Blood Pressure Values in 8–12 Year Old Children with a History of Intrauterine Growth Retardation

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ABSTRACT: **Background:** Epidemiological studies have found that intrauterine growth retardation (IUGR) is closely related to hypertension and is associated with a reduced number of nephrons that may be a predisposing factor for the development of hypertension.

Objectives: To determine whether blood pressure levels of children with a history of IUGR are higher than those of children without IUGR.

Methods: Diastolic, systolic and mean arterial blood pressure levels were measured in 64 children aged 8–12 years old with a history of IUGR (mean birth weight 1780 ± 422 g) and compared with 64 age and gender-matched controls who had a normal birth weight (mean 3134 ± 594 g).

Results: Contrary to previous reports, systolic blood pressure values were significantly lower in the IUGR group compared to the controls (91.6 ±11.3 vs. 96.6± 13.9, $P = 0.027$). There was no difference in diastolic blood pressure values. In the IUGR group, systolic blood pressure correlated significantly with current weight ($P < 0.01$) and body mass index ($P < 0.05$), and diastolic blood pressure with weight gain between age 2 and 4 years ($P < 0.05$). None of the blood pressure values correlated with birth weight.

Conclusions: Children born with IUGR have lower systolic blood pressure levels than matched controls at age 8–12 years. These data indicate that postnatal weight gain in this group has a greater impact on systolic blood pressure than birth weight.

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KEY WORDS: hypertension, blood pressure, children, small-for-gestational age, intrauterine growth retardation

Epidemiological data indicate that hypertension is more common in adults who were smaller than normal at birth [1,2] and that adult systolic blood pressure is inversely related to birth weight [1-3]. Most theories explaining the biological mechanisms that underlie the association between birth weight and blood pressure focus on the long-term structural consequences of the in utero environment, such as reduced number of nephrons [4], altered arterial compliance [5], and fetal exposure to glucocorticoid excess [6]. These hypotheses have been supported by a series of animal and human studies [7,8], according to which intrauterine growth retardation is associated with a reduced number of nephrons and may be a predisposing factor for the development of hypertension.

A negative relationship between birth weight and high blood pressure has also been reported in children [2,3,9,10] and adolescents [11]. However, another study found an association between high systolic blood pressure and the proportion of placental weight to birth weight, but not with birth weight, in 7 year old children with IUGR [12]. The present study was conducted to determine whether a history of IUGR poses a risk of hypertension developing at age 8–12 years.

SUBJECTS AND METHODS

This report is part of a long-term prospective follow-up study designed to determine school-age developmental/cognitive outcome of infants with IUGR [13,14]. Since 1992, all infants born at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, with a birth weight below the 5th percentile for gestational age according to Israeli percentile curves [15], have been followed at the Child Development Center. Children with genetic syndromes, major malformations or congenital infection were excluded from the current study. The remaining children had mainly vascular-induced IUGR of a late-onset asymmetric type.

We analyzed diastolic, systolic and mean arterial blood pressure values in 64 consecutive children with a history of IUGR who were around 9 years old (range 8.01–11.90 years). Their findings were compared with those of 64 gender-matched children within a similar age range (7.71–14.05 years) who had been born with appropriate-for-gestational-age weight and were recruited from among healthy and normal children who

IUGR = intrauterine growth retardation

Table 1. Characteristics of intrauterine growth retardation and control groups

	IUGR (n=64)	Controls (n=64)	*P*
Age (yrs)	9.4 ± 0.6	9.1 ± 1.4	0.214
Gender (M:F)	36:64	42:58	0.294
Neonatal parameters			
Mean birth weight (g)	1780 ± 422	3134 ± 594	‹ 0.001
Mean gestational age (wks)	36.4 ± 2.6	39.2 ± 2.2	‹ 0.001
Premature infants (n, %)	27 (42)	6 (9)	‹ 0.001
Growth measurements			
Current weight (kg)	27.4 ± 6.8	29.4 ± 7.7	0.118
Current height (cm)	131.4 ± 5.2	131.9 ± 9.9	0.763
BMI	15.8 ± 3.2	16.7 ± 2.6	0.073

IUGR = intrauterine growth retardation, M = male, F = female, BMI = body mass index

were followed at general pediatric community clinics. Children who were born prematurely (gestational age < 37 weeks) were included in the study if their birth weight was < 5th percentile for gestational age. Overall, 27 children in the IUGR group (42%) and 6 in the control group (9.3%) were born prematurely [Table 1].

Systolic, diastolic and mean arterial blood pressure values were routinely measured by the same specially trained nurse who was unaware of the aim of this study and who performed all the measurements for both the study and control children. A standard clinical mercury sphygmomanometer with an appropriate cuff size was used, with the cubital fossa supported at heart level. Measurements were performed in a controlled environment, with the child in a seated position and after 5 minutes of rest [15]. Systolic pressure was determined by onset of the "tapping" Korotkoff sounds, and diastolic pressure was defined as the fifth Korotkoff sound (K5). Two consecutive measurements were performed three times with 5 minute intervals between each pair, for a total of six measurements. The averages of the six systolic and diastolic blood pressure measurements were used in the data analysis. The mean arterial pressure was computed as the sum of the diastolic pressure and one-third of the pulse pressure. Body weight and height were measured in all children and body mass index was calculated accordingly. Height for age was determined by the height percentile according to standard growth curves. Blood pressure was rated as normal, high-normal or high (hypertension) by height percentile on the basis of the normative tables published in 2004 by the National High Blood Pressure Education Program [16]. 'Normal' blood pressure was defined as a systolic and diastolic pressure < 90th percentile for age and gender, 'high-normal' blood pressure ≥ 90th but < 95th percentile, and 'hypertension' as an average ≥ 95th percentile for age and gender on at least three separate occasions. Details of birth weight and gestational age were obtained from hospital charts. A family history (first and second-degree relatives) of hypertension, renal disease and diabetes mellitus was obtained by means of a questionnaire during a personal interview with the parents.

STATISTICAL ANALYSIS

The unpaired *t*-test was used to compare between-group differences in mean systolic, diastolic and mean arterial pressure, as well as age, birth weight, current weight, height and BMI. The frequency of children with high-normal blood pressure in each group was compared by the chi-square test, as was the frequency of hypertension and renal disease in family members. The groups were also compared for the three blood pressure parameters by the univariate analysis of variance (ANOVA) with adjustment for current weight and height. We calculated three sequential child weight gains (birth to 2 years, 2–4 years and 4–9 years) for each IUGR subject. Pearson's correlation was used to correlate blood pressure values with the birth weight, length and head circumference, child weight gains, and current weight, height and BMI of the IUGR children. Spearman's correlation was used to correlate blood pressure values with maternal hypertension and maternal pregnancy weight gain (defined as > 12 kg weight gain during pregnancy). Differences between full-term IUGR and controls were also measured by the unpaired *t*-test. The multivariate regression analysis was used to search for the best predictor for systolic, diastolic and mean arterial blood pressure.

RESULTS

Table 1 summarizes the demographic data, perinatal parameters and current weight, height and BMI of the IUGR and control groups. As expected, the mean birth weight was significantly lower among the children with a history of IUGR compared to the controls ($P < 0.001$). There were no significant differences between the IUGR and control groups in male:female ratio, current age, and family history of hypertension, renal disease and diabetes mellitus. Systolic blood pressure values were significantly lower for the IUGR group than for the controls ($P = 0.027$), while there was no group difference in diastolic blood pressure values. Mean arterial pressure was also lower in the IUGR group than in the control group ($P = 0.051$) [Table 2]. A comparison of the rates of high blood pressure in the two groups yielded similar findings. None of the IUGR children had high systolic blood pressure, while among the control children four had high and seven had high-normal systolic blood pressure levels. Diastolic blood pressure was high-normal in one IUGR child and in three control children [Table 2]. Current weight and height were similar in both groups [Table 1]. When current weight was used as a covariate, however, there were no group differences in blood pressure values: systolic ($F = 3.114$, $P = 0.08$), diastolic ($F = 1.159$, $P = 0.284$) and mean arterial pressure ($F = 2.212$, $P = 0.139$).

BMI = body mass index

Table 2. Blood pressure and growth parameters at age 9 years in the IUGR and control groups

	IUGR (n=64)	Controls (n=64)	*P*
Blood pressure values			
Systolic BP (mmHg)	91.6 ± 11.3	96.6 ± 13.9	0.027
Diastolic BP (mmHg)	56.0 ± 8.5	58.4 ± 9.0	0.133
Mean arterial pressure (mmHg)	67.8 ± 8.4	71.7 ± 10.0	0.051
High blood pressure			
Systolic BP ≥ 95th (n, %) 95th › systolic BP ≥ 90th (n, %)	0 (0) 0 (0)	4 (6.2) 7 (10.9)	0.003
Diastolic BP ≥ 95th (n, %) 95th › diastolic BP ≥ 90th (n, %)	0 (0) 1 (1.6)	0 (0) 3 (4.7)	0.310
Mean arterial pressure ≥ 95th (n, %) 95th › mean arterial pressure ≥ 90th (n, %)	0 (0) 1 (1.6)	3 (4.7) 9 (14.1)	0.018

BP = blood pressure

In the IUGR group, the mean weight gain between 0 and 2 years was 9.0 ± 1.5 kg, between 2 and 4 years 3.6 ± 1.6 kg and between 4 and 9 years 13.3 ± 5.1 kg. The correlations between blood pressure values and birth parameters, weight gain and current measurements are presented in Table 3. No significant correlation was found between any of the three blood pressure values and birth weight, length and head circumference, maternal hypertension, and maternal weight gain during pregnancy [Table 3]. However, it is notable that the correlation with birth parameters was negative (i.e., the lower the birth weight, length and head circumference, the higher the blood pressure), but with no statistical significance [Table 3].

To exclude the effect of prematurity, we compared the full-term IUGR children (n = 37) with the full-term controls [Table 4] and found similar results: there were no differences in diastolic blood pressure values, but significantly lower systolic and mean arterial pressures were calculated in the full-term IUGR group compared to the controls. A regression analysis revealed that the best predictor for systolic blood pressure was weight gain between age 0 and 2 years, and that the best predictor for diastolic and mean arterial blood pressures was weight gain between age 2 and 4 years.

Table 3. Correlation of blood pressure values and growth parameters in children with IUGR (n=64)

	Systolic BP	Diastolic BP	Mean arterial pressure
Birth weight	*r* = -0.170, *P* = 0.178	*r* = -0.045, *P* = 0.722	*r* = -0.107, *P* = 0.402
Birth length	*r* = -0.082, *P* = 0.562	*r* = -0.010, *P* = 0.944	*r* = -0.044, *P* = 0.757
Birth head circumference	*r* = -0.147, *P* = 0.278	*r* = 0.042, *P* = 0.760	*r* = -0.038, *P* = 0.783
Maternal hypertension	*r* = 0.100, *P* = 0.449	*r* = 0.156, *P* = 0.234	*r* = 0.151, *P* = 0.248
Maternal weight gain (› 12 kg)	*r* = 0.147, *P* = 0.275	*r* = 0.162, *P* = 0.228	*r* = 0.175, *P* = 0.193
Weight gain	*r* = 0.297, *P* = 0.036	*r* = 0.168, *P* = 0.244	*r* = 0.249, *P* = 0.081
2–4 yrs	*r* = 0.248, *P* = 0.117	*r* = 0.330, *P* = 0.035	*r* = 0.336, *P* = 0.031
4–9 yrs	*r* = 0276, *P* = 0.045	*r* = 0.201, *P* = 0.149	*r* = 0.257, *P* = 0.063
Current height	*r* = 0.208, *P* = 0.099	*r* = 0.238, *P* = 0.058	*r* = 0.253, *P* = 0.044
Current weight	*r* = 0.355, *P* = 0.007	*r* = 0.226, *P* = 0.072	*r* = 0.302, *P* = 0.015
BMI	*r* = 0.313, *P* = 0.012	*r* = 0.176, *P* = 0.174	*r* = 0.258, *P* = 0.040

DISCUSSION

The results of the present study demonstrated that mean blood pressure values were not higher for 8–12 year old children who had a history of IUGR compared to normal age-matched controls. On the contrary, systolic and mean arterial blood pressures were significantly lower for the IUGR children. These findings do not concur with previous studies which reported that blood pressure is inversely related to birth weight in children as in adults [9,10,17]. Other studies, however, pointed out that correction for body weight should be considered [18]. Several investigators reported a direct relationship between weight and height and blood pressure already appearing at age 5 years in children with normal birth weight [19]. There apparently had been an adequate catch-up

Table 4. Blood pressure and growth parameters in full-term IUGR and control groups

	Full-term IUGR (n=37)	Full-term controls (n=58)	*P*
Age (yrs)	9.4 ± 0.6	9.3 ± 1.6	0.755
Gestational age (wks)	38.2 ± 0.9	39.7 ± 1.6	0.001
Mean birth weight (g)	2069 ± 204	3218 ± 549	0.001
Blood pressure values			
Systolic BP (mmHg)	88.7 ± 10.5	96.4 ± 14.2	0.003
Diastolic BP (mmHg)	54.9 ± 8.4	58.4 ± 9.1	0.065
Mean arterial pressure (mmHg)	66.2 ± 8.1	71.1 ± 10.3	0.017
High blood pressure			
Systolic BP ≥ 95th (n, %) 95th › systolic BP ≥ 90th (n, %)	0 (0) 0 (0)	3 (5.2) 7 (12.1)	0.028
Diastolic BP ≥ 95th (n, %) 95th › diastolic BP ≥ 90th (n, %)	0 (0) 0 (0)	3 (5.2) 8 (13.8)	0.223
Mean arterial pressure ≥ 95th (n, %) 95th › mean arterial pressure ≥ 90th (n, %)	0 (0) 0 (0)	3 (5.2) 8 (13.8)	0.094
Growth measurements			
Weight (kg)	26.7 ± 4.9	28.8 ± 7.1	0.982
Height (cm)	131.1 ± 4.8	131.1 ± 9.9	0.138
BMI	15.4 ± 2.1	16.5 ± 2.4	0.030

of growth parameters among our IUGR children, since there were no differences in their weight and height compared to the controls. When we adjusted for the parameter of current weight, there were no group differences in mean blood pressure values. This suggests that the differences that had been detected for systolic and mean arterial pressure were associated with the current weight. Furthermore, the weight gain was significantly associated with mean blood pressure, suggesting that the mean blood pressure of the IUGR children reflected their catch-up growth and correlated with their final weight. It is possible that the higher BMI among the controls was enough to raise their blood pressure to a level that surpassed the effect of IUGR.

A recent study concluded that although a U-shaped relationship between birth weight and blood pressure was found in a contemporary, well-nourished western population of full-term newborns, postnatal weight gain was the dominant factor associated with the high-risk children [20]. A more rapid increase in weight-for-length in the first 6 months of life was reportedly associated with higher early childhood systolic blood pressure, particularly in children who are thin at birth [21]. Another study suggested that higher weight gain in the first 2 years of life of children who were small for gestational age was associated with higher mean blood pressure levels in adulthood [22]. This supports our findings that blood pressure correlated with weight gain and current weight, but not with birth weight, and indicates that the effect of current weight is greater than the effect of birth weight. Our findings thus emphasize that follow-up studies of blood pressure in IUGR children must correct for weight and weight gain in their analysis.

Finally, recent data have indicated that obesity and other lifestyle factors, such as physical inactivity and increased intake of high-calorie high-salt foods, are responsible for the trend of a substantial rise in average blood pressure levels among American children over the last decade [23]. Thus, environmental factors may overshadow the prenatal factors described in this paper in terms of the pathogenesis of hypertension in children.

One of the limitations of this work was the reliance on resting casual blood pressure and not on ambulatory measurements, thus precluding detection of occult blood pressure abnormalities. The sample size was also relatively small. Additionally, a relatively large number (42%) of our IUGR study children were born prematurely, mostly due to induced early labor to prevent further fetal distress. This characteristic apparently did not have any effect on blood pressure, since the blood pressure trends were similar for term-born IUGR children and controls [Table 4]. These findings are in disagreement with those of a recent study of IUGR children who were born very preterm and who had a higher incidence of high blood pressure in adulthood [24]. Another study concludes that individuals born very preterm have higher daytime systolic blood pressure and a higher risk of hypertension at a young adult age. However, this study did not find a difference between small- or appropriate-for-gestational age prematurely born individuals [25].

In conclusion, our findings did not support the notion that children born with IUGR are at higher risk for developing hypertension, but rather that the rate of postnatal weight gain was a stronger determinant for blood pressure levels. We therefore recommend that IUGR children be followed routinely, starting in childhood, to prevent excessive weight gain and hypertension.

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