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Hiponatremia during pregnancy with adriamycin-induced nephrotic syndrome in rats

The influence of pregnancy and nephrotic syndrome is a still discussed and investigated problem. Even during physiological pregnancy temporary a kidney function disturbance could appear with proteinuria similar to nephrotic syndrome. During complicated pregnancy proteinuria is one of the signs of preeclampsia. In this study the electrolyte serum blood level of pregnant rats with adriamycin-induced nephrotic syndrome was studied.

MATERIAL AND METHODS

The studies were performed on white female Wistar rats chosen randomly (2, 8). At the beginning of the experiment female rats from experimental groups were given intraperitoneally (i.p.) adriamycin in the dose 5 mg/kg of body weight to obtain nephrotic syndrome. Female rats from control groups were administrated intraperitoneally 0.5 ml 0.9% NaCl. The animals were divided into 8 groups, 8 individuals in each group (4 first experimental groups, then next 4 corresponding control groups) (Tab. 1). 4 weeks after adriamycin administration female rats from experimental groups III and IV and corresponding control groups VII and VIII were paired with male rats.

The animals were decapitated as follows: a) after 4 weeks (experimental group I and control group V) to assess the features of nephrotic syndrome, b) after 7 weeks (experimental group II and control group VI) to compare a group of female rats with adriamycin-induced nephrotic syndrome to a group of pregnant female rats with adriamycin-induced nephrotic syndrome, c) on 20 day of pregnancy (experimental group III and control group VII), d) 4 weeks after termination (experimental group IV and control group VIII).

The animals were weighed once a week and after decapitation the blood from heart was collected to investigate – electrolytes – Na^+, K^+, Ca^{+2}. In blood and urine of females from experimental group I and control group V, the features of nephrotic syndrome were studied: total protein concentration, albumin, lipids, cholesterol and creatinine concentration in blood serum and in urine from 24 hours collection – protein concentration.

All results were statistically estimated with t-student test and displayed as averages and standard deviation. Statistical significance of differences was stated at $p<0.05$.

Table 1. Groups

Experimental groups						
Gr.	characteristic of group	given	amount of drug	pregnancy	decapitation	number of rats in group
I	female rats	Adriamycin	5 mg/kg of body weight- intraperitoneally		4 weeks after drug administration	8 rats
II	female rats	Adriamycin	5 mg/kg of body weight- intraperitoneally		7 weeks after drug administration	8 rats
III	pregnant rats	Adriamycin	5 mg/kg of body weight- intraperitoneally	4 weeks after drug administration	20 day of pregnancy (about 3 weeks)	8 rats
IV	mothers	Adriamycin	5 mg/kg of body weight- intraperitoneally	4 weeks after drug administration	4 weeks after delivery	8 rats
Control groups						
V	female rats	0.9% NaCl	0.5 ml intraperitoneally		4 weeks after drug administration	8 rats
VI	female rats	0.9% NaCl	0.5 ml intraperitoneally		7 weeks after drug administration	8 rats
VII	pregnant rats	0.9% NaCl	0.5 ml intraperitoneally	4 weeks after drug administration	20 day of pregnancy (about 3 weeks)	8 rats
VIII	mothers	0.9% NaCl	0.5 ml intraperitoneally	4 weeks after drug administration	4 weeks after delivery	8 rats

RESULTS

Four weeks after adriamycin administration full signs of nephrotic syndrome were presented with the following features: extensive proteinuria, hipoproteinemia, hipoalbuminemia, hiperlipidemia, hipercholesterolemia with creatinine level in the normal range – Tab. 2 (6).

Table 2. Analysis of biochemical results

Material	Study	Control group (V)	Experimental group (I)	Significance	T-student Test
Blood serum	creatinine (mg/dl)	0.71(+/-0.16)	0.65(+/-0.08)	p=0.53	0.68
	total protein (g/dl)	7.06(+/-0.50)	6.00(+/-0.33)	p=0.01	3.6
	albumin (g/dl)	3.82(+/-0.40)	2.93(+/-0.40)	p=0.02	3.08
	lipids (mg/dl)	110.10(+/-30.08)	202.75(+/-22.92)	p=0.003	4.9
	cholesterol (mg/dl)	86.47(+/-4.79)	138.02(+/-12.75)	p=0.002	7.57
Urine	protein (mg/24 h)	7.96(+/-0.27)	84.38(+/-5.40)	p<0.0001	31.57

Initial body mass of female rat from control and experimental groups was similar and ranged from 200 to 250g. After 4 weeks of experiment animals from all groups had similar mass increase. Pregnant rats from experimental groups weighed less than pregnant rats from control groups with statistical significance, and mothers from experimental groups weighed more than mothers from control groups (Tab. 3).

Table 3. Body mass

Grups	Nr	Average initial body	Average body mass after 4	Increase of body mass after 4	Average body mass after 7	Increase of body mass after 7	Average body mass 4 weeks after
		mass	weeks	weeks	weeks	weeks	delivery
		(g)	(g)	(g)	(g)	(g)	(g)
Experimental	I II	220.36+/-1.59 225.33+/-0.65	270.04+/-1.98 276.1+/-7.11	49.68 50.77	240+/-8.01	-36.1	
Control	VI VII	212+/-15.27 224.62+/-0.77	266.44+/-16.15 272.66+/-7.59	54.44 48.04	274+/-4.72	1.34	
Significance	gr.I to gr. VI gr.II to gr.VII	p=0.14 p=0.051	p=0.525 p=0.337		P<0.0001		
Exp. with pregnant rats	III IV	232.54+/-1.95 248.5+/-11.91	284.55+/-85.91 300.66+/-25.0	52.01 52.16	364.5+/-42.06 379.25+/-14.02	79.95 78.59	352.6+/-3.97
Control with pregnant rats	VIII IX	233.83+/-0.86 240.02+/-5.76	313.3+/-28.96 286.66+/-24.49	79.47 46.64	395.5+/-8.15 396.75+/-10.3	82.2 110.09	343.62+/-3.65
Significance	gr. III to gr.VII I	P=0.09	P=0.36		P=0.049		
	gr. IV to gr. IX	P=0.07	P=0.247		P=0.01		P=0.005

Table 4. Sodium concentration in blood serum

Study	Gr.	Average	Standard deviation	To group:			To control:		
				significance	t -student test		significance	t-student test	
Na^+ (mmol/l)	C:								
	V	140.75							
	VI	141.25		p=0.83	0.22	V			
	VII	138.75		p=0.10	2.07	VI			
	VIII	139.5		p=0.72	0.39	VII			
	EX:								
	I	138	(+/-4.32)				p=0.38	0.95	V
	II	137.25	(+/-4.27)	p=0.81	0.25	I	p=0.16	1.66	VI
	III	130.75	(+/-3.09)	p=0.056	2.46	II	p=0.008	4.93	VII
	IV	139	(+/-1.82)	p=0.006	4.59	III	p =0.82	0.24	VIII

K^+ and Ca^{+2} concentration did not differ very much between experimental and control groups and was: K^+ control group – 4.97(+/-0.32) mmol/l, experimental group – 4.91(+/-0.62) mmol/l. Ca^{+2} control group – 2.90(+/-0.16) mmol/l, experimental group – 2.66(+/-0.14)mmol/l.

Sodium concentration decreased in the group of pregnant rats, which had administrated adriamycin as compared to other groups (control and experimental). Puerperium sodium concentration was like before pregnancy (Tab. 4, Fig. 1).

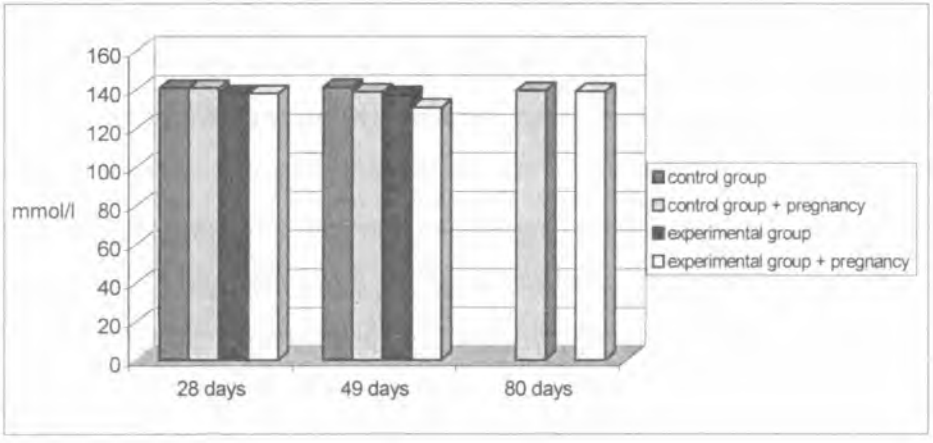

Fig. 1. Sodium concentration in blood serum

DISCUSSION

In the present study nephrotic syndrome appeared after a single dose of adriamycin after 4 weeks. It confirms the studies of other authors (4,7). Soares (9), 10 weeks after adriamycin administration in the dose 3 mg/kg of body weight noticed an increase of protein in urine even to 250.0 (+/-25.9) mg/24 hours. Extensive proteinuria causes decrease of total protein in blood in comparison to control groups. In the present study, after 4 weeks it decreased to 6.00 (+/-0.33) g/dl. Hipoalbuminemia noticed in this experiment was also described Wang et al. (11) and Feehally (3). Other factors investigated in this study were cholesterol concentration and lipids. 4 weeks after adriamycin administration the lipids level increased almost twice in comparison to control groups (202.75 +/-22.92 mg/dl). After 6 weeks Tesar et al. (10) noticed lipids concentration 810.0+/-86.0mg/dl. Wang (11) and Feehally (3) observed hiperchlesterolemia. The dose of adriamycin 5 mg/kg of body weight used in this study seems to be optimium. It caused quick appearance (after 4 weeks) of the nephrotic syndrome and it did not cause lethal disorders in organs (especially in kidneys). In the experiment the increase of creatinine concentration was not observed, which is the feature of kidney insufficiency. Similar observations were reported by other authors, for example Bertani (1) 5 weeks after adriamycin administration in the dose 5 mg/kg of body weight did not notice any increase of creatinine and urea in blood serum in rats.

In the present study the decrease of sodium concentration in blood of pregnant rats after adriamycin administration was noticed in comparison to controls and virgin rats after adriamycin administration. Decreased sodium concentration could cause neurological complications, which stimulate eclampsia in pregnant rats. Hiponatremia is also one of other factors activating RAA system. As a cause of decreased sodium concentration in blood, Heystett (5) described decrease of effective volume of plasma in pregnancy coexisting with

nephrotic syndrome. It stimulates vasopresin secretion, which stops water discharge and decrease of sodium concentration. Heystett (5) also noticed hiponatremia in blood serum of women with pregnancy complicated by preeclampsia due to the nephrotic syndrome.

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SUMMARY

The purpose of the studies was to assess the electrolyte concentration in blood serum of pregnant Wistar rats, in which pregnancy coexisted with adriamycin-induced nephrotic syndrome. The results displayed hiponatremia in serum blood of these female rats. After puerperium sodium concentration came to the level similar to that before pregnancy, in comparison to control. Hiponatremia could cause neurological complications, which in pregnancy could activate eclampsia.

Hiponatremia w przebiegu ciąży współistniejącej z zespołem nerczycowym po adriamycynie u szczurów

Przeprowadzone badania miały na celu ocenę stężenia elektrolitów w surowicy krwi ciężarnych samic szczura szczepu Wistar, u których ciąża współistniała z zespołem nerczycowym wywołanym doświadczalnie Adriamycyną. Otrzymane wyniki wykazały hiponatremię w surowicy krwi tych samic. Po zakończonym połogu poziom sodu powrócił do poziomu sprzed ciąży – porównywalnego z kontrolą. Hiponatremia może powodować neurologiczne powikłania, które w ciąży mogą stymulować rzucawkę.