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Original Scientific Paper

SEX DIFFERENCES IN CARDIOVASCULAR RISK FACTORS AND RENAL FUNCTION AMONG YOUNG ADULTS AFTER INTRAUTERINE GROWTH RESTRICTION

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SUMMARY – *Introduction:* Intrauterine growth restriction (IUGR) is linked to a higher incidence of cardiovascular and renal diseases.

Methods: A total of 91 healthy individuals were included, 40 women and 51 men, born below the 10th percentile of birth weight for gestational age. Anthropometric parameters, arterial pressure (AP), blood glucose, estimated glomerular filtration rate (eGFR), albumin/creatinine ratio, lipid profile, uric acid, renal volume by ultrasound, pulse wave velocity, central arterial pressure (cAP), and augmentation index (Aix) were measured.

Results: Men have higher body mass index (BMI), waist circumference, ambulatory and continuous AP, lower eGFR, pulse, higher uric acid and LDL cholesterol, lower HDL cholesterol, higher cAP and Aix, higher corrected renal volume, and birth weight than females. Overweight men had hypertension, lower eGFR, and dyslipidemia more often. Systolic pressure correlated positively with BMI in men. In women, systolic pressure correlated positively with heart rate and negatively with gestational age. BMI affected the systolic pressure in men and eGFR in women.

Conclusion: Results indicate the more unfavourable effect of IUGR on men. Higher AP, vascular dysfunction, poorer renal function, and dyslipidemia predispose men to earlier chronic disease development.

Key words: *intrauterine growth restriction, arterial pressure, renal function*

Introduction

Arterial hypertension is one of the most important risk factors for cardiovascular mortality and one of the main causes of chronic kidney disease [1,2]. Despite various surveys being conducted, the precise pathogenesis of arterial hypertension still remains unsolved.

We are currently witnessing a silent epidemic of kidney diseases, which is predicted to affect more than 200 000 people in Croatia [3]. Since the morbidity and mortality of these diseases are on the rise, and the financial demands of treatment are high, attempts to prevent them are aimed at suppressing the risk factors. As hypertension is often associated with diabetes mellitus type 2, dyslipidemia, coronary heart disease, and chronic kidney disease, the aim is to find the mutual cause [1,4]. Besides the "classic" risk factors, the highlight is on the "new" ones, where the inadequate fetal growth could be included.

Around 1980, Barker showed that people born with a lower birth weight have a higher incidence of cardiovascular diseases in adult age (so-called Barker's hypothesis)[5]. Since then, numerous epidemical studies have confirmed this thesis for the genesis of hypertension and renal damage [6,7,8]. Although the coherence of

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fetal programming of future diseases and these diseases in adult age exists, the mechanisms causing this process are still not entirely known. A possible theory is Brenner's about the reduction of nephrons [9]. He assumed that intrauterine exposure to negative factors causes the redistribution of nutrients to essential organs, causing damage to the rest, such as kidneys – leading to a congenital reduction in the number of nephrons.

Inadequate synthesis of elastin and dysfunctional endothelium are the result of vascular damage [10,11]. Arterial stiffness is an independent risk factor for cardiovascular diseases [12], but also an important predictor of mortality in patients with essential hypertension and chronic kidney disease [13]. Many studies have tested the hypothesis of the impact of intrauterine events on arterial stiffness, but results were rarely distinctive [14,15].

Much evidence indicates that sex plays a great role in predisposing people to cardiovascular, renal diseases, or metabolic disorders [16]. In general, men have a higher blood pressure than women of the same age during the premenopausal period [17]. Men also suffer faster impairment of renal function [16,18].

It is unclear how and what intrauterine growth restriction (IUGR) changes in an organism and how it affects future disorders. One answer could include the fact that male fetuses grow faster, making them more sensitive to disturbances during pregnancy. Female fetuses grow much slower, and because of that, they have time to adapt to any unfavourable conditions [19]. This difference between sexes has been used by Gilbert and Nijland to explain the higher incidence of coronary heart disease, heart failure, left ventricular hypertrophy, or sudden heart-related death in men. They also enhanced the role of sex hormones [20]. Estrogen has been found to have a protective role in premenopausal women, while testosterone was linked to higher blood pressure, probably via activation of renin-angiotensin-aldosterone system [21,22]. However, some research reports the highest mortality of ischemic heart disease in the group of men with the lowest levels of testosterone [23].

Sex differences in fetal programming could manifest in the quality of blood vessels. In experimental studies, it is dominantly expressed in males [24]. Clinically, increased peripheral vascular resistance and arterial pressure have been found in boys born after IUGR, while only increased sympathetic activity in girls [25]. These results stress the complexity but also the lack of research on this subject. It is unclear whether these people differ from the general population or whether gender impact is additionally modified by the IUGR effect.

The aim of our study was to analyse sex differences in cardiovascular risk factor and renal function in young adults born after IUGR.

Methods

This research included 91 healthy persons, 40 women and 51 men born after IUGR (birth mass below 10th percentile of birth weight to gestational age, according to the sex) [26]. Birth data for women were recorded from birth registers of Clinic for women's diseases and births of University hospital center Zagreb for years 1999-2001 while data about men were taken from the previous cohort.

Inclusion criteria were: age 20–23 years; no medical history of renal, cardiovascular disease, or diabetes; and signed informed consent.

Every examinee had their personal and family history taken and a physical exam was performed. Weight, height, and waist circumference were noted, and body mass index (BMI) was calculated. BMI 25-30 kg/m^2 was considered overweight, and BMI over 30 kg/m^2 obesity. Increased waist circumference was over 88 cm for women and over 102 cm for men. Body surface area (BSA) was calculated via:

$$BSA = 71{,}84 \times Weight^{0{,}425} \times Height^{0.725} \times 10^{-4} \left[m^2 \right]$$

Arterial pressure was measured with an automatic sphygmomanometer (Omron M3) and 24hour blood pressure monitoring (Spacelab Medical 90207). Measurement was set to daytime mode (7 am to 10 pm) and night mode (10 pm to 7 am), every 20 minutes during the daytime and every 30min during the night. Average blood pressure over 135/85mmHg in continuous monitoring was considered as hypertension. Every participant had an electrocardiogram recorded.

Laboratory results included complete blood workup, blood glucose, creatinine, uric acid, cholesterol, HDL and LDL cholesterol, triglyceride. The first-morning urine was taken to determine the albumin/creatinine ratio (ACR). ACR in range 1.1 - 2.2 mg/mmol are high normal, and over 2.2 mg/mmol microalbuminuria. The CKD-EPI formula was used to estimate GFR (eGFR).

Table 1. Clinical and laboratory characteristics of subjects according to gender. All values are expressed as mean ± standard deviation.

	WOMEN n = 40			MEN n = 51			*P*
Age (years)	20.63	±	0.49	21.06	±	0.90	**0,008**
Body mass (kg)	56.00	±	8.80	75.28	±	11.18	**<0.001**
Height (cm)	163.48	±	6.77	176.78	±	5.75	**<0.001**
Body mass index (kg/m^2)	21.01	±	3.54	24.06	±	3.11	**<0.001**
Waist circumference (cm)	67.88	±	6.37	81.53	±	8.33	**<0.001**
Systolic blood pressure (mmHg)	113.67	±	8.18	127.45	±	15.19	**<0.001**
Diastolic blood pressure (mmHg)	73.81	±	6.79	80.37	±	9.10	**<0.001**
Heart rate (bpm)	79.63	±	11.04	71.28	±	10.09	**<0.001**
Blood glucose (mmol/L)	4.63	±	0.66	4.42	±	0.49	0.079
Creatinine (μmol/L)	67.08	±	8.42	94.06	±	9.89	**<0.001**
eGFR (mL/min/1.73m^2)	113.34	±	24.53	94.87	±	16.12	**<0.001**
Uric acid (μmol/L)	252.75	±	36.07	336.24	±	78.94	**<0.001**
Cholesterol (mmol/L)	4.13	±	0.66	4.23	±	0.73	0.500
Triglyceride (mmol/L)	0.89	±	0.36	1.10	±	0.88	0.155
HDL cholesterol (mmol/L)	1.64	±	0.39	1.30	±	0.24	**<0.001**
LDL cholesterol (mmol/L)	2.08	±	0.52	2.45	±	0.71	**0.006**
Albumin/creatinine ratio (mg/mmol)	3.04	±	7.50	1.55	±	4.39	0.239
Augmentation index brachial artery (%)	-52.79	±	13.60	-58.75	±	12.17	**0.035**
Augmentation index Aorta (%)	11.93	±	8.06	7.97	±	5.93	**0.010**
Pulse wave velocity (m/s)	6.72	±	1.20	7.41	±	2.78	0.157
Central arterial pressure (mmHg)	105.32	±	17.83	116.07	±	12.87	**0.001**
Renal volume (cm^3/1.73m^2)	92.14	±	16.30	101.22	±	13.90	**0.005**
Birth weight (g)	2333.25	±	423.32	2521.24	±	184.44	**0.005**
Birth length (cm)	46.23	±	2.94	47.35	±	1.62	**0.022**
Gestational age (weeks)	38.26	±	2.62	38.53	±	1.05	0.500

eGFR - glomerular filtration rate

A kidney ultrasound was performed with Siemens Sonoline SI 250, convex probe 3,5 MHz. We measured length (L), width (W), depth (D), and parenchyma of both kidneys. With these measurements, we used the Solvig and Dinkel's formula to get the kidney volume (KV):

$$V = 0,523 \times L \times W \times D$$

Kidney shape index:

$$\frac{L}{W + D}$$

The combined kidney volume (*Comb.corr.KV*) was corrected to the BSA with:

$$Comb.corr.KV = 1.73 \times \frac{1}{2} \times \frac{KV_{left} + KV_{right}}{BSA}$$

Arteriograph, Tensio Clinic Inc. was used to measure the pulse wave velocity (PWV), augmentation index (Aix) in the Aorta and brachial artery, and central arterial pressure. These results were used to estimate arterial stiffness.

The Ethical Boards of birth hospitals and University Hospital Centre Zagreb, approved the study pro-

Table 2. Blood pressure (BP) values measured during 24hour continuous monitoring according to gender. All values are expressed as mean ± standard deviation (SD).

	WOMEN n = 40			MEN n = 51			*P*
Daytime values							
Systolic BP (mmHg)	117.85	±	7.37	125.43	±	9.84	**<0.001**
Diastolic BP (mmHg)	73.00	±	6.39	71.28	±	6.17	0.216
Heart rate (bpm)	84.06	±	9.37	76.73	±	11.95	**0.003**
Variability of daytime values (SD)							
Systolic BP (mmHg)	11.43	±	2.33	10.48	±	2.23	0.061
Diastolic BP (mmHg)	10.36	±	1.86	9.51	±	2.02	0.052
Night-time values							
Systolic BP (mmHg)	105.56	±	9.81	116.02	±	8.05	**<0.001**
Diastolic BP (mmHg)	60.79	±	6.88	61.71	±	5.98	0.519
Heart rate (bpm)	68.35	±	9.11	64.02	±	9.64	**0.041**
Variability of night-time values (SD)							
Systolic BP (mmHg)	9.06	±	2.87	10.51	±	3.02	**0.031**
Diastolic BP (mmHg)	7.37	±	2.55	8.83	±	2.80	**0.017**

BP - blood pressure

tocol. All work was conducted in accordance with the Declaration of Helsinki

Statistical analysis

The distribution of variables was analysed with the Smirnov-Kolmogorovljev's test. Continuous variables were presented as a mean and standard deviation or median and interquartile range. Differences in quantities between the groups were analysed by the t-test or Mann-Whitney. The Chi-square test was used to analyse differences in categorical variables between the groups. Pearson's coefficient (*r*) or Spearman's test of linear correlation were used to determine correlations between the variables. An estimation of the effects of variables on blood pressure and renal function was made with multiple regression analysis. Values of *P* less than 0.05 were considered to be statistically significant. The programme we used for statistics was STATISTICA, vers.8 (StatSoft., Inc).

Results

A total of 91 healthy individuals were included, 40 women of the average age of 20.6 years (range 20-21 years) and 51 men of the average age of 21.1 years (range 20-23 years) born after IUGR. Table 1 shows clinical and laboratory characteristics regarding gender.

Family history of hypertension, renal diseases, and cardiovascular diseases did not differ between the groups (c^2 = 0.51, *P* = 0.477). Women were smokers more often (37.50% *vs.* 25.49%, c^2 = 1.52, *P* = 0.218) and had less physical activity (50% *vs.* 70.59%, c^2 = 4.01, *P* = 0.045). Males had higher BMI and waist circumference, ambulatory systolic and diastolic blood pressure, higher continuous systolic blood pressure in continuous monitoring during the 24 hours period. During the 24 hours, women had higher values of heart frequency (Table 1 and 2). Men had hypertension more often (15%, *vs.* 0%, c^2 = 5.95, *P* = 0.0147).

Inverse correlation of systolic blood pressure with gestational age was noted only in the women's group and was enhanced if they had a birth weight below 2500 g (*r* = -0.478, *P* = 0.033). A positive correlation between systolic blood pressure and heart frequency was noted as well. Male examinees had their systolic blood pressure correlating with BMI and waist circumference (Figure 1).

Men had lower eGFR (<100 ml/min/1.73m^2) (72.5% *vs.* 22.5%, c^2 = 22.46, *P* < 0.001) more often despite having greater kidney volume and higher birth

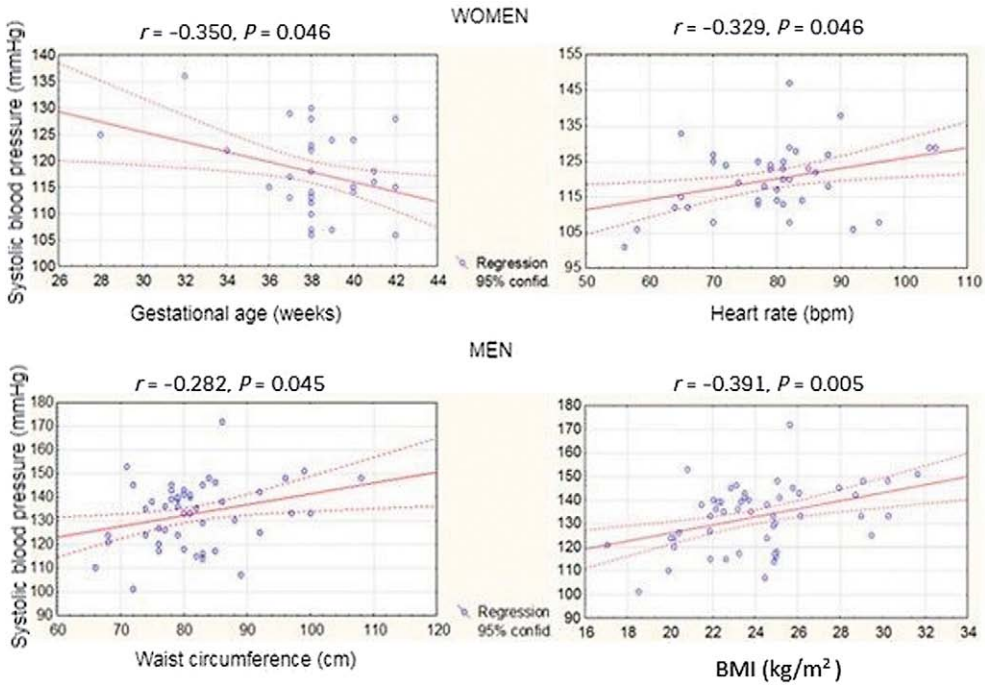

Figure 1. Correlations of systolic blood pressure with gestational age and heart rate in women and with waist circumference and body mass index (BMI) in men.

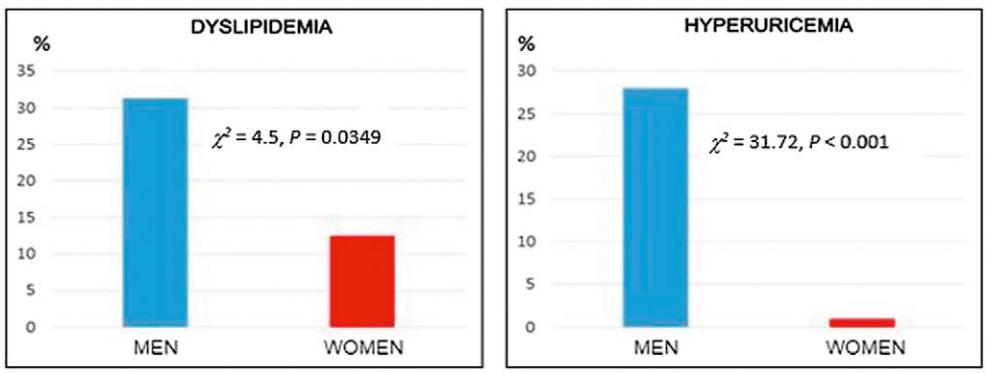

Figure 2. Gender differences in metabolic parameters.

parameters (Table 1). They had higher LDL cholesterol values and lower HDL cholesterol, meaning a higher incidence of dyslipidemia (Figure 2). Higher uric acid values were noted in men, while women have not had values over 340 μmol/L (Figure 2).

Similar results were noticed when comparing male examinees with BMI over 25 kg/m^2 and birth weight lower than 2500 g. A significant increase in ambulatory blood pressure (134/84 *vs.* 124/78 mmHg, $P < 0.016$) as well as central arterial pressure (113 *vs.* 122 mmHg, $P = 0.013$) with pronounced dyslipidemia (triglyceride 0.91 *vs.* 1.50 mmol/L, $P = 0.027$) and hyperuricemia (317 *vs.* 377 μmol/L, $P = 0.011$) was noticed in men who were overweight.

There were no differences in blood glucose, ACR, PWV, and gestational age between the groups. Kidney dimensions are shown in Table 3.

Men had a significantly greater kidney volume in comparison to women (Table 3.).

Although women had thinner kidneys, the kidney shape index did not significantly differ between the sexes. The bigger the index or the thinner the kidney, the estimated glomerular filtration was more reduced. This correlation was especially expressed in women

Table 3. Kidney dimensions in women and men. All values are expressed as mean ± standard deviation.

	WOMEN n = 40			MEN n = 51			*P*
RIGHT KIDNEY							
Length (mm)	100.89	±	8.35	108.29	±	7.04	**<0.001**
Width (mm)	37.07	±	6.67	41.57	±	3.56	**<0.001**
Depth (mm)	38.66	±	4.31	42.55	±	4.36	**<0.001**
Volume (cm^3)	75.84	±	18.85	101.13	±	19.20	**<0.001**
Parenchyma (mm)	14.58	±	1.95	16.90	±	4.57	**0.003**
LEFT KIDNEY							
Length (mm)	101.87	±	8.06	109.67	±	6.54	**<0.001**
Width (mm)	43.06	±	4.43	47.12	±	3.77	**<0.001**
Depth (mm)	40.75	±	4.27	45.47	±	3.43	**<0.001**
Volume (cm^3)	93.92	±	18.32	123.29	±	19.11	**<0.001**
Parenchyma (mm)	15.83	±	3.21	17.88	±	2.25	**0.001**
Combined kidney volume (cm^3/1.73m^2)	92.14	±	16.30	101.22	±	13.90	**0.005**

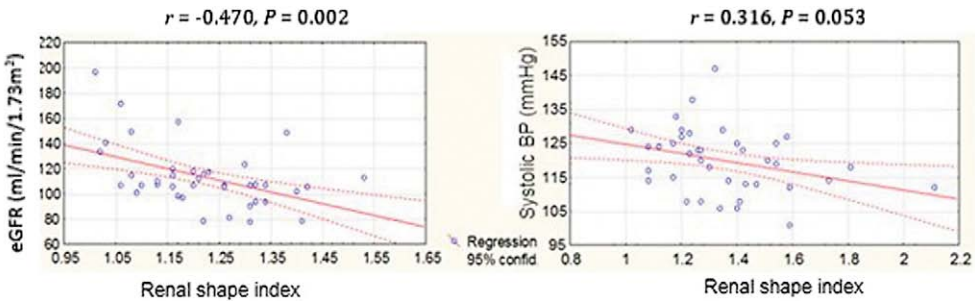

Figure 3. Correlations of renal shape index and estimated glomerular filtration rate (eGFR) and systolic blood pressure (BP) in women

born with a birth weight below 2500 g (r = -0.505, P = 0.012). Also, an inverse correlation of systolic blood pressure with kidney shape was found only in women (Figure 3).

Arterial stiffness was examined by measuring the PWV and Aix in the Aorta and brachial artery. Women had lower central aortic pressure but higher augmentation indices. No differences in PWV were found between the groups (Table 1.).

In multiple regression analysis, BMI was crucial in determining systolic blood pressure only in the men's group (β = 0.322, P = 0.036).

Discussion

The results of this research indicate the more negative effect of IUGR on men. Men had higher blood pressure, enhanced metabolic disorders – dyslipidemia and hyperuricemia, and poorer renal function even though they had a greater renal volume. Although there were no differences in the family history of cardiovascular and renal diseases reported, women are more prone to unhealthy lifestyle habits so are exposed to more "well-known" risk factors.

The mentioned effects of IUGR are known but as yet have not been observed through the influence of sex[6, 7, 27]. Experimental studies regarding this problem are numerous, revealing almost exclusively a higher risk in younger men, but there are far fewer clinical ones[18, 22]. The inverse correlation of arterial pressure and birth weight has been described in both men and women but is often modified with age. While at the younger age, there are mainly no differences in blood pressure values between the sexes, at the age of 22,

Law and al. reported significantly higher arterial pressure in men born after IUGR in comparison to women[28, 29]. Our results are accordant to this study; 15% of men were hypertensive, while none of the women were. Systolic blood pressure showed a positive correlation to BMI in men, while women had an inverse correlation to gestational age and a positive correlation to heart frequency. Heart frequency was increased during 24 hours monitoring in women only. That could indicate the higher activity of the sympathetic system as one of the mechanisms that are well known on an experimental level[30]. Female participants had higher augmentation indices, which could be related to higher heart frequencies. Differences in pulse wave velocity were not found.

The relationship between the metabolic parameters and IUGR exists[31]. Our participants did not have different blood glucose levels, which was to be expected according to data from other studies[32], but a significantly higher incidence of dyslipidemia was marked in the men's group. Uric acid, which is considered to be an independent risk factor for cardiovascular diseases, was found to be increased in men. Hyperuricemia worsened even more with an increase in BMI. Park and al. have reported a similar finding – preterm birth and current BMI significantly impacted levels of uric acid[33]. Despite the greater renal volume (as an approximation of nephron number) modified to BSA, men had a poorer renal function, while no differences between groups were reported for albuminuria. Taking Brenner's hypothesis into consideration about the reduction of nephron number, we would expect the opposite. Similar results were reported in the HUNT study – that men born after IUGR had impaired renal function[9, 34] and the causes are numerous[35]. This poses the question: Is it a matter of hyperfiltration for the women in our research? Although there were twice as many hyperfiltrators in the women's group compared to the men's group, statistical significance was not reached since a small group of participants was involved (7 *vs.* 3, $\chi^2 = 3.09$, $P = 0.078$). An interesting result was discovered when analysing renal shape in men and women. An inverse correlation of renal function and systolic blood pressure to renal shape was found only in the women's group – the thinner the kidneys, the lower the eGFR and higher arterial blood pressure. If observed, renal parameters showed the biggest difference in kidney thickness, 20% thicker in men. Thinner parenchyma may be developed at the expense of juxtamedullary nephron development. Juxtamedullary nephrons are the most sensitive to any adverse stroke, which has already been shown on animal models. Nevertheless, a bigger group with a control group (individuals born without IUGR) should be formed for further research[36, 37].

These observations show the various mechanisms of fetal programming. While men had significance in metabolic disorders and higher blood pressure induced by a greater BMI, women had a greater influence of birth parameters, size, and shape of kidneys.

Higher values of blood pressure and worsening of metabolic parameters in men, and a further rise of blood pressure in men with lower birth weight or smaller gestational age speak in favour of the "second hit" theory. The second hit theory stands for developing a disorder much earlier in life after more than one "insult" has appeared. Gjerde and al. have noticed the same, unless participants had at least 2 or 3 risk factors present (low birth weight, preterm birth, IUGR), the disease did not develop[38]. The age of participants should be taken into consideration[29].

In conclusion, our results indicate the unfavourable effect of IUGR, especially in men. Men have higher blood pressure values, poorer renal function, and metabolic disorders. These, in fact, predispose them to earlier development of chronic diseases. Also, the impact of obesity on arterial pressure points out the importance of timely lifestyle changes in the group of IUGR individuals.

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Sažetak

SPOLNE RAZLIKE U KARDIOVASKULARNIM ČIMBENICIMA RIZIKA I RENALNOJ FUNKCIJI KOD MLADIH ODRASLIH OSOBA ROĐENIH NAKON INTRAUTERINOG ZASTOJA U RASTU

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Uvod: Intrauterini zastoj u rastu (IUGR) povezan je s povećanom incidencijom kardiovaskularnih i bubrežnih bolesti.

Ispitanici i metode: Uključena je 91 zdrava osoba, 40 žena i 51 muškarac, rođenih ispod 10. percentile porodne mase za gestacijsku dob. Izmjereni su antropometrijski parametri, arterijski tlak (AT), glukoza u krvi, procijenjena brzina glomerularne filtracije (eGFR), albumin/kreatinin omjer, lipidogram, urati, volumen bubrega ultrazvukom, brzina pulsnog vala, centralni arterijski tlak (cAT) i indeks augmentacije (Aix).

Rezultati: Muškarci imaju veći indeks tjelesne mase (ITM), opseg struka, ambulantni i kontinuirani AT, nižu eGFR, srčanu frekvenciju, povišene urate i LDL kolesterol, niži HDL kolesterol, viši cAT i Aix, veći korigirani volumen bubrega i porodnu težinu od ispitanica. Pretili muškarci češće imaju hipertenziju, sniženu eGFR i dislipidemiju. Kod muškaraca je sistolički tlak korelirao s ITM. Kod žena je sistolički tlak pozitivno korelirao sa srčanom frekvencijom i negativno s gestacijskom dobi. ITM je utjecao na sistolički AT kod muškaraca, a kod žena na eGFR.

Zaključak: Rezultati ukazuju na nepovoljniji učinak IUGR na muškarce. Viši AT, vaskularna disfunkcija, slabija bubrežna funkcija i dislipidemija predisponiraju muškarce ranijem razvoju kroničnih bolesti.

Ključne riječi: *intrauterini zastoj u rastu, arterijski tlak, bubrežna funkcija*