PEDIATRIA POLSKA 90 (2015) 372–377

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/pepo

Original research article/Artykuł oryginalny

Influence of low birth weight on blood pressure and kidney volume in healthy 2–3 years old children

Wpływ małej masy urodzeniowej na ciśnienie tętnicze i objętość nerek u zdrowych dzieci w 2. i 3. roku życia

Monika Pawlak-Bratkowska [1], *Małgorzata Stańczyk* [1,*], *Dobromiła Barańska* [2], *Anna Kałużyńska* [3], *Anna Stańczyk-Przyłuska* [1,4], *Jolanta Lukamowicz* [5], *Aneta Czupryniak* [3], *Marcin Tkaczyk* [1,6]

[1] *Department of Paediatrics and Immunology with Nephrology Division, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland*
[2] *Department of Imaging Diagnostics, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland*
[3] *Paediatric Ward, District Hospital of Tomaszow Mazowiecki, Poland*
[4] *Department of Paediatrics, Preventive Cardiology and Immunology of Developmental Age, Medical University of Lodz, Poland*
[5] *Medical Laboratory Diagnostics Center, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland*
[6] *Department of Didactics in Paediatrics, Medical University of Lodz, Poland*

ARTICLE INFO

Article history:
Received: 23.01.2015
Accepted: 14.02.2015
Available online: 09.06.2015

Keywords:
- Low birth weight
- Blood pressure
- Kidney volume

Słowa kluczowe:
- Mała masa urodzeniowa
- Ciśnienie krwi
- Objętość nerek

ABSTRACT

Introduction: The influence of low birth weight on development of hypertension and chronic kidney disease progression was confirmed in adolescent and adult population. There has been scarce data published on this topic in younger children and toddlers. **Purpose:** The aim of the study was to assess the influence of low birth weight on blood pressure and kidney volume in youngest children. **Material and methods:** The study group consisted of 38 children (2–3 years), born with low birth weight. The control group consisted of 35 children, born with normal birth weight. Kidneys size and volume were assessed in ultrasonography. Serum cystatin and urine albumin concentrations were assessed. Blood pressure was taken on 4 limbs with oscillometric method. **Results:** There was tendency for the study group to have lower weight (Z-score −1.1418 *vs.* −0.5092, $p = 0.0507$). They have lower height and lower head and chest circumference. They tended to have lower total kidney volume (52 474 mm^3 *vs.* 57 451 mm^3, $p = 0.055$), but that relation disappeared after adjustment to body height. There was no significant difference in blood pressure values and between GFR

* *Corresponding author at*: Klinika Pediatrii, Immunologii i Nefrologii ICZMP, ul. Rzgowska 281/289, 93-338 Łódź, Poland. Tel.: +48 42 271 13 94; fax: +48 783 937 788.
E-mail address: mbstanczyk@gmail.com (M. Stańczyk).

http://dx.doi.org/10.1016/j.pepo.2015.05.007

estimated with Filler formula (125.9 *vs.* 134.2, $p = 0.16$). **Conclusions:** Presented study revealed no significant influence of low birth weight on kidney size and function in children in 2nd and 3rd year of life.

Introduction

Fetal development *in utero* depends on environmental and genetic factors. Recently, factors acting during prenatal life are considered to have influence on pathogenesis of many diseases of adulthood. These have essential meaning in development of hypertension, cardiovascular diseases, diabetes mellitus type 2 and kidney diseases [1].

Through last years it has been revealed that developing fetus adjusts the growth dynamic to environmental conditions. It has been proven on animal models that mothers malnutrition during pregnancy, especially low-protein diet throughout second half of pregnancy, has negative influence on intrauterine fetus growth development [2]. Similarly, disturbances of placental blood flow and glucocorticosteroids administration during pregnancy could lead to growth retardation and abnormal development of certain organs, such as kidneys, pancreas, heart and brain [2, 3]. In experimental studies featuring rats the association between low birth weight and hypertension has been proven. It is connected with factors acting during nephrogenesis, that is mainly (in 60%) throughout the third trimester in humans, that cause decrease of nephron number [4]. This leads to reduction of kidney filtrating capacity and results in deterioration of kidney sodium transport. Natriuresis impairment is followed by increase of systemic blood pressure regulated by renin–angiotensine–aldosterone system and pressure inside kidney glomeruli causing hyalinosis [2, 3].

Several epidemiological studies raised an association between low birth weight (LBW), especially intrauterine growth retardation (IUGR), and elevated systolic blood pressure in children before puberty and evident hypertension in adults [4–6]. Kidney biopsy in individuals with hypertension proved decreased amount of nephrons and glomeruli of greater size in those who were born with low birth weight. It confirms the Baker et al. [6] hypothesis of hyperfiltration due to nephrons deficit. Compensatory overgrowth of glomeruli and hyperfiltration arises from overload of normal nephrons which causes their further hyalinosis and tubular atrophy with concomitant development of inflammatory lesions and fibrosis in interstitial tissue. These lead to further destruction of other nephrons, and this so called vicious circle cause chronic kidney disease progression [4, 7].

The influence of LBW on development of hypertension and chronic kidney disease (CKD) progression was confirmed in adolescent and adult population. There has been scarce data published on this topic in younger children and toddlers. Therefore, we constructed the cross-sectional study in LBW children currently aged 2–3 years without any other risk factors in order to assess the kidney volume and function, with special regard to blood pressure.

Material and methods

The study group consisted of children aged 2 and 3 years, who were participants of cohort of european research program ''Euro Prevall – Food Allergy Across Europe'' [8]. Among these children there were selected 38 who were born between 36 and 42 week of pregnancy with birth weight below 5th percentile.

The control group of 35 children was age-matched (head-to-head) and consisted of children born on term and with normal birth weight.

In all children a perinatal history of mother ilnesses and pharmacotherapy was taken. Anthropometric measurements were performed (body weight and height, head and chest circumference). On the basis of ultrasound examination kidneys sizes were evaluated what enabled to calculate their volume (according to formula: kidney volume = 0.52 × width × thickness × length). Blood pressure was taken on four extremities with automatic oscillometric method (MINDRAY Patient Monitor MEC-1200). Urine albumin was assessed with standard biochemical methods. Serum cystatin C was analyzed with ELISA method (Quantikine ELISA Test, BIOCOM).

As the previous analyzes showed that cystatin-C based GFR estimation is associated with less bias and in children is better indicator of kidney function than creatinine based estimation, authors have decided to use this tool in the study [9, 10]. Glomerular filtration rate was estimated with Filler formula ($eGFR = 91.62 \times (cysC)^{-1.123}$). Exclusion criteria included congenital defects, chronic diseases (especially concerning urinary system, secondary hypertension and cardiac failure), nutrition disturbances and diabetes in mother.

The statistical analysis was performed by Statistica 10 PL software. Median and percentile values were applied to descriptive statistics. Normality of distribution was tested by Shapiro–Wilk test. Parametric test was applied (t-Student). Statistical significance treshold was set at 0.05.

Local Ethical Committee approved the study. Parents of all participants gave an informed consent.

Results

Birth weight of children from the study group was significantly lower compared to control group (2400 g *vs.* 3380 g) what was consistent with premises of the study. Duration of pregnancy was shorter in children from the study group (38 *vs.* 39 hbd, $p < 0.05$). Mothers of children from the study group during pregnancy were more frequently diagnosed with hypertension and other concomitant health problems (single cases of: colitis ulcerosa, hyperthyroidism,

Table I – The prevalence of mothers hypertension, concomitant health problems, pharmacotherapy and cigarette smoking during pregnancy

	Control group	Study group
Hypertension	2.8%	21%
Pharmacotherapy	31%	36%
Cigarette smoking	8.5%	7.8%
Concomitant health prob	8.5%	18%

antyphospholipid syndrome, urolithiasis, teratoma). Cigarette smoking was more frequent in mothers of children from the control group (Table I).

Anthropometrics (Table II)

There were no differences in body weight between children form study group compared to control group. When related to population distribution there was only a tendency for the study group to have lower weight (Z-score −1.1418 *vs.* −0.5092, $p = 0.0507$). Comparison of absolute values of body height did not reveal significance. It gained importance when related to population distribution – Z-score −0.8139 *vs.* −0.3533; $p < 0.05$. Children from LBW group had significantly smaller head and chest circumference ($p < 0.05$).

Kidneys size (Table III)

In ultrasound test volume of right kidney was lower in children from the study group ($p < 0.05$). There was no difference if volume of the kidney is adjusted to body height. Volume of left kidney was comparable in both groups. Moreover, there was tendency for study group to have lower cumulative kidneys volume ($p = 0.055$). The observation was not confirmed when adjusted to body height.

Blood pressure (Table IV)

Results of office measurements of blood pressure did not reveal significant differences between children from both groups (Table IV). Due to lack of reference values for thigh measurements, only blood pressure values taken on arms were related to the population standards.

Kidney function assessment (Table V)

There were no differences between both groups according to serum cystatin C level and urine albumin. There was no significant difference between GFR estimated with Filler formula for serum cystatin C (125.9 *vs.* 134.2, $p = 0.16$).

Discussion

In many epidemiological studies dependence between birth weight and indicators of physical development in first years of life was postulated. It has been proven that children born with low birth weight (below 2500 g) are smaller and lighter than peers born with normal birth weight, and also has smaller head and chest circumferences before 5th year of life [11–13]. This tendency was confirmed by authors of this study.

According to the kidney size, we showed comparable kidney volume between LBW and normal weight born peers. The blood pressure in these groups was similar too.

Brenner et al. published a scheme that described relation between low birth weight and elevated arterial blood pressure. It assumed that the main cause of hypertension development in such individuals is decreased amount of nephrons that lead to hyperfiltration. Described reduction of nephrons amount has multifactorial origin and does not

Table II – Anthropometric measurement in children from study and control group. Data showed as median and value of 25th and 75th percentile

	Control group	Study group	Significance
Birth weight [g]	3380 (3200–3630)	2400 (2150–1550)	**$p < 0.05$**
Week of birth	39 (38–40)	38 (36–40)	**$p < 0.05$**
Body weight	12.35 (10.8–13.5)	11.5 (9.3–13.27)	$p = 0.07$
Body weight – Z-score	−0.5092	−1.1418	$p = 0.05$
Body height	87 (81.7–93.5)	84 (76.5–91.5)	$p = 0.08$
Body height – Z-score	−0.3533	−0.8139	**$p < 0.05$**
Head circumference [cm]	48 (47.5–49.5)	46 (45–46)	**$p < 0.05$**
Chest circumference [cm]	49.5 (48–51.375)	48 (46–48)	**$p < 0.05$**

Table III – Kidneys volume assessed in ultrasound examination. Data showed as median and values of 25th and 75th percentile

Kidney volume	Control group	Study group	Significance
Right kidney volume [mm^3]	29 023 (24 373–33 714)	24 585 (19 445.4–32 278.2)	**$p < 0.05$**
Right kidney volume adjusted to body height	33.24 (28.43–39.345)	32.545 (25–35.7)	$p = 0.29$
Left kidney volume [mm^3]	28 953 (23 868–31 338)	255 547 (22 706–32 573)	$p = 0.23$
Left kidney volume adjusted to body height	32.12 (28.41–38.21)	31.16 (28.4–35)	$p = 0.57$
Total kidneys volume [mm^3]	57 451.7 (51 129–63 869.5)	49 185 (43 386–64 822)	$p = 0.055$
Total kidneys volume adjusted to body height	63.8 (57.5–77.9)	65.3 (53.6–72.8)	$p = 0.36$

Table IV – Blood pressure values for measurements on four extremities. Data showed as median and values of 25th and 75th percentile. SBP – systolic blood pressure. DBP – diastolic blood pressure

Blood pressure	Control group	Study group	Significance
SBP – right arm	91.5 (88–96.75)	91 (80–100.5)	$p = 0.97$
Z-score	0.291 (0.123–0.825)	0.097 (−0.183–1.549)	$p = 0.34$
DBP – right arm	58 (55–66)	57 (51–64)	$p = 0.54$
Z-score	1.554 (0.966–1.9159)	1.463 (0.346–2.102)	$p = 0.97$
SBP – left arm	93.5 (90.25–103)	91 (87–102)	$p = 0.76$
Z-score	0.68 (0.023–1.116)	0.581 (0.0968–1.162)	$p = 0.33$
DBP – left arm	59.5 (53.5–65)	60 (51–70)	$p = 0.48$
Z-score	1.472(1.029–1.905)	1.462 (0.914–2.377)	$p = 0.28$
SBP right leg	106.5 (100.25–108.75)	105 (97–118.5)	**$p < 0.05$**
DBP right leg	64 (55.25–67)	65 (56–74)	**$p < 0.05$**
SBP left leg	105 (97–111)	113.5 (99.75–120)	$p = 0.11$
DBP left leg	63 (52–67)	65 (57–73)	$p = 0.08$

depend only on birth weight [14]. Previous studies on high blood pressure in LBW patients were conducted in adolescents and adults. They were based on large groups but they did not contain longitudinal data. The cut-off time limit of detection of increased blood pressure has not been established yet. Therefore we postulate that in youngest children the LBW has little effect on kidney size and blood pressure. As it was showed earlier, there was no relation between volume of kidneys and amount of nephrons because density of nephrons distribution in kidney was individually variable [14].

Studies revealed that there is a significant inverse relation between birth weight and systolic blood pressure both in children and adults [15, 16]. Vancheri et al. showed that in children between 3 and 12 year of life for every 1 kg increase of birth weight a 2.68 mmHg decrease of blood pressure is observed [17]. In adults aged between 20 and 40 years the decrease of blood pressure was even higher – 3.82 mmHg. However, in adults, such a relation was observed only between birth weight and diastolic blood pressure.

Whincup et al. showed that some of sizes at birth (birth weight, birth length, head circumference) were inversely related to blood pressure at the age of 3 [18]. However, birth weight itself had the strongest association. There was no influence of maternal, ethnic or socioeconomical factors on this relation. Also Japanese studies detected similar correlation [19] – the average systolic blood pressure at the age of 3 in children with birth weight over 3510 g was 3.0 mmHg lower than in children with birth weight equal to or less than 2990 g. According to Lurbe et al. birth weight is a positive determinant of blood pressure at birth. The acceleration of weight gain may aggravate the effects of LBW on systolic blood pressure, what become significant at the age of 2 [20]. Available from literature data concerning adolescents are incoherent. Falkner et al. detected no significant inverse relationship between birth weight and blood pressure in adolescence, which is in contrast to the low-birth-weight hypothesis [21]. Study group in this report was composed of adolescents aged between 11 and 14 years and low birth weight was present in 36% of the sample. Walker et al. found a significant negative relationship of birth weight and later values of blood pressure in Jamaican children aged 11–12 years [22].

British study showed the role of lower birth weight in deterioration of kidney function. There was strong evidence that every 1 kg decrease of birth weight was associated with a 2.25 ml/min/1.73 m^2 lower glomerular filtration rate calculated using cystatin C (eGFRcys). These associations with eGFR were not explained by diabetes or hypertension [23]. A recent systematic review and meta-analysis also revealed association between low birth weight and kidney disease in middle-aged and older populations [24–26]. The association between cystatin C serum level and birth weight was not confirmed in present study what could be caused by the fact that the study group was composed of the youngest children. Authors from Poland revealed that serum cystatin C levels were significantly higher in school-aged extremely low birth weight (ELBW) children compared to children with normal birth weight [27]. Genetic and numerous pre- and postnatal environmental factors can affect kidney condition [14, 26, 28]. Among them are listed medications, nutritional state of mother, function of placenta and duration of pregnancy. All these factors may cause harmful effects on fetal development. Our study shows that mothers of children born small to gestational age were more frequently diagnosed with hypertension during pregnancy and other concomitant health problems. However, glomeruli damage process *in situation* of minor hyperfiltration is very slow. Therefore, it seems that no significant changes in clinical parameters occurred due to young age of assessed population.

Table V – Serum biochemistry assays. GFR estimated with Filler formula. Data showed as median and values of 25th and 75th percentile

Parameter	Control group	Study group	Significance
Serum cystatin C (ng/ml)	753.6 (698.4–834.9)	711.7 (662.7–764.6)	$p = 0.06$
eGFR (ml/min/1.73 m^2)	125.9 (112.2–137.1)	134.2 (125.9–145.6)	$p = 0.16$
Urine albumin (mg/l)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	$p = 0.09$

Epidemiological studies showed that prenatally acting factors influencing birth weight might take part in development of hypertension and kidney damage [4–6, 29]. In other studies low birth weight was considered to be an indicator of intrauterinal growth retardation (IUGR) that causes in consequence abnormal development of organs and reduction of nephrons number in kidney [29]. However, among children with low birth weight, about 20% have constitutional low body weight and do not present growth retardation [14]. These children have no decrease of nephrons number and no disturbances leading to hypertension. Therefore, the small number of patients in the present study might have influence on the results by the selection bias.

Conclusion

In conclusion, the present study based on clinical measurements, ultrasound assessment and laboratory glomerular filtration rate estimation, showed no significant influence of low birth weight on kidney size and function in children aged 2 and 3 years. This observation does not stand in opposition to previous studies based on adolescents or adults, but supports the hypothesis that clinical effect of lower nephron number may develop with time and indicates the need of the further studies in this field.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

The study was supported by the Polish Mother's Memorial Hospital Research Institute, Poland.

Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES/PIŚMIENNICTWO

[1] Fan ZJ, Lackland DT, Lipsitz SR, Nicholas JS. The association of low birthweight and chronic renal failure among Medicaid young adults with diabetes and/or hypertension. Public Health Rep 2006;121(3):239–244.

[2] Baum M. Role of the kidney in the prenatal and early postnatal programming of hypertension. Am J Physiol Renal Physiol 2010;298(2):F235–F247.

[3] Luyckx VA, Brenner BM. Low birth weight, nephron number, and kidney disease. Kidney Int Suppl 2005;(97):S68–S77.

[4] Hughson M, Farris 3rd AB, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. Kidney Int 2003;63 (6):2113–2122.

[5] Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation 2002;105:1088–1092.

[6] Barker DJ, Godfrey KM, Osmond C, Bull A. The relation of fetal length, ponderal index and head circumference to blood pressure and the risk of hypertension in adult life. Paediatr Perinat Epidemiol 1992;6(1):35–44.

[7] Mañalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 2000;58(2):770–773.

[8] Keil T, McBride D, Grimshaw K, Niggemann B, Xepapadaki P, Zannikos K, et al. The multinational birth cohort of EuroPrevall: background, aims and methods. Allergy 2010 Apr;65(4):482–490.

[9] Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol 2003;18:981–985.

[10] Filler G, Huang SH, Yasin A. The usefulness of cystatin C and related formulae in pediatrics. Clin Chem Lab Med 2012;50(12):2081–2091.

[11] Clarkson JE, Silva PA, Buckfield PM, Hardman J. The later growth of children who were preterm and small for gestational age. N Z Med J 1975;26(81(536)):279–282.

[12] Bjerre I. Physical growth of 5-year-old children with a low birth weight. Stature, weight, circumference of head and osseous development. Acta Paediatr Scand 1975;64(1):33–43.

[13] Binkin NJ, Yip R, Fleshood L, Trowbridge FL. Birth weight and childhood growth. Pediatrics 1988;82(6):828–834.

[14] Schreuder MF, Nauta J. Prenatal programming of nephron number and blood pressure. Kidney Int 2007;72:265–268.

[15] Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, et al. Birth weight and subsequent blood pressure: a meta-analysis. Arch Cardiovasc Dis 2012;105:99–113.

[16] Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens 2000;18:815–831.

[17] Vancheri F, Alletto M, Burgio A, Fulco G, Paradiso R, Piangiamore M. Inverse relationship between fetal growth and arterial pressure in children and adults. G Ital Cardiol 1995;25:833–841.

[18] Whincup PH, Bredow M, Payne F, Sadler S, Golding J. Size at birth and blood pressure at 3 years of age. The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). Am J Epidemiol 1999;149:730–739.

[19] Hashimoto N, Kawasaki T, Kikuchi T, Takahashi H, Uchiyama M. The relationship between the intrauterine environment and blood pressure in 3-year-old Japanese children. Acta Paediatr 1996;85:132–138.

[20] Lurbe E, Garcia-Vicent C, Torro MI, Aguilar F, Redon J. Associations of birth weight gain with cardiometabolic risk parameters at 5 years of age. Hypertension 2014;63 (6):1326–1332.

[21] Falkner B, Hulman S, Kushner H. Effect of birth weight on blood pressure and body size in early adolescence. Hypertension 2004;43(2):203–207.

[22] Walker SP, Gaskin P, Powell CA, Bennett FI, Forrester TE, Grantham-McGregor S. The effects of birth weight and

postnatal linear growth retardation on blood pressure at age 11–12 years. J Epidemiol Community Health 2001;55:394–398.
[23] Silverwood RJ, Pierce M, Hardy R, Sattar N, Whincup P, Ferro C, et al. Low birth weight, later renal function, and the roles of adulthood blood pressure, diabetes, and obesity in a British birth cohort. Kidney Int 2013;84:1262–1270.
[24] Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989;298:564–567.
[25] Eriksson JG, Forsen TJ, Kajantie E, Osmond C, Barker DJ. Childhood growth and hypertension in later life. Hypertension 2007;49(6):1415–1421.
[26] Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 1996;49:1774–1777.
[27] Kwinta P, Klimek M, Drozdz D, Grudzień A, Jagła M, Zasada M, et al. Assessment of long-term renal complications in extremely low birth weight children. Pediatr Nephrol 2011;26(7):1095–1103.
[28] Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1988;1:335–347.
[29] Hinchliffe SA, Lynch MR, Sargent PH, Howard CV, Van Velzen D. The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol 1992;99(4):296–301.