

Blood Pressure Profile in the 7th and 11th Year of Life in Children Born Prematurely

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Abstract

Background: Several research trials have analyzed the impact of prematurity on the prevalence of hypertension (HT). However, prospective long-term studies are lacking.

Objectives: The aim of this study was to evaluate the prevalence of HT at the age of 7 and 11 years in a regional cohort of preterm infants with a birth weight of ≤ 1000 g.

Patients and Methods: This study included 67 children with a birth weight of ≤ 1000 g who were born in Malopolska between September 2002 and August 2004. The control group consisted of 38 children born at term, matched for age. Each child underwent 24-h ambulatory blood pressure measurement (ABPM) twice, once at the age of 7 and again at 11 years. The presence of HT was estimated according to the mean arterial pressure (MAP) and a number of individual measurements.

Results: At aged 7 years, preterm infants had a significantly higher incidence of HT, defined on the basis of MAP (15% vs. 0%; $P < 0.02$) and on the percent of individual measurements (56% vs. 33%, $P < 0.036$). After taking into account the group of patients who received anti-HT treatment after the first part of the study, the incidence of HT at the age of 11 years based on MAP was 19% vs. 10%. Based on the individual measurements, it was 36.5% in the preterm infants vs. 24% in the control group. The differences were not statistically significant. At both time points, the preterm group had a higher mean heart rate (HR) than the control group.

Conclusions: Children born prematurely are predisposed to HT in later life, in addition to the persistence of an increased HR.

Keywords: Hypertension, Premature Infant, Extremely Low Birth Weight

1. Background

Preterm births account for 5.2 - 10.4% of live births in European countries (1). In the U.S., the percentage is even higher and reaches 12.5% (2). Mortality associated with dynamic complications that occur in the first few weeks of a preterm infant's life has markedly decreased in the last decade (3, 4). Despite this, preterm births continue to pose a challenge in perinatal healthcare, and they remain the major cause of death in the first years of a child's life (5, 6).

The most severe complications of prematurity are respiratory distress syndrome, intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, and sepsis. Prematurity also influences health issues in later life, with the complications including bronchopulmonary dysplasia, retinopathy (7, 8), learning difficulties, and behavioral disorders (9). Recently, several multicenter research trials have analyzed the impact of prematurity on health problems of children and adolescences. This research demonstrated that prematurity was an indepen-

dent risk factor for obesity, eclampsia, type 2 diabetes, and even breast cancer (10, 11). Many studies have also proven that hypertension (HT) occurs more often in ex-preterm infants. In a study of children with appropriate birth weight, significantly higher pressure values were measured already after the first month of preterms' life (12). Furthermore, birth parameters determine higher blood pressure (BP) values stronger than any anthropometric measurement (13).

Prospective studies are lacking on the health problems of ex-preterms throughout childhood and adulthood. This issue is more important than ever today, with increasing numbers of ex-preterms entering adulthood every year with many complications.

HT is one of the major causes of untimely death in the world (14). Pediatric HT is also a significant problem, as it frequently persists in adulthood and increases cardiovascular risks in later life (15-17). HT is present in 30 - 45% of adults, and its incidence increases with age (14). It was shown that only in a small percentage of HT patients, ele-

vated BP was an isolated problem. Many patients with HT were shown to have multiple cardiovascular risk factors and to have target organ damage. The most frequent types of target organ damage due to HT are left ventricular hypertrophy, intima-media thickening, and kidney damage (18). In children and adolescents, the most common HT-related organ damage is left ventricular hypertrophy, with a reported prevalence in children of 14 - 42%. Complications of elevated BP are often observed at the time of its diagnosis in children and affect subsequent health (19, 20). Therefore, HT in the first years of life is not only a pediatric problem.

We previously published the results of 24-h BP measurements of ex-preterms acquired at the age of 7 years. In this paper, we discuss the results collected at the age of 11 years. We selected the age of 6 - 7 years as the time of the first follow-up on the basis that this is when children in Poland start school. The second follow-up (age 11 years) was selected because it is just before maturation. Furthermore, in the second decade of life, the frequency of primary HT increases, which could influence outcomes. In our opinion, a 4-year-long follow-up is sufficient to observe changes in BP profiles.

2. Objectives

This was a prospective, 4-year-long observation study of the BP profiles of a large cohort of preterm infants with extremely low birth weights (ELBWs) and those of full-term infants. The hypothesis was that preterms with an ELBW (i.e., ≤ 1000 g) would have a greater risk of HT compared with that of full-term infants. Moreover, we speculated that proper management of early-diagnosed HT would have a beneficial effect and decrease the risk of severe HT (SHT) in later life.

3. Materials and Methods

A cross-sectional observational study was conducted in the outpatient pediatric department of the Polish-American children's hospital, Krakow, Poland between 30 December 2013 and 30 April 2015. The study cohort consisted of ELBW survivors recruited at birth and full-term, control participants enrolled when both groups were 6 - 7 years old. From 1 September 2002 to 31 August 2004, 169 newborns with a birth weight of < 1000 g were born alive in the southeast region (Malopolska) of Poland. All the children were hospitalized in three tertiary care neonatal intensive care units (NICU) in southeast Poland. Neonatal data were recorded daily during their stays in the NICUs in a prospective manner and stored in computer databases.

Ninety-one survivors were discharged from the NICUs and followed longitudinally. Those patients were subsequently invited to participate in the follow-up assessment at 6 - 7 years and in the present follow-up study. The inclusion and exclusion criteria are presented in Box 1. Detailed results of the follow-up performed at 6 - 7 years have already been published (21). The control group included age-matched children from one general practice office. The ethical committee for clinical investigations of Collegium Medicum, Jagiellonian University approved the study. All the parents signed informed consent prior to the study procedures.

Box 1. Eligibility Criteria for the Study Group

Criteria
Inclusion criteria
Birth weight ≤ 1000 g
Place of birth - Malopolska region
Exclusion criteria
Lack of parental consent
Chromosomal aberrations Multiple congenital malformations

3.1. Study Size Calculation

The study size was calculated using PS Power and Sample Size Calculations, version 3.0 (January 2009). Previous data indicated that systolic BP (SBP) and diastolic BP (DBP) were normally distributed, with a standard deviation (SD) of 10 mmHg (22). A difference in systolic and diastolic pressure lower than 6 mmHg is (in our opinion) clinically insignificant. We calculated that at least 60 experimental subjects and 30 control subjects were needed to reject the null hypothesis that the population means of the experimental and control groups were equal, with a probability (power) of 0.8. Our study allows detecting the lowest value that is relevant in clinical practice. The type I error probability associated with the test of the null hypothesis was 0.05.

3.2. Follow-Up at Age 10 - 11 Years

For all children, the parents of the child completed a questionnaire about the child's demographic data and health status. All the children underwent a physical examination, in addition to anthropometric measurements and 24-h BP monitoring.

3.3. Anthropometric Measurements

Using a stadiometer (SECA 214, Germany), body height was measured to an accuracy of 1 mm while the patient stood in an upright position, with his/her head set to the

ocular-ear position. Body mass was measured to an accuracy of 10 g, using a calibrated scales (Lublin, Poland). For each patient, the SD of height and weight was calculated to two decimal places.

3.4. Ambulatory BP Measurement (ABPM)

The Spacelabs Healthcare device, model 92017, with a properly matched pediatric cuff was used for 24-h ABPM. The device was programmed to obtain BP readings every 20 minutes during daytime and every 30 minutes during nighttime. Recordings with at least 80% validity were included in the analysis. Licensed ABPM software was used to calculate the following parameters: mean SBP, mean DBP, mean arterial pressure (MAP), and mean heart rate (HR). Each parameter was calculated for the daytime period, nighttime period, and 24-h period. The data obtained were converted to SD scores (z-scores). The daytime and nighttime periods in the first ABPM were based on those accepted in the literature as time slots, which for the majority of children are the time of activity (8.00 - 22.00 h) and the rest of the night (0.00 - 6.00 h). At the second visit, daytime and nighttime periods were defined on the basis of a diary completed by the child's parents. This approach was used due to the presence of huge differences in the sleep profiles of the children. Then, for each child, the 95th percentiles of SBP and DBP were found on the basis of proper charts (12). Nocturnal dipping was calculated as the percentage of nighttime decreases in MAP. Normal dipping was defined as a decline of $\geq 10\%$ (23).

3.5. Outcome Variables

The primary outcomes were HT and SHT (Table 1).

Two definitions of HT were used. The first definition was based on MAP. HT was diagnosed if the MAP value was equal to or higher than the 95th percentile for height and gender. The second definition utilized single BP measurements: the BP load. HT was confirmed when more than 25% of the measurements were in the ≥ 95 th percentile for height, gender, and age (24). Due to a lack of data necessary to analyze the MAP in children with a height below 120 cm, in children measuring between 110 and 120 cm, the standard for 120 cm was used. Due to exceptionally low heights, the presence of HT based on MAP was not evaluated in two children in the 7th year of life.

The presence of SHT was evaluated in children with confirmed HT. SHT poses a direct risk of target organ damage. SHT was diagnosed when SBP was ≥ 95 pc for height and gender, and the percent of SBP single measurements in ABPM ≥ 95 pc for height, gender and age was $\geq 50\%$ (25).

The secondary outcomes were as follows: 24-h, daytime, and nighttime SBP, DBP, MAP, HR, and nighttime dip-

ping. All data were analyzed as absolute values and z-scores.

The statistical analysis was performed with the use of Statistica 10.0 software. Qualitative values were compared by Fisher's exact test. To test for differences in continuous variables between the groups, a Student's t-test and the Mann-Whitney U test were used. Differences were considered statistically significant at a probability (type I error) of $\alpha \leq 0.05$.

4. Results

4.1. Population

The study group comprised 67 children born prematurely (mean gestational age of 27 ± 2.27 weeks) with ELBWs (mean birth weight of 850 ± 128 g). The mean age at the time of the measurements was 6.58 ± 0.37 years and 10.99 ± 0.34 years. The control group consisted of 38 children (95% of the available cohort) born full-term (mean gestational age of 39.8 ± 1.42 weeks), with a mean birth weight of 3571 ± 538 g. The mean age of the controls was 6.99 ± 0.88 years and 10.61 ± 0.85 years. The characteristics of the ELBW group and control group are presented in Table 2.

Children born prematurely were significantly shorter than full-term children. The mean height difference in the 7th year of life in the preterm vs. full-term group was 1SD (z-score: -0.89 vs. 0.18 , $P < 0.01$), and it remained at the same level 4 years later (z-score: -1.09 vs. 0.21 , $P < 0.01$). Moreover, the preterms' weight was also significantly lower than that of the controls (7 years: z-score -0.89 vs. 0.2 , $P < 0.01$; 11 years: z-score -1.3 vs. 0.12 , $P < 0.01$).

4.2. Prevalence of HT

In the 7th year of life, the presence of HT based on MAP was significantly higher in the ex-preterm children. HT based on MAP was diagnosed in eight children, whereas none of the children in the control group were diagnosed with HT (15% vs. 0%; $P < 0.02$). Thirty-two ex-preterms and 12 controls were diagnosed with HT based on BP measurements alone (56% vs. 33%; $P < 0.036$). In the 11th year of life, the difference between these two groups was statistically insignificant (HT based on MAP: 15% vs. 10%, HT based on BP measurements alone: 30.7% vs. 24%). After taking into account the children who had started treatment of HT after the first follow-up visit, the incidence of HT based on MAP was 19% vs. 10%, and the incidence of HT on the basis of individual measurements was 36.5% vs. 24%. The differences were not statistically significant.

Table 1. Definitions of the Primary Outcomes Based on the Results of 24-H ABPM

	Diagnosis of HT
HT based on MAP	MAP in the \geq 95th percentile for gender and height
HT based on single BP measurements	More than 25% of single measurements in the \geq 95th percentile for age, gender, and height
SHT	Mean SBP in the \geq 95th percentile for gender and height and Less than or 50% of single measurements in the \geq 95th percentile for age, gender, and height

Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; HT, hypertension; MAP, mean arterial pressure; SHT, severe hypertension.

Table 2. Comparison of Selected Data Between ELBW Children and the Control Group

	Study Group	Control Group	P Value
Birth parameters			
Female/male	44/23	19/23	0.15
Birth weight (g)	850 \pm 128	3571 \pm 538	< 0.001
Gestational age (wk)	27 \pm 2.27	39.8 \pm 1.42	< 0.001
Neonatal period interventions			
Mechanical ventilation (%)	91	0	< 0.001
Surfactant administration (%)	73	0	< 0.001
PDA ligation (%)	27	0	< 0.001
First follow-up			
Height (cm)	115.5 \pm 6.7	124.9 \pm 7.4	< 0.001
Height (z-score)	-0.89	0.18	< 0.001
Weight (kg)	19.5 \pm 3.9	25.2 \pm 5.3	< 0.001
Weight (z-score)	-0.9	0.2	< 0.001
Second follow-up			
Height (cm)	142 \pm 7	145 \pm 9	0.09
Height (z-score)	-1.09	0.21	< 0.001
Weight (kg)	34 \pm 8	39 \pm 8	0.017
Weight (z-score)	-1.32	0.12	< 0.001

Abbreviation: ELBW, extremely low birth weight.

4.3. SHT

Five of eight hypertensive preterms suffered from SHT in the 7th year of life. In the 11th year of life, SHT was diagnosed in four patients in the ex-preterm group and in two controls. One child with SHT did not attend the second follow-up visit. In three children who had SHT in the 7th year of life, BP values decreased as a result of treatment below the level thought to pose a direct risk of target organ damage.

4.4. BP Values

In the 7th year of life, the ex-preterms had significantly higher 24-h, daytime, and nighttime MAP z-scores than the controls. In the 11th year of life, the difference remained only in daytime MAP z-scores. In both the 7th and 11th years of life, there were no statistically significant differences in absolute values of SBP, DBO, or MAP between the ex-preterms and controls. The observed BP values are presented in Table 3.

4.5. BP Profiles (24 h)

The children with ELBWs had significantly higher nighttime MAP (1.15 vs. 0.2 SDS; $P = 0.02$). However, both in the 7th and 11th years of life, there were no significant differences in the drop in mean nocturnal MAP (7th year: 12.9% vs. 14.8%, $P = 0.28$; 11th year: 13.8 vs. 13.4%; $P = 0.74$). The percentage of children without proper (minimum 10%) nocturnal MAP dipping was 22.8% in the group of children born prematurely and 19.4% in the control group. In the 11th year of life, this percentage was 22% in the first and 17% in the second group.

4.6. HR Measurement

In both measurements, the ELBW children had a significantly higher HR in comparison to that of the full-term children (7th year of life: 93 vs. 87/min, $P < 0.001$; 11th year of life: 87 vs. 83/min, $P = 0.039$). Moreover, in the 7th year of life, there was a significant difference in the daytime and nighttime HRs between the ex-preterm group and the controls (daytime HR: 99 vs. 94/min, $P = 0.01$, nighttime HR: 86 vs. 79/min, $P < 0.001$).

5. Discussion

Prematurity and low birth weight are strong risk factors for HT in the first decade of life. In studies evaluating BP in children younger than 12 years old, the prevalence of HT ranged from 10 to 25% (26, 27). A higher frequency of HT was observed in young adults born with a very low birth (25). The present study revealed a significant difference in

Table 3. Comparison of 24-H Abpms Between the ELBW Group and Controls

	7th Year of Life			11th Year of Life		
	Study Group	Control Group	P Value	Study Group	Control Group	P Value
MAP 24 h (mmHg)	79 ± 6	77 ± 5	0.12	82 ± 4	82 ± 5	0.89
MAP day (mmHg)	83 ± 6	82 ± 5	0.46	84 ± 5	83 ± 5	0.79
MAP night (mmHg)	72 ± 6	70 ± 4	0.23	72 ± 4	73 ± 6	0.62
SBP 24 h (mmHg)	104 ± 7	103 ± 6	0.5	109 ± 7	108 ± 8	0.84
SBP day (mmHg)	106 ± 7	106 ± 6	0.97	111 ± 7	110 ± 8	0.77
SBP night (mmHg)	100 ± 7	98 ± 6	0.26	99 ± 7	99 ± 8	0.9
DBP 24 h (mmHg)	65 ± 5	64 ± 5	0.56	67 ± 4	67 ± 5	0.69
DBP day (mmHg)	68 ± 5	69 ± 5	0.66	69 ± 5	69 ± 5	0.94
DBP night (mmHg)	60 ± 5	59 ± 5	0.53	55 ± 5	57 ± 6	0.4
MAP 24 h (z-score)	0.5 ± 1.1	-0.3 ± 0.78	< 0.01	0.26 ± 0.6	0.19 ± 0.7	0.61
MAP day (z-score)	-0.36 ± 0.9	-0.7 ± 0.73	0.05	-0.01 ± 0.78	-0.34 ± 0.73	0.04
MAP night (z-score)	1.15 ± 0.84	0.2 ± 0.72	0.02	0.58 ± 0.71	0.23 ± 0.91	0.0508
SBP 24 h (z-score)	-0.13 ± 1.14	-0.45 ± 0.86	0.15	-0.08 ± 1.02	-0.31 ± 1.2	0.34
DBP 24 h (z-score)	-0.08 ± 1.07	-0.4 ± 0.96	0.14	0.06 ± 0.82	0.01 ± 0.89	0.78
Nocturnal MAP dipping (%)	15.9 ± 17.4	14.8 ± 5	0.28	13.8 ± 6	13.4 ± 4	0.74

Abbreviations: ABPM, ambulatory blood pressure measurement; DBP, diastolic blood pressure; ELBW, extremely low birth weight; MAP, mean arterial pressure; SBP, systolic blood pressure.

the frequency of HT between prematurely born children and controls in the 7th year of life (eight patients vs. zero controls). In the 11th year of life, there were eight diagnoses of HT in the ex-preterm group compared to three diagnoses in the control group. After taking into account the children who had started pharmacological treatment for HT after the first follow-up visit, the incidence of HT was 10 versus three cases. There were two new diagnoses at the second follow-up visit in the ex-preterm group and three in the control group. The frequency of HT in the control group was in accordance with previously published data, which showed that the prevalence of HT in previously healthy children reached 4% in the first and 12% in the second decades of life (28).

As mentioned before, complications of elevated BP are often observed at the time of its diagnosis in children (19, 20). Performing ABPM at a young age makes it possible to identify children with SHT, who have a high risk of end-organ damage (29). In the present study, five of eight 7-year-old patients in whom HT was diagnosed already had SHT. It is worth noting that in 75% of these SHT cases, by appropriate treatment, we were able to decrease BP values below the level that presents a direct risk of target organ damage.

Due to the consequences of HT in later life and the possibility of prevention, it is necessary to conduct

widespread screening and detect high BP among children. Especially insightful attention is required in patients from a group of HT risk because early diagnosis with adequate treatment can avoid complications and reduce cardiovascular risks in subsequent years.

In recently published studies, besides HT diagnoses, absolute values of SBP and DBP were analyzed. Many of those studies reported that the main concern in prematurely born children was elevated SBP. Much more studies of former preterm newborns detected significantly higher SBP (19, 22, 25, 26, 30-33), then elevated DBP values (25, 31, 33, 34). A few studies reported significantly higher MAP in ex-preterm infants compared to controls (31-33). The present study confirmed the presence of higher values of MAP in children who had a low birth weight when they reached the 7th year of life. In the 11th year of life, this difference was not statistically significant. However, we have to take into account the fact that the children in the study group were significantly shorter than those in the control group, and this difference reaches a value of 1 SD.

Another parameter that must be considered in children born prematurely is nighttime BP. Research has demonstrated that a lack of nocturnal MAP dipping is a risk factor for cardiovascular events (35). Moreover, increased nighttime BP was shown to predict the occurrence of mi-

croalbuminuria in children with diabetes (36). Bayrakci et al. demonstrated a reverse correlation between high nighttime z-scores for SBP and birth weight in a group of children aged 5 - 17 years (26). In the present study, the significant difference in the nocturnal MAP in the 7th year of life indicates an increased risk of HT and associated complications in infants with birth weights of < 1000 g. The lack of nighttime elevation in MAP in the 11th year of life can be attributed to the success of the HT treatment.

According to the literature, children born prematurely also show enhanced sympathetic nervous system activity (26). This phenomenon, in addition to lower myocardial mass, explains the higher HR occurring in children born with a low birth weight (25). This relation was confirmed in the present study, both at the age of 7 and 11 years.

Current guidelines recommend that every child above the age of 3 years who is seen in a medical setting should undergo BP monitoring (12, 37). In younger children, the BP should be measured in cases where there is an increased risk of HT, including neonatal conditions requiring intensive care, congenital heart disease, renal disease, or treatment with drugs known to raise BP (12, 38). However, recently published studies have shown that these recommendations are rarely applied, either in Europe or the U.S. (39, 40). This problem may be explained by technical difficulties associated with correct BP measurement in children (appropriate cuff size, difficulties in auscultation) (19). However, routine BP measurements are necessary, as HT in children is often asymptomatic or presents as non-characteristic symptoms, such as headaches, nose bleeding, shortness of breath, changes in behavior, or learning difficulties (19).

In the present study, all the children were treated according to ESH/ESC Guidelines for the management of arterial hypertension (latest update published in 2013) (14). The necessity of treatment intensification was assessed on the basis of casual BP measurements. In ABPM performed after 4 years of HT therapy, few children were still managed with elevated BP. This finding indicates that recommended casual BP measurements are an important screening tool, but these may be insufficient in children at risk of HT. In such cases, 24-h ABPMs offer a valuable method of pressure measuring (12). 24-h-long registration allows evaluating the SBP profile regarding to physical activity and the rest of the night. It also eliminates so-called white coat hypertension and masked hypertension, both of which are common in children. Instead of routine measurements, in preterms with ELBWs, 24-h ABPM should be considered as an initial tool to screen for HT.

5.1. Strengths and Limitations

In our opinion, this study has significant value and provides new insights into HT in 10 - 11-year-olds who had ELBWs. First, the study group included the majority of newborns from the entire Malopolska region who were born within a 2-year period and reached the age of 11 years. The data in this multicenter study were obtained from all the tertiary referral centers in this region. It is a complete group of patients, with a high percentage of observation. In addition, the assessment of HT was based on 24-h BP monitoring.

The limitation of our study is the unequal size of the study and control groups. Furthermore, the analyses may be limited in power due to the small sample size of the groups.

5.2. Conclusions

Children born prematurely are predisposed to HT in later life. Furthermore, the increase in the HRs of ex-preterms is maintained in the 7th and 11th years of life, despite anti-HT treatment. Rapid implementation of HT treatment in ex-preterm infants can reduce their BP values to those of the general population. We propose that 24-hr ABPM should be considered as an initial screening tool or in the follow-up of children born prematurely with ELBWs.

Footnotes

Authors' Contribution: Study concept and design: Przemko Kwinta, Acquisition of data: Dorota Drozd, Malgorzata Klimek, and Andrzej Grudzien, Analysis and interpretation of the data: Maja Gilariska and Dorota Drozd, Drafting of the manuscript: Maja Gilariska, Critical revision of the manuscript for important intellectual content: Dorota Drozd, Malgorzata Klimek, Andrzej Grudzien, and Przemko Kwinta, Statistical analysis: Maja Gilariska, Study supervision: Przemko Kwinta

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