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State of Pituitary-Ovarian Axis of the Neuroendocrine Regulation System in Women of Reproductive Age with Ovarian Hyperandrogenism

Marina A. Darenskaya, Liliia V. Belenkaia, Alina V. Atalyan, Lydmila M. Lazareva, Yana G. Nadelyaeva, Irina N. Danusevich, Leonid F. Sholokhov, Larisa V. Suturina, Lyubov I. Kolesnikova

Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation

Abstract

Background: This study aimed to evaluate the state of the pituitary-ovarian axis of the neuroendocrine regulation system in women of reproductive age with ovarian hyperandrogenism (OH) of the main ethnic groups of the Baikal region.

***Methods and Results*:** Groups of women with OH of Buryat (n=35) and Caucasian (n=97) ethnic groups were formed. Data from somatically healthy women of Buryat (n=42) and Caucasian (n=87) ethnic groups were used for comparison. A comparative characterization of clinical data and indicators of the pituitary-ovarian link of the neuroendocrine regulation system was carried out. ELISA methods were used to determine thyroid-stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), 17-OH-progesterone (17-OH-Pg), and sex hormone-binding globulin (SHBG). Testosterone levels were analyzed by liquid chromatography-mass spectrometry.

Buryat ethnic group women with OH had higher values of body weight, BMI, waist and hip circumference, and % fat compared to the corresponding control group. In the group of Caucasian women with OH, higher values of height, systolic blood pressure, and diastolic blood pressure were registered compared to the control group. In Buryat women with OH, higher TSH, anti-Mullerian hormone (AMH), free androgen index (FAI), and dehydroepiandrosterone sulfate (DHEA-S) values were found compared to controls. In the group of Caucasian women with OH, higher values of PRL, AMH, TSH, FAI, 17-OH-Pg, and DHEA-S were registered compared to the control. In Buryat women with OH, LH values were higher only in phase 2 compared to controls. In Caucasian women with OH, LH values increased both in phase 1 and phase 2 compared to controls.

***Conclusion*.** A comprehensive analysis of the state of the neuroendocrine regulation system in women of reproductive age with OH showed certain changes in the level of a number of hormones relative to control groups, most pronounced in the group of Caucasian women. At the same time, there were no differences in the studied indicators between ethnic groups with OH. The data obtained indicate the necessity of assessing and controlling the state of the neuroendocrine regulation system in female patients with OH for PCOS prevention and treatment. The ethnic component may have a certain contribution to the realization of further risks of the disease. **(International Journal of Biomedicine. 2024;14(1):66-71.)**

Keywords: pituitary-ovarian axis • ethnos • ovarian hyperandrogenism • polycystic ovary syndrome

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Abbreviations

AMG, anti-Mullerian hormone; **BMI,** body mass index; **BP**, blood pressure; **DBP**, diastolic blood pressure; **DHEA-S**, dehydroepiandrosterone sulfate; **FAI**, free androgen index; **FSH,** follicle-stimulating hormone; **HC**, hip volume; **HR**, heart rate; **LH,** luteinizing hormone; **MS**, metabolic syndrome; **OH,** ovarian hyperandrogenism; **PCOS**, polycystic ovary syndrome; **PRL,** prolactin; **TSH,** thyroid-stimulating hormone; **17-OH-Pg**, 17-OH-progesterone; **SBP**, systolic blood pressure; **SHBG**, sex hormone-binding globulin; **WC**, waist circumference.

Introduction

Ovarian hyperandrogenism (OH) is a polygenic endocrine disorder most commonly found in women of reproductive age.[1] The prevalence of OH in the female population ranges from 8-21%.[2,3] OH has a serious impact on the reproductive system and contributes to the development of infertility.[4] Neuroendocrine, metabolic, psychological, and other factors play a significant role in the OH pathogenesis.[5,6] Androgen excess is a characteristic feature of OH, determining many of its phenotypic features.[7] The clinical course of OH depends on a number of factors, including the ethnicity of the features.[5]

Several studies demonstrated global differences in the phenotypes of polycystic ovary syndrome (PCOS), of which OH is a major feature, in women of different racial and ethnic groups. For example, Middle Eastern, Mediterranean, Indian, and South Asian women with PCOS have a higher prevalence and/or severity of hirsutism than East Asian or Caucasian women.[8-10] Thirty studies were evaluated, and metabolic outcomes in women with PCOS from different nationalities worldwide were compared in a systematic review by Chan et al.[11] South Asian, Indian, and Norwegian women with PCOS, in particular, are at increased risk for metabolic syndrome (MS), Hispanic and Mexican women are at high risk for insulin resistance, and black women in the United States are at increased risk for hypertension compared with white women.[11-13] In a cross-sectional study of over 1000 women with PCOS in 5 countries, Chan et al.[11] found a significant difference in the prevalence of MS and the clustering of its components in different racial/ethnic groups. In Russia, there were practically no studies on the prevalence of OH; there are only single works.[10]

In the pathogenesis of OH, the leading role is played by changes in the pituitary-ovarian link of the neuroendocrine regulation system, including circadian rhythm disorders, isolated secretion of luteinizing hormone (LH), hyperinsulinemia, insulin resistance, ovarian theca-cell dysfunction, and hyperandrogenism.[10,14] The outcome of pathogenetic disorders in OH is progesterone deficiency, the main source of steroid hormone production.[14]

The Baikal territory is characterized by multinationals, where representatives of different ethnic groups coexist in the same zone of residence in the same climatic-geographical and social conditions.[15,16] The indigenous ethnic groups are Buryats, Evenks, Yakuts, Tofalars, and mixt-races.[17] Their gene pool is of special interest to researchers since it was formed over a long period of time under conditions of a sharply continental climate.[18] Buryats belong to the largest indigenous ethnic group - 3.3% of the total population of the Irkutsk region. Currently, there are negative trends in the growth of morbidity of this ethnic group, in particular, the increase in the number of diseases of the reproductive system - infertility, miscarriage, and endometriosis.[19-21] However, the pathogenetic mechanisms of these diseases remain unclear. In particular, the mechanisms of disorders of the pituitary-ovarian link in OH in the ethnic aspect are not fully disclosed.

This study aimed to evaluate the state of the pituitary-ovarian axis of the neuroendocrine regulation system in women of reproductive age with OH of the main ethnic groups of the Baikal region.

Material and Methods

The objects of the study were women of reproductive age, subject to annual preventive examination at the place of work, living in the Irkutsk region and Buryatia.

The following groups were formed: groups of women with OH of Buryat (n=35; mean age - 30.7±5.81 years) and Caucasian (n=97; mean age - 29.6±5.79 years) ethnic groups and groups of somatically healthy women without signs of OH (control groups) of Buryat (n=42; mean age - 36.28±5.45 years) and Caucasian (n=87; mean age - 34.4±6.1 years) ethnic groups.

Belonging to a specific ethnic group was determined by taking into account the duration of residence in a territory (at least one generation), genealogical history (women with two generations of parents of the same nationality), self-identification and taking into account the phenotypic characteristics of women.

Inclusion criteria for the control groups: menstrual cycle length of 21-34 days; modified Ferriman-Galvey score < 3, no alopecia or acne; ovarian volume < 10 cm^3 or a number of follicles with a diameter of 2-9 mm < 12 on transvaginal ultrasound; systolic BP <140 mmHg, diastolic BP <90 mmHg; fasting glucose level ≤ 6.1 mmol/L; PRL ≤ 727 IU/mL, TSH ≤ 4 IU/mL, 17-OH-Pg ≤ 6.91 nmol/L, and DHEA-S ≤ 430 μg/dL.

Exclusion criteria for the control groups: current pregnancy or lactation; history of hysterectomy, bilateral ovariectomy, endometrial ablation, and/or uterine artery embolization; current or previous (within 3 months) taking hormonal drugs (thyroid hormones, glucocorticoids, as well as insulin sensitizers); chronic diseases in the history (cardiovascular, oncologic, genitourinary diseases, diabetes mellitus, hypertension, etc.); BMI ≥ 30 kg/m^2; hormonal drugs (thyroid hormones, glucocorticosteroids, insulin sensitizers); chronic diseases in the history (cardiovascular, cancer, genitourinary diseases, diabetes mellitus, hypertension, etc.).

Inclusion criteria for women with OH: OH according to the current international diagnostic criteria ESHRE/ASRM[1] based on the use of two of the following three parameters (1 - oligo- or anovulation; 2 - clinical or/and biochemical hyperandrogenism; 3 - signs of polycystic ovaries according to pelvic ultrasound).

Exclusion criteria for women with OH: hyperprolactinemia; hypothyroidism; current pregnancy or lactation; taking hormonal drugs; removal of uterus and/or appendages from both sides; endometrial ablation and/or uterine artery embolization.

An anthropometric examination was carried out (measurement of height, weight, BMI, waist circumference (WC), hip volume (HC), % fat, % visceral fat). Waist circumference (WC) was measured with a measuring tape to the nearest 0.5 cm in a standing position at the end of

exhalation. The location of the tape was strictly horizontal at the level of the crista iliaca. Blood pressure (BP) was measured in a sitting position on the subject's right shoulder with an Omron automatic tonometer after a 5-minute rest.

Determination of the concentrations of TSH, PRL, LH, FSH, AMH, 17-OH-Pg, and sex hormone-binding globulin (SHBG) was carried out by the method of competitive enzyme-linked immunosorbent assay using Alkor-Bio test systems on the enzyme immunoassay analyzer ELx808 "Bio Tek" (USA). The level of DHEA-S was determined using a set of reagents on a Siemens Immulite 1000 immunochemical analyzer (USA).

The study was carried out in accordance with the Helsinki Declaration of the World Medical Association (1964, ed. 2013) and approved by the Committee on Biomedical Ethics under the Scientific Centre for Family Health and Human Reproduction (Extract from the meeting No. 2.1 as of 24.02.2016).

Statistical analysis was performed using STATISTICA v.10.0 software package (Stat-Soft Inc, USA). The normality of the distribution of continuous variables was tested by the Kolmogorov-Smirnov test with the Lilliefors correction and Shapiro-Wilk test. For descriptive analysis, results are presented as median (Me) and interquartile range (IQR; 25th to 75th percentiles). Differences in continuous variables departing from the normal distribution were tested by the Mann-Whitney U-test. A probability value of $P<0.05$ was considered statistically significant.

This work was carried out using the equipment of the Center for the Development of Advanced Personalized Health Technologies, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk.

Results and Discussion

In the first stage, a comparative characterization of clinical data in women with OH of the Caucasian and Buryat ethnic groups was performed (Table 1). Buryat ethnic group women with OH had higher values of body weight (P=0.007), BMI (P=0.003), WC (P=0.004), HC (P=0.010), % fat (P=0.030) compared to the corresponding control group (Table 1).

The group of Caucasian women with OH had higher values of height (P=0.03), SBP (P=0.030), and DBP ($P<0.0001$) compared to controls. Ethnic differences in control groups were expressed in increased body weight (P=0.011), BMI (P=0.024), HC (P=0.026), and WC/HC (P=0.004) in Caucasians compared to Buryats. No ethnic differences were recorded in the groups with OH ($P>0.05$) (Table 1).

Next, the state of the neuroendocrine regulation system in the studied groups was analyzed (Table 2). In Buryat women with OH, statistically significant differences in AMH ($P<0.001$), testosterone ($P<0.0001$), FAI ($P<0.0001$), DHEA-S (P=0.003) were found in the direction of increase compared to the control. The group of Caucasian women with OH had higher values of PRL (P=0.090), AMH ($P<0.0001$), testosterone ($P<0.0001$), FAI ($P<0.0001$), 17-OH-Pg ($P<0.0001$), and DHEA-S ($P<0.0001$) compared to controls (Table 2). Ethnic differences in controls were high PRL values ($P<0.0001$) and low testosterone levels (P=0.011) in Buryat women compared to Caucasians. At the same time, there were no differences in the studied indicators between ethnic groups with OH ($P>0.05$) (Table 2).

The level of gonadotropins was analyzed depending on the menstrual cycle phase (Table 3).

Table 1.

Clinical characteristics of reproductive-age women with OH, depending on ethnicity.

Parameters	Control groups		OH groups		P
	Buryats (1)	Caucasians (2)	Buryats (3)	Caucasians (4)	
	n=42	n=87	n=35	n=97	
	Me (25%;75%)		Me (25%;75%)		
Height, cm	160 (158;165)	163 (158;167)	162 (159;167)	165 (161;168)	P_{2-4}
Weight, kg	61.15 (55;66)	65.5 (57.1; 74.6)	69.7 (57;82)	67.2 (59.4;76.1)	P_{1-2} P_{1-3}
BMI, kg/м^2	23.32 (20.8;25.8)	25.02 (22.31; 27.88)	26.1 (21.4;31.6)	24.96 (21.77;28.87)	P_{1-2} P_{1-3}
WC, cm	75.5 (68;81)	77 (68;82)	82 (71;91)	75 (67;86)	P_{1-3}
HC, cm	95 (92;100)	99 (93;104)	102 (93;106)	100 (93;105)	P_{1-2} P_{1-3}
WC/HC	0.78 (0.75;0.83)	0.76 (0.73;0.82)	0.8 (0.77;0.84)	0.76 (0.71;0.82)	P_{1-2}
WC/height	0.47 (0.42;0.5)	0.47 (0.41;0.5)	0.48 (0.43;0.56)	0.46 (0.4;0.52)	
% fat	35.45 (30.1;40.7)	37.2 (30.2; 40.9)	40 (31.9;47.4)	35.8 (29.35;41.85)	P_{1-3}
Visceral fat, %	5 (4;7)	6 (4.0;7.0)	6 (4.0;7.0)	5 (4.0;7.0)	
SBP, mmHg	117 (110;127)	117 (112;123)	120 (113;131)	121 (113;132)	P_{2-4}
DBP, mmHg	75.5 (69;82)	74 (70;79)	78 (70;82)	80 (71;83)	P_{2-4}
HR, bpm	74.5 (69;82)	74 (68;82)	76 (69;81)	76 (70;85)	

P - statistically significant differences between groups (P<0.05)

Table 2.

The state of the neuroendocrine regulation system in reproductive-age women with OH, depending on ethnicity.

Parameters	Control groups		OH groups		*P*
	Buryats (1)	Caucasians (2)	Buryats (3)	Caucasians (4)	
	n=42	n=87	n=35	n=97	
	Me (25%;75%)		Me (25%;75%)		
TSH, IU/mL	1.8 (1.2;2.1)	1.4 (1.0;2.0)	1.4 (0.8;1.9)	1.6 (1.1;2.2)	
PRL, IU/mL	422.5 (329 ;491)	251 (197;336)	325 (242;490)	312 (224;437)	P_{1-2} P_{2-4}
AMH, ng/mL	1.6 (1.0;2.9)	2.1 (1.0 ;4.4)	4.7 (2.8 ;8.0)	6.7 (3.3 ;13.4)	P_{1-3} P_{2-4}
Testosterone, nmol/L	187.6 (104.7;293.5)	247.5 (166.9;366.5)	369.7 (297.5; 475.1)	381.15 (264.05;560.74)	P_{1-2} P_{1-3} P_{2-4}
SHBG, nmol/L	60.3 (54.1;79)	68.7 (46.7;104.2)	45.3 (31.4;89.6)	57.6 (36.3;90.9)	
FAI ,%	0.98 (0.63;1.44)	1.3 (0.58;2.2)	2.38 (1.16;4.68)	2.63 (1.23;4.32)	P_{1-3} P_{2-4}
17-OH-Pg, nmol/L	3.4 (1.7;8.1)	4.3 (2.1;7.1)	4.8 (2.4;6.4)	6.2 (4.6;8.9)	P_{2-4}
DHEA-S, μg/dL	141.5 (92.8;182.0)	161 (117;214)	190 (134;254)	231 (173;337)	P_{1-3} P_{2-4}

P - statistically significant differences between groups (P<0.05)

Table 3.

Level of gonadotropic hormones in reproductive-age women with OH in Phases 1 and 2 of the menstrual cycle, depending on ethnicity.

Parameters	Control groups				OH groups				*P*
	Buryats		Caucasians		Buryats		Caucasians		
	n=42		n=87		n=35		n=97		
	Me (25%;75%)				Me (25%;75%)				
	(1) MC-P1	(2) MC-P2	(3) MC-P1	(4) MC-P2	(5) MC-P1	(6) MC-P2	(7) MC-P1	(8) MC-P2	
LH, IU/mL	4.9 (4,0; 7,9)	4.0 (3,0; 6,1)	4.3 (3.3;6.4)	4.9 (3.2 ;8.9)	3.8 (3.3 ; 9.7)	8.9 (4.4 ; 14.4)	7.0 (5.4; 7.6	8.0 (4.3; 13.2)	P_{2-6} P_{3-7} P_{4-8}
FSH, IU/mL	6.5 (5.3; 8.0)	4.6 (2.7; 6.9)	6.7 (5.5;7.6)	5.0 (3.5 ;7.9)	5.9 (5.8; 7.0)	5.3 (3.1; 7.6)	5.6 (5.2; 6.8	4.9 (3.3; 6.3)	

MC-P2, Menstrual cycle: Phase 2 (P2); MC-P1, Menstrual cycle: Phase 1 (P1); P - statistically significant differences between groups (P<0.05)

In Buryat women with OH, LH values were higher only in Phase 2 (*P*=0.005) compared to the control. In Caucasian women with OH, LH values increased both in Phase 1 (*P*=0.002) and in Phase 2 (*P*=0.003) compared to controls (Table 3).

Comparative characterization of clinical data in women of control groups of Caucasian and Buryat ethnic groups showed higher values of anthropometric parameters in Caucasians. This concerned the increased indicators - BMI, weight, HC, WC/HC. In women with OH, no ethnic peculiarities with regard to these parameters were observed, however, the group of women of Buryat ethnicity was characterized by increased values of BMI, weight, WC, HC, % fat in comparison with the control.

In Caucasian women with OH, the changes in relation to the control data were insignificant (height, BP). Increased anthropometric indices in indigenous women with OH probably reflect the significance of the metabolic component in Buryat women.[17,19] Undoubtedly, it may be of importance in relation to clinical manifestations of OH.

The state of the neuroendocrine regulation system significantly influences the course of OH. The main indices of a neuroendocrine regulation system in the studied groups were within the reference values. In the control group of Buryat women, the levels of PRL demonstrated higher values, and testosterone decreased in comparison with Caucasians. This fact can be explained by the mechanism of increased conversion of testosterone into estradiol, corresponding to an increase in estradiol under conditions of optimal aromatase activity in granulosa cells. Estradiol, in turn, may contribute to enhanced synthesis of PRL. Despite the increased PRL values in Buryat women in the control group, no interethnic differences were recorded in the groups with OH. The difference in PRL values was observed only in the group of Caucasian women with OH relative to the control.[22]

The level of circulating AMH increased in both Buryat and Caucasian women with OH. This may be due to the increased secretion of AMH by granulosa cells in OH and to an increase in the number of mature follicles in the ovaries.[23] Increased AMH level, in turn, leads to a decrease in estrogen

content, the deficiency of which, according to the principle of positive feedback, contributes to the activation of gonadotropic function of the pituitary gland with a natural increase in the level of LH.[9] In our study, we found a significant increase in the LH content in the group of Caucasian women with OH, both in the first and second phases of the menstrual cycle, while in Buryat women, it was only in the second phase. No interethnic differences were revealed with regard to this indicator. These changes may be due to excessive LH receptivity of granulosa cells synthesizing progesterone. However, relative estrogen deficiency leads to low luteinization of this cell type, which results in decreased serum progesterone concentration.[14,24] At the same time, androgens in women with OH inhibit the negative feedback effect of progesterone on gonadotropin-releasing hormone pulse frequency.[25]

High levels of androgens of both adrenal (DHEA-S, 17-OH-Pg) and ovarian (testosterone) genesis play an important role in this process. It should be noted that in both groups with OH (to a greater extent in Caucasian women), there was an increase in FAI. This index reflects the level of free testosterone in the blood, as only it is able to bind to tissue receptors to exert its effect. It is believed that free testosterone is the best marker for assessing androgen status as one of the manifestations of hyperandrogenism of ovarian genesis.[26]

Several studies found that OH in 20-30% of women is due to excess adrenal androgens such as DHEA-S, which can alter cytochrome P450c 17 alpha-hydroxylase activity and increase peripheral cortisol metabolism, resulting in negative feedback dysregulation of adrenocorticotropic hormone.[7]

Hypersecretion of androgens by the adrenal reticular zone after conversion to estrogens by the surrounding adipose tissue and/or liver by feedback increases LH secretion, which promotes androgen synthesis by the ovaries. Consequently, androgens synthesized by the adrenal glands may cause changes in ovarian steroid synthesis. Conversely, elevated levels of exogenous androgens may have a positive feedback loop at the hypothalamic-pituitary level, and elevated LH levels, in turn, promote steroidogenesis in the ovaries.[27] Clinically, ovarian dysfunction is mainly expressed in ovulatory dysfunction, theca-cell, and oocyte dysfunction.

Conclusion

A comprehensive analysis of the state of the neuroendocrine regulation system in women of reproductive age with OH showed certain changes in the level of a number of hormones relative to control groups, most pronounced in the group of Caucasian women. At the same time, there were no differences in the studied indicators between ethnic groups with OH. The data obtained indicate the necessity of assessing and controlling the state of the neuroendocrine regulation system in female patients with OH for PCOS prevention and treatment. The ethnic component may have a certain contribution to the realization of further risks of the disease.

Competing Interests

The authors declare that they have no competing interests.

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***Corresponding author:** Prof. Marina A. Darenskaya, PhD, ScD. Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, the Russian Federation. E-mail: marina_darenskaya@inbox.ru*

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