race and socioeconomic factors have been shown to influence hypertension. Black Americans are at higher risk for hypertension than white Americans, and an increase in overweight and obesity in Hispanic individuals has been reported.^{25,26,29} Among minorities, the relative risk for hypertension is significant for both sex and overweight status. The majority of the children in our study were black; however, no risk for hypertension was attributed to race. Unfortunately, we did not measure maternal BP at the child's 6-year clinic visit because this is an important confounder. We are currently obtaining BP measurements at the 9-year visit of the children. We did find clinical site differences, which need to be explored. In our study, at 6 years of age, we did not find a relationship between sex and hypertension. Socioeconomic status was measured as maternal education in our study and was not associated with hypertension.

The association between maternal lifestyle during pregnancy and risk for hypertension in the offspring is unclear when examining prenatal cocaine exposure and elevated BP in childhood. Horn⁸ examined 12 infants following in-utero cocaine exposure and noted that half of the infants had hypertension or normal BP. Needlman et al⁹ found no differences in BP between 32 cocaine-exposed and 23 nonexposed infants at 8 to 26 months of age. Echocardiography of infants born to women following cocaine exposure and comparison infants (total of 87 infants evaluated) has not demonstrated any difference in the shortening fraction of the left ventricle or abnormalities in cardiac rhythm.³⁰ Prenatal exposure to cigarettes has been associated with elevated BP at birth and at 12 months of age.³¹ We did not find any association with either cocaine, opiate, marijuana, tobacco, or alcohol use during pregnancy and hypertension at 6 years of age.

Additional risk factors for hypertension are diet^{32,33} and genetic determinant of cardiovascular risk.³⁴ New arteriosclerosis risk factors in obese children and adolescents and children and adolescents with hypertension and diabetes are now available.³⁵ As we follow up our cohort longitudinally we will obtain data on these risk factors.

Sixteen percent of children who did not have growth restriction at birth were found to have hypertension at 6 years of age. We suggest that this high rate reflects an atypical study group that is predominantly inner city and African American and has a low socioeconomic status.

In summary, in this study we have demonstrated an association between IUGR status at birth and elevated BP at 6 years of age among full-term infants. Six years of age may be too young to label a child at risk for hypertension; however, an awareness of the prehypertensive status in childhood may serve as a signal to institute healthful lifestyle changes that might avert future cardiovascular disease.³⁶

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