American Journal of Medicine and Medical Sciences 2019, 9(2): 54-57
DOI: 10.5923/j.ajmms.20190902.04

Influence of Prenatal Hyperandrogenization on the Condition of Indicators of the Endocrine Profile in Rats

Khamid Yakubovich Karimov, Feruza Tairovna Maksudova*

Department of Molecular Medicine and Cell Technologies, Scientific Research Institute of Hematology an Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan

Abstract The aim of the study was to evaluate the effect of prenatal hyperandrogenism on the endocrine profile indicators in rats fed different levels of calories. Studies were performed on 90 outbred white pregnant rats fed on a high-calorie diet (HCD) and rational diet (RD). Concentrations of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (Est), total testosterone (TTS), cortisol (Cort) and dehydroepiandosterone sulfate (DHEA-s) were measured. Results showed that prenatal androgenization caused an imbalance of the endocrine profile in rats, which is more pronounced with a high-calorie diet.

Keywords Hyperandrogenism, High-calorie diet (HCD), Endocrine profile, Pregnant rats

1. Introduction

Currently, the increasing interest of scientists all over the world is attracted to the study of one of the important problems of medicine - the study of the reproductive health of women [1, 2]. The urgency of the problem is emphasized by the increase in recent years in the frequency of various pathologies of the reproductive system in women, developing under the influence of various exogenous and endogenous factors [4]. Today, one of the most frequent causes of impaired fertility in women [8, 10], i.e. infertility, are disorders of the mechanisms of the endocrine profile, in particular polycystic ovary syndrome (PCOS, Stein-Leventhal syndrome) [5, 6, 7].

Taking into account the fact that PCOS is a multiendocrine pathology, research is being actively conducted to study the mechanisms of formation of the syndrome involving the hypothalamic-pituitary system, adrenal glands and ovaries [9, 11, 12]. Available publications of the results of studies on the pathogenetic aspects of the syndrome emphasize that hyperandrogenism is one of the important links in its development. There are also opinions that already in the prenatal period, prolonged exposure of the androgens to the fetus may lead to the formation of this type of steroidogenesis in the ovary, in which PCOS may later occur [3].

* Corresponding author:
alteam2201@gmail.com (Feruza Tairovna Maksudova)
Published online at http://journal.sapub.org/ajmms

According to statistics, pathology is often combined with obesity. In the period of postnatal development, obesity acts as an additional factor leading to the aggravation of PCOS and gross hormonal disorders. High-calorie diet (HCD) with this pathology leads to the development of complications and significantly affects the quality of life of patients with PCOS.

The presence of certain restrictions in conducting scientific experiments with the participation of people, to study the mechanisms of PCOS formation, which allow a better understanding of the mechanism of development of pathology, determine the need for their implementation in laboratory animals [13].

2. Main Body

2.1. Purpose of the Study

Study of the effect of prenatal hyperandrogenism on the state of endocrine profile indicators in the experiment.

2.2. Material and Methods of Investigation

Studies conducted on 90 mongrel white pregnant rats that are on a normal laboratory diet. All animal procedures were carried out in accordance with ethical rules. On the 15th day of pregnancy, the rats were divided into 3 groups:

1. 1st group (intact) - 30 pregnant rats,
2. 2nd group (comparisons) - 30 pregnant rats,
3. 3rd group (main) - 30 pregnant rats.

From the 16th to the 19th day of gestation, daily sesame oil was administered subcutaneously to females of the 2nd group at a dose of 1.0 ml, whereas females of the 3rd group were injected subcutaneously with 5 mg of “Testosterone” to females of the 3rd group (T-1500; Sigma) dissolved in 1.0 ml

of sesame oil.

Each pregnant female rat was set apart separately. Births occurred on the 20-22nd days of pregnancy. The rats were selected from the offspring in such a way as to equalize the size of groups (10 calves (T2) per mother (T1)).

On the 30th day after the birth, the female cubs were separated from the male calves. At the same time, T2 females in the 2nd and 3rd groups were divided into 2 subgroups of 48 in each:

1. subgroup A (T2) (n = 32) received a high-calorie diet (HCD) (5.24 kcal / g: 60% fat, 20% carbohydrate, 20% protein) and water on demand;
2. subgroup B (T2) (16 female rats each) - normal (RD) (3.30 kcal / g: fat 15%, carbohydrates 62%, proteins 23%) diet [7. 9].

During the experiment, animals were slaughtered by decapitation under light ether anesthesia on the 60th day from birth (in 1-group-10 (T2) females, in the 2nd A and B subgroups of 6 (T2) females, in the 3rd A - 7 (T2) females in the 3rd B subgroup - 6 (T2) females.

To achieve this goal, this study carried out studies of hormones in the blood serum of animals by enzyme immunoassay (ELISA) on an enzyme immunoassay analyzer from Human (Germany) using standard kits of the same company. The content of prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (Est), total testosterone (TTS), cortisol (Cort) and dehydroepiandosterone sulfate (DHEA-s) was determined.

2.3. Results and Discussion

The results of a comparative analysis of the level of the main hormonal parameters showed that in prenatally hyperandrogenized rats the mean serum level of PRL increased significantly (P <0.001), while there was some difference in the values between subgroups A (14.9 ± 0.40 ng / ml) and B (12.6 ± 0.19 ng / ml). The level of PRL in the 3rd group exceeded that in the 1st and in the 2nd group on average 2.7 and 2.1 times, respectively. A high level of PRL in prenatally hyperandrogenized animals is explained by a violation of the regulation of its synthesis and secretion, which is especially pronounced in rats that were on a lipid diet.

The average levels of LH in animals of the 2A subgroup were significantly higher, the average values in the subgroup 2B (3.9 ± 0.2 IU / l; P <0.001) in the intact group (4.0 ± 0.16 IU / l) and on average amounted to 7.1 ± 0.37 IU / l (P <0.001). In 3A (19.1 ± 0.57 IU / l; P <0.001) and 3B subgroups (11.5 ± 0.36 IU / l; P <0.001) the level of LH significantly exceeded the corresponding figure in the 1st group on average 3.8, and in the 2nd combined group on average 2.8 times. The increase in LH in the group of prenatally androgenated rats is probably associated with the stimulation of its production by the pituitary gland, as indicated by the literature data [12].

Along with the above changes, the average FSH level of 3 A (3.3 ± 0.22 IU / l; P <0.001) and 3 B (2.7 ± 0.22 IU / l; P <0.001) of the subgroups tended to decrease in relation to animals of the intact and 2nd group (Table 1.). These differences, characterized by a decrease in FSH in prenatally hyperandrogenic animals, indicate a violation of the folliculogenesis period, in which the basal growth of follicles occurs only in the presence of a sufficient level of FSH. In our study, disorders of folliculogenesis are confirmed by morphological studies of the structure of the ovaries.

Conducted correlation analysis established a direct correlation of LH with PRL (r = 0.14), FSH (r = 0.36), TTS (r = 0.27) and DHEA-s (r = 0.16), FSH with TTS and TTS (r = 0.25) and DHEA-s (r = 0.27) (Table 1.).

The mean values of serum Est and TTS in the group of intrauterine hyperandrogenized animals differed significantly from those in the intact group: in the 3A subgroup, these values were 211.4 ± 2.1 pg / ml (P <0.001) and 0.98 ± 0.09 pg / ml (P <0.001), respectively, whereas in the B subgroup these values were slightly lower - 97.5 ± 3.3 pg / ml (P <0.001) and 0.81 ± 0.05 pg / ml (P < 0.001), respectively. However, it should be noted that the average geometric values of these parameters in animals of the 2nd A subgroup (81.6 ± 1.6 pg / ml; P <0.001 and 0.46 ± 0.02 pg / ml; P <0.05, respectively) also exceeded those of animals of the 1st group and 2B subgroups on average 1.74 and 1.2 times, respectively (Table 2.).

A correlation analysis established a direct correlation between the increase in Est concentration, TTS level (r = 0.46) and Cort content (r = 0.49), as well as TTS with Cort (r = 0.10) and DHEA-s (r = 0, 04) in the serum of animals.

Table 1. The initial values of the average values of the studied hormones in the serum of animals of the studied groups on the 60th day of the experiment

Groups			Hormone levels studied		
№	Name & composition of the group	n	Prolactin (PRL), (ng / ml)	Luteinizing hormone (LH), (IU / l)	Follicle-stimulating hormone (FSH), (IU / l)
1	intact	20	5.1±0.32	4.0±0.16	6.0±0.31
2	A (HCD)	12	7.9±0.28***	7.1±0.37	5.9±0.25
2	B (RD)	12	5.1±0.43	3.9±0.20	6.1±0.40
3	A (HCD)	12	14.9±0.40***	19.1±0.57***	3.3±0.22***
3	B (RD)	12	12.6±0.19***	11.5±0.36***	2.7±0.22***

Note: * - statistical significance of differences in the parameters of the main group in relation to those of the control group, where *** - P <0.001

Table 2. Initial values of the average values of the studied hormones in the blood serum of the studied groups on the 60th day of the experiment

Groups			Hormone levels studied			
№	Name & composition of the group	n	Est (pg / ml)	TTS, (ng / ml)	Cort, (mg / dl)	DHEA-s, (mkg / ml)
1	intact	20	46,9±1,3	0,38±0,11	62,7±1,2	1,3±0,10
2	A (HCD)	12	81,6±1,6	0,46±0,02	73,0±1,3	1,6±0,11
2	B (RD)	12	47,0±1,6	0,39±0,01	63,6±2,0	1,5±0,08
3	A (HCD)	12	211,4±2,1	0,98±0,09	193,4±6,5	3,1±0,08
3	B (RD)	12	97,5±3,3	0,81±0,05	163,7±4,3	2,8±0,14

* - statistically significant compared with the intact group (* -P <0.05; ** - P <0.01; *** - P <0.001).

The study of the content of adrenal hormones in the serum also revealed certain changes. So the content of Cort showed significant differences between groups of animals. In the 3 A subgroup of animals androgenated in the prenatal period, the mean value of Cort was 193.4 ± 6.5 mg / dl (P <0.001). At the same time, the average concentration of Cort in the B subgroup was 163.7 ± 4.3 mg / dl (P <0.001), on average, in the combined 3 group of animals, this indicator was 2.8 times higher than in the intact group, while in the 2nd in 2.6 times, it should be noted that the content of Cort in the 2A subgroup (73.0 ± 1.3 mg / dl; P <0.001) was slightly higher than in the 1st group (62, 7 ± 1.2 mg / dl) and 2B subgroup (63.6 ± 2.0 mg / dl).

Analysis of the content of DHEA-s in the studied groups showed differences that are evident from the data given in Table 2. The average metabolite level of DHEAA in the 3A subgroup (3.1 ± 0.08 mkg / ml; P <0.001) was 2.4 times higher than in the control group (1.3 ± 0.10 mkg / ml). At the same time, the average level of DHEAs in the B subgroup was 2.2 times higher (2.8 ± 0.14 mkg / ml; P <0.01) than in animals of the intact group and 1.75 and 1, 9 times higher than those in 2 A (1.6 ± 0.11 mkg / ml; P <0.05) and 2 B (1.5 ± 0.08 mkg / ml) in subgroups of the compared group.

A correlation analysis of the endocrine profile indices established a direct correlation between the level of Cort and DHEA-s (r = 0.24).

The revealed facts of changes in the content of adrenal hormones indicate, above all, the activation of the adrenocorticotropic function of the pituitary gland, and it should also be noted that they are the result of an increase in the steroid-producing function of the adrenal glands [8]. The most obvious profound changes were observed in prenatally hyperandrogenized animals that were on a lipid diet, which further aggravated the existing disorders on the background of androgenization. Impaired function of the adrenal system in turn, which leads to the accumulation of antral follicles, and as a result of this to the development of hyperandrogenism and the formation of polycystic ovary syndrome (PCOS) [8].

Thus, the analysis of the results of the study of the endocrine profile in prenatally-hyperandrogenic animals showed significant changes characterized by an increase in the level of PRL and LH, between which a positive correlation was found [2]. In turn, the growth of follicles is disturbed in the ovaries, with their subsequent cystic atresia [8, 9]. These disorders were combined with a decrease in the content of FSH. Against the background of a low level of FSH, the aromatase activity of granular cells decreases, which contributes to the mechanism of transformation of androgens into estrogens and, as a result, androgen accumulation and estrogen deficiency occur. These processes lead to atrophy of the cell of granulose, which even more inhibits the secretion of FSH, thus closing the vicious circle leading to hyperandrogenism in PCOS [9, 13].

Along with this, there was a significant increase in the values of Est and TTS, as well as adrenal hormones, which were in a positive correlation relationship. An increase in TTS is observed, probably due to a decrease in the synthesis of TTS-Est-binding globulin (TESG). The revealed facts testify to deep abnormalities in folliculogenesis, which is confirmed by the detected structural changes in the ovaries and adrenal glands during morphological examination.

3. Conclusions

1. Prenatal hyperandrogenization in rats in the postnatal period of development leads to an imbalance of the endocrine profile.
2. The most pronounced changes among the indicators of the endocrine profile are observed in rats that were on a high-calorie diet (HCD), while HCD is an additional factor aggravating endocrinological disorders.

ACKNOWLEDGEMENTS

The author thanks the scientific adviser and the head of the Department of Molecular Medicine and Cell Technologies of, Scientific Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan Khamid Yakubovich Karimov for assistance in the management and organization of the conducted studies.

REFERENCES

[1] Adamyan L. V., Andreeva E. N., Gasparyan S. A. et al. Polycystic ovary syndrome in reproductive age (current approaches to diagnosis and treatment). Clinical recommendations (treatment protocol). - M., 2015. - 22 p.

[2] Azizova M. E. Polycystic ovary syndrome from the standpoint of modern concepts. Kazan Medical Journal, 2015. - Volume 96, No. 1.- P.77-80.

[3] Blesmanovich A. E., Petrov Yu. A., Alekhina A.G. Polycystic ovary syndrome: classic and modern nuances. The Journal of Scientific Articles "Health and Education Millennium", 2018. Vol. 20. No 4.

[4] Manukhin I. B. and others. Gynecological endocrinology. Clinical lectures - 4th ed., Revised and enlarged - M.: GEOTAR-Media, 2017.-304 p.: ill. - "Series" Library of a specialist doctor).

[5] Grankina A. S., Nekrasova E. G. The relationship between skin manifestations and hormonal changes in polycystic ovary syndrome. In the collection of scientific papers: "Youth and Medical Science" - Proceedings of the V Interuniversity Scientific Practical Conference of Young Scientists. 2018. p. 134.

[6] Grigoryan O. R, Andreeva E. N. Polycystic ovary syndrome - long-term risks. Effective pharmacotherapy. 2015; 5: 20-25.

[7] Grodnitskaya E. E., Ilina N.A., Dovzhenko TV, Latyshkevich O.A., Kurtser M.A., Melnichenko G.A. Polycystic ovary syndrome is an interdisciplinary problem. Doctor.ru, 2016; 3: 59–65.

[8] Guriev T. Polycystic ovary syndrome. Obstetrics, gynecology, reproduction. 2010; 4 (2): p. 10-17.

[9] Kirillova E. N., Korshikova R. L., Savochkina Yu. V. Neuroendocrine syndromes in gynecological practice. Minsk: Belarusian State Medical University, 2013. 43 p.

[10] Shustov S. B., Baranov V. Ya., Halimov Yu. Sh. Clinical endocrinology. M.: LLC Publishing Medical Information Agency, 2012. - 632 p.

[11] Marinkin I. O., Kuleshov V. M., Galkina Yu. V., Aidagulova S. V. Correction of neuroexchange endocrine syndrome in women of reproductive age. Journal of Siberian Medical Sciences., 2012; 2.

[12] Sukhikh G. T., Biryukova A. M., Nazarenko T. A., Durinyan E. R. Endokrinno-metabolic features in patients with polycystic ovary syndrome. Obstetrics and gynecology. 2011; 4: 45-49.

[13] Xiao-Yan Wu, Zhi-Ling Li, Cheng-Yong Wu, Yan-Mei Liu, Hong Lin, Shao-Hong Wang and Wan-Fen Xiao Endocrine Traits of Polycystic Ovary Syndrome in Prenatally Androgenized Female Sprague-Dawley Rats. Endocrine Journal 2010, 57 (3), 201-209.