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Prematurity-related hypertension in children and adolescents born at the Baruch-Padeh medical center, Poriya, North Israel

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Abstract

Introduction: Hypertension (HTN), defined as blood pressure (BP) equal to or above 95th percentile for age, height, gender. Hypertension has a prevalence of up to 5-8% in children. It is a well-known risk factor for cardiovascular diseases affecting the heart, brain and kidneys. HTN presenting at a younger age correlates with increased severity and likelihood of finding an underlying reason for it, therefore defining it as secondary HTN. Recent studies reveal that premature infants (<37 weeks) commonly have higher BP, leading to the possibility of a certain connection between the prematurity and hypertension in future.

Methods and materials: 87 prematurely born children were examined by criteria of BP measurements at birth and at present in order to evaluate their tendency for HTN in respect to the extent of their prematurity (2009-2018).

Results: Those children presented an increased prevalence of both infantile and childhood HTN (16.7% and 20.7% respectively), compared to general population. A negative correlation between birth week and childhood BP values was found, meaning that BP increased monotonically by earlier gestational age, and was found to be statistically significant in diastolic BP.

Conclusions: Prematurely born individuals are at a higher risk to develop childhood HTN. These results encourage the initiation of screening programs for this population.

Introduction

Hypertension (HTN) has a prevalence of up to5-8% in children [1]. HTN increases the risk of ischemic heart disease, intracranial hemorrhage and renal disease. Early diagnosis and treatment can helps decrease or even prevent those damaging effects [2-5].

Blood pressure (BP) increases with body mass, those measurements should relate to a percentile according to the gender, age and height of the child [6,7]. Normal BP has systolic & diastolic values under the 90th percentile, on three measurements. Pre-HTN is defined as BP between 90-95 percentile or over 120/80 up to 95th percentile, while HTN is BP equal to or above 95th percentile for height; gender; age [7].

Etiology

In adults almost 90% of HTN is primary, while in children about 80% is secondary. The difference stems from the adolescence period in which the prevalence of primary HTN increases substantially [4]. Secondary HTN at childhood is related to obesity, chronic conditions, cardiac disease; endocrine disease; renal disease; neurological disease, post-surgical state, drugs birth control pills in adults [6-9]. Prematurely born children or those with a low birth weight have been found to be candidates of pre-HTN [10].

Prematurity and hypertension

Preterm birth is defined as a birth at fewer than 37 weeks of gestation. Depending on how early an infant is born, he or she may be: late preterm (born between 34 and 36 weeks of gestation), moderately preterm (32-34 weeks), very preterm (<32 weeks) or extremely preterm (born at or before 28 weeks of gestation) [1]. The prevalence of preterm birth in developed countries is about 5-7%, and up to 12% in the USA [1]. Recent studies reveal that premature infants commonly have higher BP [10-12]. The reason for it remains unclear. Some blamed low birth weight, but no significant difference in BP has been found between infants with low birth weight respective to their gestational age (SGA) and infants with appropriate weight for their gestational age (AGA) [9].

The research of Shankaran, *et al.* supports this theory by displaying higher BP values among children in term with IUGR compared to a control group [13]. The pathophysiology of this may be related to incomplete intra-uterine growth of the kidney, among other reasons [14,15].

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Methods and materials

Study design

This research is both of retrospective and prospective, examining the relationship between prematurity and HTN in childhood.

87 constitute the study population

Children with comorbidities such as any type of syndromes, a single kidney or an ectopic kidney were excluded from the trial.

Data collection

Demographic data and clinical data regarding the birth was extracted from medical archives. Measurements of BP, weight and height were taken, in addition to blood and urine tests to evaluate kidney function.

Statistical analysis

Data analysis was performed using SPSS software, 25th version. Correlation between quantitative variables was assessed using the Spearman Correlation test. Correlation between qualitative variables was assessed using Chi-square test. Correlation between two groups with continuous variables was assessed using T-test. For evaluation of statistical significance, a P-value of 0.05 or under was used.

Results

Demographic data of research population

Overall, this research examined 87 pediatric patients born before 37 weeks of gestation. The male to female ratio among our subjects (Table 1) was consisting with the ratio in Israel's northern district [16]. Also the distribution of ethnic origin is consistent to this area, with a slightly higher prevalence of Arab-Muslims in our research population (43.7% of subjects compared to 37.7% in general population).

Our research population are 1-10 years old. The mean age is 7.34 with a standard deviation (SD) of 2.08. The distribution of ages according to genders is similar. Observing the birth weight of our subjects, the lowest birth weight recorded was 0.875 kg and the highest was 3.52 kg. Overall, the mean birth weight is 2.20 kg, with a SD of 0.58.

The mean gestational age among our subjects is 34.56 (equivalent to 34 weeks and 4 days), with a SD of 2.25. The minimal value is 27.14 (27 weeks and 1 day) and the maximal is 36.86 (36 weeks and 6 days). The distribution is presented in (Figure 1).

Hypertension prevalence in research population

BP measurements on the first day of life were recovered from medical archive for 72 patients. BP measurements were categorized into groups of Normal BP (<90th percentile), Pre-HTN (90th-95th percentile) and HTN (≥ 95th percentile), according to Pejovic, *et al.* Studies [17]. Overall, 58 of the subjects (80.6%) were normotensive at birth, 2 of them (2.8%) had Pre-HTN and 12 (16.7%) had HTN at birth (Figure 2). Current BP was measured from all 87 subjects compiling this study and grouped according to American Academy of Pediatrics' 2017 Clinical Practice Guidelines [18]. Overall, only 53 of the subjects (60.9%) are currently normotensive, 16 of them (18.4%) have pre-HTN and 18 (20.7%) have HTN. When reviewing the incidence of HTN according to gender, no substantial difference was found (Figure 3). HTN prevalence was also examined in respect to the ethnicities comprising the Galilee region (Figure 4). Among the Arab-Christian population a substantially higher prevalence of Pre-HTN (28.6%) was noted. Similarly, Druze patients had a higher prevalence of Pre-HTN (12.5%), Stage 1-HTN (25%) and Stage 2-HTN (12.5%). No connection between ethnicity and BP was found to be significant (P-value=0.590, 0.173, 0.891 for total BP, systolic & diastolic accordingly).

Table 1. Demographic data of research population

		Count	%
Gender	Male	47	54%
	Female	40	46%
Pregnancy	Singleton	45	51.7%
	Multiple gestation	42	48.3%
Ethnicity	Jewish	30	34.5%
	Arab Muslim	38	43.7%
	Arab Christian	7	8%
	Druze Circassian	8 1	9.2% 1.1%
	Other	3	3.5%

Characteristics of current BP groups

A statistical analysis was performed on several criteria in an effort to define the main features of each BP group, according to current BP measurements (Table 2). Birth week and birth weight maintained a coordinated mean value in every BP group, suggesting of a strong association between the two. Overall, the mean birth week of normotensive patients and pre-hypertensive ones was similar, at about 34 weeks of gestation. Paradoxically, patients with Stage I HTN had a higher mean of gestational age compared to patients with Stage II HTN. The mean birth weight of those groups followed the same pattern.

Blood pressure values correlation to birth week in prematurely born children

In order to establish a correlation between birth week and BP values, the Median of birth week (35.14) was used. A significant positive correlation between birth week and BP at birth was found (P-value=0, 0.009, 0.001 for systolic, diastolic and Mean Arterial Pressure (MAP) respectively). Systolic and MAP at birth had a medium strength while diastolic BP showed only a weak correlation. This means that a lower birth week correlates to lower BP values at birth specifically (Table 3). When inspecting the connection between birth week and current BP, we can see a negative correlation of low strength. Hence, a lower birth week correlates to higher BP values. This correlation is significant in diastolic BP measurements (P-value=0.036), but not in the systolic and MAP ones (P-value=0.473, 0.073 respectively).

Distribution of BP groups according to levels of prematurity (Figure 5) did not detect a specific pattern, though it is suggesting a higher prevalence of HTN in those born 'late preterm' (34-36+6 weeks).

To further explore the effect of prematurity on HTN, we checked whether or not the research population kept their BP percentiles from birth to present days. Of the 58 children who have had a normal BP at birth, 37 (63.8%) kept a normal BP to today, but the rest, 21 children (36.2%) progressed to pre-HTN or HTN (10 (17.2%), 11 (19%) respectively).

When examining the population with pre-HTN according to current BP measurements, we can see that 71% of them were normotensive at birth. This is true also for the population with stage I HTN (73% of them were normotensive at birth) and stage II HTN (all of them were normotensive at birth) (Figure 6).

Factors in the neonatal period influencing current BP

Different medical conditions and interventions in the neonatal period may explain any variance between BP values at birth

Table 2. Characteristics of current blood pressure groups

		Normal BP		Pre-HTN		Stage 1 HTN		Stage 2 HTN	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total BP	Birth week	34.51	2.29	34.25	2.76	35.34	1.51	33.68	1.53
	Birth weight	2.20	0.52	2.18	0.66	2.34	0.73	1.85	0.42
	Current age	7.62	1.99	6.81	2.01	7.64	1.69	4.75	3.30
	Current BMI	16.33	2.50	16.49	2.73	15.45	2.54	15.63	3.70

Table 3. Blood pressure values correlation to birth week in prematurely born children

		BP measurement at birth			Current BP measurement		
		Systolic	Diastolic	MAP	Systolic	Diastolic	MAP
Week of birth	**Pearson Correlation**	0.436	0.281	0.379	-0.007	-0.194	-0.157
	P-value (Significant<0.05)	0	0.009	0.001	0.946	0.036	0.074
	Number of subjects	72	72	72	87	87	87

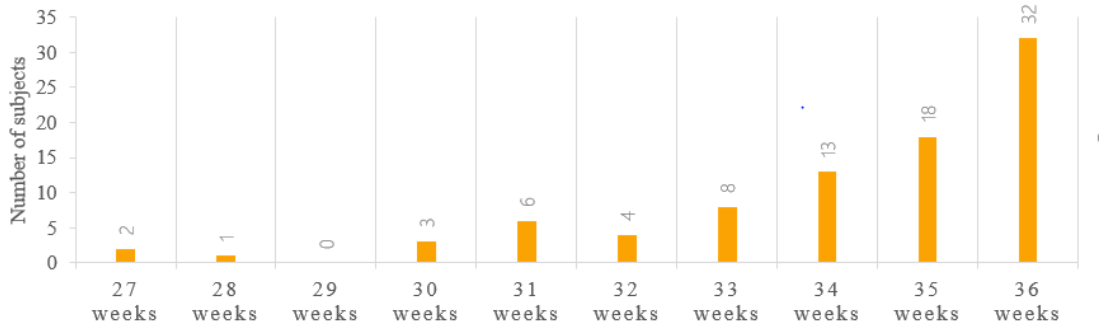

Figure 1. Gestational age distribution

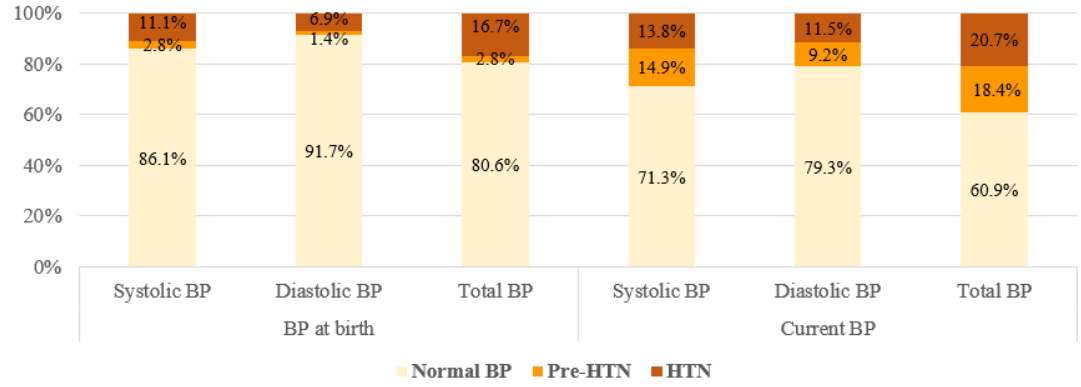

Figure 2. Hypertension prevalence in research population

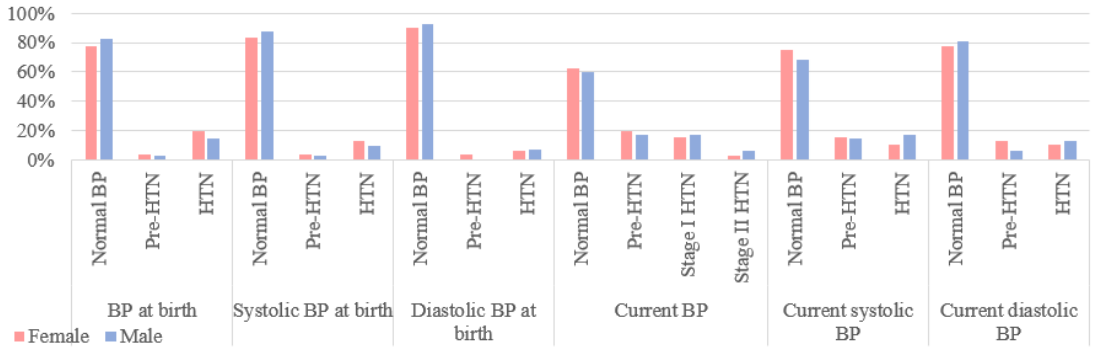

Figure 3. Hypertension prevalence according to gender

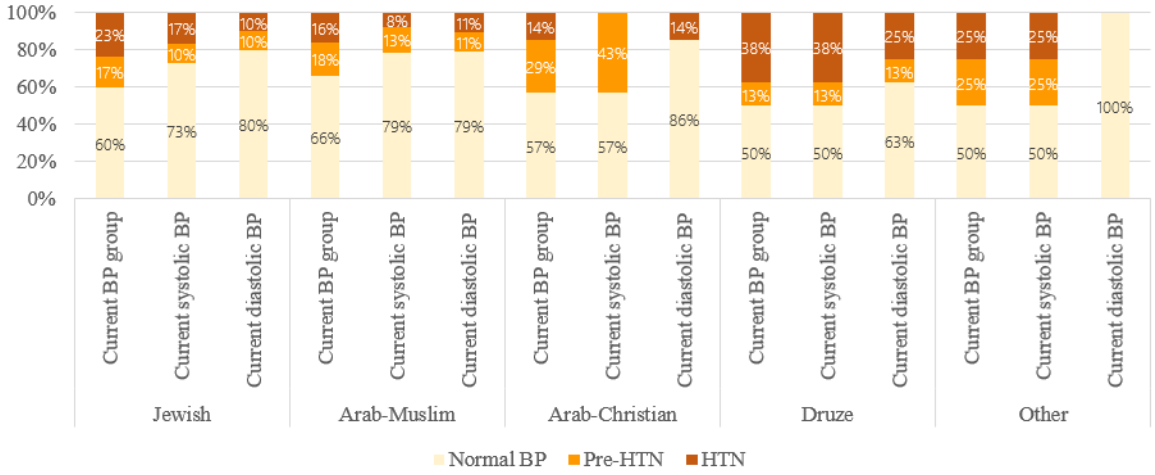

Figure 4. Hypertension prevalence among different ethnic groups

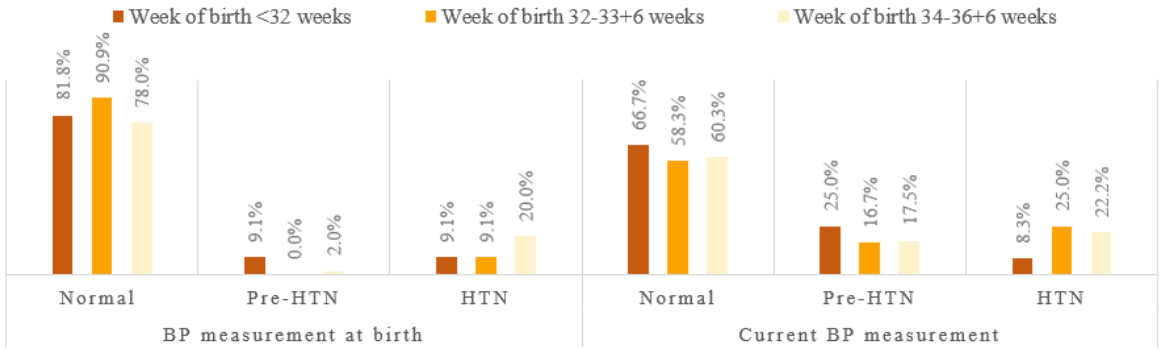

Figure 5. Distribution of BP groups according to gestational age

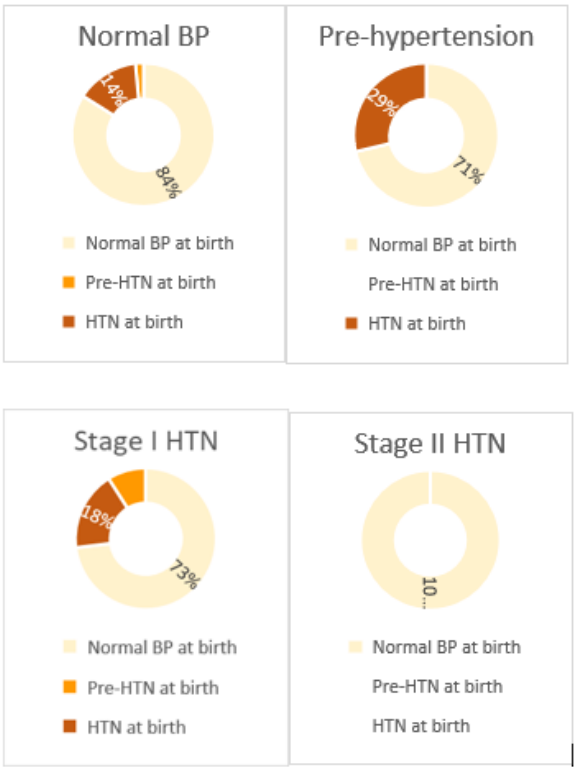

Figure 6. Origin of current blood pressure group

and those measured in present days. Patients who underwent umbilical catherization had a higher prevalence of Pre-HTN & HTN (50%) compared to others (39.1%). The correlation between umbilical catherization and current BP is significant in diastolic BP (P-value=0.013). Patients affected with prematurity related conditions investigated show a small increase in Pre-HTN & HTN states combined (46.2%) compared to research population (39.1%). The relationship between BPD and NEC to BP was found to be significant in Diastolic BP (P-value= 0.0007).

Discussion

In this research we sought to establish a connection between the week of birth and BP values. Our main hypothesis was that prematurity is correlated to a higher risk of HTN in childhood. Though most reports claim that the incidence of HTN in neonates (termed infantile HTN) is quite low, ranging from 0.2%-3% [19] our data showed the incidence among preemies is 16.7%. This can also be seen in current BP measurements. While publications report of a childhood pre-HTN prevalence of 2.2% to 3.5% and childhood HTN prevalence of 3.5% [18], our patients had a prevalence of 18.4% and 20.7%, respectively. Considering this, one can conclude that prematurity, being the common ground in all of our patients, is correlated to a higher prevalence of elevated BP and HTN.

The prevalence of HTN was found to be similar in males and females. Among the different ethnicities tested, Druze were found to have a particularly high incidence of HTN. This may be explained by a very early gestational age, small sample size and an increased mean

age among those patients. No updated data regarding the incidence of pediatric HTN in the different ethnicities residing in Northern Israel was found in order to compare.

A certain degree of correlation between the week of birth and BP values was found. At birth, a lower birth week correlated to lower BP values. This result corresponds to Pejovic, *et al.* and other studies of this nature which determined lower values to be normotensive for premature infants [17]. At childhood we found a negative correlation between the week of birth and current BP values, meaning that an earlier week of birth was associated with higher BP values. This correlation was significant in diastolic BP measurements but not in systolic and MAP measurements. We can assume that these results were insignificant due to the young age of our patients, since similar studies on adolescents are more positive [12], and due to a low portion of children who were born before 32 weeks, which are probably the ones most affected by this condition. In fact, distribution of BP groups according to gestational age suggests a slightly higher prevalence of HTN among those born at 34-36+6 weeks of gestation. This correlation agrees with the study of Crump, *et al.* in a Swedish national study of 636,000 births [12]. This study showed that a higher risk of HTN was not only found in correlation to delivery in a very early gestational age, but also among those born near term (35-36 weeks of gestation).

During pregnancy, mothers with gestational diabetes, pre-eclampsia and medication use had children more prone to childhood HTN. Since both gestational diabetes and maternal use of medication were associated with increased birth week, we can deduce that those conditions are not responsible to the correlation of early birth week and HTN. On the other hand, pre-eclampsia was associated with a lower birth week and with childhood HTN and so might be one of the contributing factors to HTN in this population. This is reasonable considering the fact that maternal HTN is an important risk factor for pre-eclampsia and maternal-child transmission of vascular dysfunction is one of the proposed mechanisms for childhood HTN [12].

Current laboratory measurements of creatinine and urea did not correlate positively to increased BP and therefore do not suggest renal damage as a contributing factor responsible for HTN in this population. It is possible that imaging studies of kidneys may shine another light on this situation. Instead, blood and urine sodium levels showed a very significant positive correlation to BP, indicating some role in HTN development.

Patients diagnosed with HTN in our research had a lower BMI compared to their companions, ergo ruling out obesity, a major risk factor for HTN, as the reason for the increased HTN prevalence found among our patients [18].

Conclusion

To summarize, this study suggests that prematurity correlates to lower BP at birth, but also to higher BP in childhood. In addition, prematurely born children have a much higher prevalence of elevated BP compared to general population, even in those born near term. These results encourage the initiation of HTN screening programs for this population. This work can aid in early diagnosis and treatment of such individuals, which are crucial in order to delay and possibly prevent the development of HTN-related morbidity and mortality in adulthood.

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