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"FREQUENCY OF ENDOGENOUS HYPERCORTISOLISM IN WOMEN WITH POLYCYSTIC OVARY SYNDROME ACCORDING TO REFERRAL DATA

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Abstract

The main investigation-to study the frequency of subclinic Cushingoid at women with polycystic ovaries syndrome (PCOS)

Material and methods of investigation.120 patients of fertile age were examined with polycystic ovary syndrome (PCOS).. Middle age of patients - 25.5 ± 4. 3 years. . The remoteness of disease doubted within limits from 7 months to 9 years. 20 healthy women of corresponding age made a control group.

The complex of researches, including clinical (global analysis of blood and urine), biochemical (glucose of blood, test of tolerance to glucose) hormonal (LH, FSH, prolactin, estradiol, progesteron, free orchidic hormone, dehydroepiandrostendion (DHEA), 17 – oxyprogesterone, antimuller hormone (AMH), insulin on 14 day of cycle), was executed all patients, ULTRASONIC of uterus and ovaries (transabdominal and transvaginal) on 14 day of cycle with follikulometriya in a dynamics, and also MRI of pituitary.

Results.Patients were divided into three groups: 1 group. are patients with primary PCOS-23 cases (19%), 2 gr. are patients with secondary PCOS at obesity are 89 cases (74%), 3 gr. are patients with secondary PCOS and subclinical Cushingoid are 8 cases (7%). A control group is 20 women of similar age.

In our research prevailed on the whole 2 degree of obesity in 2 and 3 groups of patients - 53 cases from 120 (44.1%).

In the 1 group of patients the reliable decline of both pituitary and ovarian hormones registered on a background of hyperandrogenemia. So, as compared to the group of control on the 14th day of cycle were for LH, FSH, IGF-1 and also estradiol, progesterone, while free testosterone, DGEA - were enhanceable as compared to control data.

Further in the second group of patients the reliable decline of pituitary hormones was also educated on a background hyperandrogenemia, while an ovarian function was within the limits of norm. So, as compared to the group of control on the 14 day of cycle

In the third group of patients, the reliable decline of pituitary hormones was also educated on a background hyperandrogenemia, while an ovarian function was within the limits of norm. So, as compared to the group of control on the 14th day of cycle were for LH, FSH, IGF-1, here free testosterone, DHEA, 17 OKS, insulin, - were for certain enhanceable as compared to control data.
Conclusions.1) Frequency of met subclinical Cushing among women with PCOS 6.6% is equal. ; 2) In all groups on 14 day of cycle the reliable decline of basale values of for LH, FSH, IGF-1 was marked, progesterone, estradiol on a background hyperandrogenemia (enhanceable level of free testosterone.). Thus in 2 and 3 groups a hyperinsulinemia was marked. Only for patients 3 groups were marked for certain enhanceable values of DHEA, 17 OKS and cortisol of blood. Mean values of prolactin, AMG were in a norm.
3) a further supervision is Needed in a dynamic after probability of renewal of fertile function in all groups of patients with PCOS

Keywords: Androgen excess; polycystic ovary syndrome; prevalence Cushing syndrome.

Introduction

Today, KS is still associated with an increased incidence of subclinical disease [1], but excess mortality has also been reported in patients with Cushing's disease [2–5] and in patients with subclinical Cushingoid [6]. In contrast, the mortality rate was not as high in patients with Cushing's disease who recovered after initial surgery [7,8]. This is obviously reassuring that treatment reduces mortality, but the data also highlight the need to start treatment as early as possible and to pay special attention to patients with Cushing's disease who have not recovered from initial surgery. A reliable therapeutic approach remains open to debate, but the opinion regarding staged bilateral adrenalectomy should not be forgotten.
In conclusion, KS remains a diagnostic and therapeutic challenge. Available data show that early and effective treatment improves survival, but later relapses after initial successful surgery occur even in the best centers. [9].
All of the above determines a possibly high frequency of cases of KS due to undiagnosed cases of subclinical variants of the disease. Widespread coverage, active detection of latent forms through screening studies in individuals with phenotypic Cushingoid, contributes to early detection, timely treatment and improvement of irreversible and severe outcomes and prognoses of this disease.
The relevance of this problem is due to the fact that timely diagnosis will allow us to identify this category of patients and refer them for further examination and treatment to specialized endocrinological centers. The real impact of these studies will be an increase in the duration and quality of life of patients with KS and the creation of an objective system for their monitoring.[10].
The results of a mass examination of patients for KS in target population groups show a prevailing number of undiagnosed and subclinical cases [11, 12], and there is accumulated

experience to suggest subclinical Cushing's syndrome (CCS) in most cases as an incidental adrenal gland.
In general, there are few works in the literature devoted to this topic, which was the reason for carrying out our study.

Purpose of the study study frequency of occurrence and characteristics of subclinical Cushingoid in women with PCOS.

Material and research methods Under our supervision, the Republican Scientific Research and Medical Center of Endocrinology M3 of the Republic of Uzbekistan named after Acad. Y.H. Turakulov, 120 patients of fertile age with PCOS (primary and secondary) were examined on an outpatient basis for primary or secondary infertility in the period from September 2022 to December 2023. The average age of the patients was 25.5 ± 4.3 years. The duration of the disease ranged from 7 months to 9 years. 20 healthy women of the appropriate age formed the control group.
All patients underwent a complex of studies, including general clinical (general blood and urine analysis), biochemical (blood glucose, glucose tolerance test), hormonal (LH, FSH, prolactin, estradiol, progesterone, free testosterone, dehydroepiandrostenedione (DHEA), 17-hydroxyprogesterone (17 ACS), anti-Mullerian hormone (AMH), insulin on the 14th day of the cycle), ultrasound of the uterus and ovaries (transabdominal and transvaginal) on the 14th day of the cycle with dynamic folliculometry, as well as magnetic resonance imaging (MRI) of the sella turcica (clinic " Diermedic Center, Tashkent) and questioning of patients. If necessary, a glucose tolerance test and determination of cortisol in the blood and free cortisol in 24-hour urine were performed.
Anthropometric study-was carried out immediately during the initial examination, in dynamics and included determination of height, BW, determination of body mass index (BMI) (Quetelet index), calculated by the formula: BMI (kg/m2) = (BW, kg) / (height, m)2 . The degree of obesity was determined in accordance with the BMI values recommended by WHO (1997).
The patients were prescribed non-drug and etiopathogenetic therapy to reduce body weight. Non-drug therapy included general recommendations for measuring weight every day before and after exercise therapy, counting daily calories, and avoiding easily digestible carbohydrates. Etiopathogenetic therapy included 3 treatment regimens in 3 groups of patients for 6 months:
Group 1 was prescribed a combination of siofor 1000 mg per day + iodomarine 100 mg in the morning + levothyroxine 50 mg in the morning + antiandrogens (Yarina, Jess, dexamethasone, etc.).
Group 2 was prescribed a combination of siofor 1000 mg per day + veroshpiron 75 mg twice a week + iodomarine 100 mg in the morning + levothyroxine 50 mg in the morning + reduxin 15 mg in the morning after meals.

Group 3 was prescribed a combination of siofor 1000 mg per day + veroshpiron 75 mg twice a week + iodomarine 100 mg in the morning + levothyroxine 50 mg in the morning + steroidogenesis blockers (ketoconazole 200 mg twice a day) + cabergoline 5 mg per week.
The second stage included stimulation of ovulation, antiandrogens (dexamethasone - tab.), progestins, etc. in order to achieve fertility.
The obtained data were processed using Microsoft Excel and STATISTICA_6 computer programs. The significance of differences in quantitative indicators (n>12) was determined using the Wilcoxon method for unrelated ranges; to determine the significance of small samples (n<12), the nonparametric Fisher component randomization test was used for independent samples; for qualitative values, the Fisher-Irvine exact test was used. Differences between groups were considered statistically significant at P □ 0.05. Mean values (M) and standard deviations of means (m) were calculated.

Research Results

The patients were divided into three groups: 1 gr. – patients with primary PCOS – 23 cases (19%), 2 gr. – patients with secondary PCOS with obesity – 89 cases (74%), 3 gr. – patients with secondary PCOS and subclinical Cushingoid - 8 cases (7%).
Table 1 shows the distribution of patients by age.

Table 1. Distribution of patients by age (WHO).

Age, years	1 group	2nd group	3 group
18 – 29	21	86	5
30-44	2	3	3
45-59	-	-	-
60-74	-	-	-
75 and >	-	-	-
Total	**23**	**89**	**8**

Table 2 givesaveragesBMI by group before treatment.As can be seen from Table 2, in our study, degree 2 obesity prevailed - 53 cases out of 120 (44.1%)

Table 2. AveragesBMI by group before treatment.

No.	GROUP	30.0-34.9 kg/m2		35.0-39.9 kg/m2		□40 kg/m2	
1	1 group	n= 9	32, 6± 3.2	n= 7	37.5± 3.8	n= 7	41.6±4.2
2	2nd group	n= 33	33, 4±4.2	n= 44	37.9±4.2	n= 12	42.7±3.9
3	3 group	n= 2	35, 7±4.3	n= 2	38.8±3.9	n= 4	42.8± 3.5
	Total	44 (36.6%)		53 (44.1%)		23 (19.1%)	

For a more in-depth analysis, we performed statistical studies of the average values of basal levels of blood plasma hormones (on the 14th day of the cycle), which is presented in table 3, in all 3 groups.

As can be seen from Table 3, As can be seen from Table 2, in group 1 of patients there was a significant decrease in both pituitary and ovarian hormones against the background of hyperandrogenemia. Thus, compared to the control group, on the 14th day of the cycle, LH, FSH, IGF-1, as well as estradiol, progesterone were significantly reduced, while free testosterone and DHEA were increased compared to control data.

Further, in the second group of patients, a significant decrease in pituitary hormones was also revealed against the background of hyperandrogenemia, while ovarian function was within normal limits. Thus, compared to the control group, on the 14th day of the cycle, LH, FSH, IGF-1 were significantly reduced, while free testosterone and DHEA were increased compared to control data.

In the third group of patients, a significant decrease in pituitary hormones was also revealed against the background of hyperandrogenemia, while ovarian function was within normal limits. Thus, compared to the control group, on the 14th day of the cycle, LH, FSH, IGF-1 were significantly reduced, while free testosterone, DHEA, 17 OCS, insulin, plasma cortisol were significantly increased compared to control data.

So, in all groups, on the 14th day of the cycle, there was a significant decrease in the basal values of LH, FSH, IGF-1, progesterone, estradiol against the background of hyperandrogenemia (increased levels of free testosterone). At the same time, hyperinsulinemia was observed in groups 2 and 3. Only patients in group 3 showed significantly increased values of DHEA, 17 OCS and blood cortisol. The average values of prolactin and AMH were normal.

Table 3. Average values of basal levels of blood plasma hormones (on the 14th day of the cycle) in group 1 in all groups

Hormones	1 group	2nd group	3group	Control	Norm
LH	6.7 ± 0.4*	7.8 ± 0.3 *	7.4 ± 0.2*	29.3 ± 2.1	From 15 to 90 mIU/ml
FSH	2.3 ± 0.2 *	2.6 ± 0.4*	2.1 ± 0.3*	15.2 ± 4.3	From 5 to 16 mIU/ml
Prolactin	223.5 ±11.3	201.2 ±12.3	243.9 ±12.3	154.3 ± 9.5	120-900 mIU/l
Free testosterone	3.3 ± 0.3*	3.4 ± 0.2*	4.3 ± 0.6*	0.2 ± 0.05	0.2-1.0 ng/ml
Progesterone	2.3 ± 0.5*	4.7 ± 0.8*	3.5 ± 0.4 *	44.3±9.3	11-80 nmol/l
Estradiol	0.18 ±0.04*	0.23 ±0.02*	0.21 ±0.05*	1.7±0.1	0.34 – 1.8 nmol/l
DHEA	6.7 ± 0.2*	6.3 ± 0.6*	8.9 ± 0.4*	3.1±0.4	0.29-7.81 mcg/ml for ages 18 to 30 years
17-OX	2.6±0.1	3.5±0.4	8.6±0.5*	2.9±0.6	1.54 – 6.1 mg/day
AMG (on day 5)	5.3± 0.3	3.2±0.6	4.8±0.5	3.9±0.6	From 1.0 to 10.6 ng/ml
IGF-1	21.4 ± 3.5*	19.2 ± 2.3*	18.3 ± 2.2*	251.4 ± 13.5	233-344 nmol/ml
Insulin	5.4 ± 0.5	11.4 ± 1.7*	13.5 ± 2.2*	5.9±0.8	Up to 10 pg/ml
Cortisol	277.5 ± 22.6	287.9 ± 24.7	797.3 ± 25.9*	294.4 ± 23.8	250-720 nmol/ml

Note: *– significance of differences compared to control, DHEA – dehydroepiandrostenedione, 17 OCS – oxyprogesterone, AMH – anti-Mullerian hormone

Table 4 shows the characteristics of MRI data of the pituitary gland.

Table 4. Characteristics of pituitary MRI datapatients with PCOS

MRI data	**1 group, n = 23**	**2 group, n = 89**	**3 group, n=8**	**Total**
Pituitary adenomatosis	14 (60.8%)	35 (39.2%)	6 (75%)	55 (45.8%)
Pituitary microadenoma	2 (6.6%)	14 (15.7%)	2 (25%)	18 (15%)
Empty sella syndrome	3 (13.0%)	23 (25.8%)	-	26 (21.7%)
Variant of the norm	4 (17.0%)	17 (19.1%)	-	21 (17.5%)

Neuroimaging of the pituitary gland in patients with PCOS revealed in many cases hyperplasia (adenomatosis) of the pituitary gland - 55 out of 120 cases (45.8%), which can be explained by ovarian failure in these patients. In second place in frequency was SPTS (empty sella syndrome) - 26 cases (21.7%), and in third place was pituitary microadenoma - 18 cases (15%).

Next, we studied the clinical characteristics in 3 groups (Table 5).

Table 5 Features of clinical characteristics in 3 groups.

Peculiarities	**1 group, n = 23**	**2 group, n = 89**	**3 group, n=8**	**Total**
Obesity	-	89 (100%)	8 (100%)	97 (80.8%)
Hirsutism	20 (86.9%)	34 (38.2%)	8 (100%)	62 (69.6%)
Acne	19 (82.3%)	47 (52.8%)	8 (100%)	74 (83.1%)
Acanthosis	9 (39.1%)	58 (42.6%)	8 (100%)	73 (60.8%)
Striae	-	-	8 (100%)	8 (6.6%)
Amenorrhea secondary	8 (34.7%)	32 (35.9%)	8 (100%)	48 (53.9%)
Primary amenorrhea	3 (13.0%)	5 (5.6%)	-	6 (6.7%)
Infertility primary	17 (73.9%)	74 (83.1%)	8 (100%)	99 (82.5%)
Infertility Secondary	5 (21.7%)	15 (16.8%)	-	20 (16.6%)
Hyperpolymenorrhea	14 (60.8%)	22 (24.7%)	-	36 (30%)
Opsomenorrhea	7 (30.4%)	16 (17.9%)	-	23 (19.2%)
Oligomenorrhea	5 (21.7%)	15 (16.8%)	-	20 (16.6%)
Hyperandrogenemia	21 (91.3%)	87 (97.7%)	-	108 (90%)
Anovulation	19 (82.3%)	78 (87.6%)	8 (100%)	103 (85.8%)
Hypoovulatory syndrome	3 (13.0%)	11 (12.3%)	-	14 (11.6%)
Arterial hypertension	-	5 (5.6%)	6 (75%)	11 (9.1%)

As can be seen from Table 5, the most pronounced neuroendocrine disorders occurred in group 3 of patients - obesity, hirsutism, acne, acanthosis, secondary amenorrhea, primary infertility, stretch marks, arterial hypertension, anovulation - in 100% of cases. In groups 1 and 2 the above complaints were also encountered, but less frequently and in an erased form.

The discussion of the results

So, in women suffering from PCOS of primary, secondary origin and PCOS with KS, serious reproductive abnormalities from dysmenorrhea up to infertility were detected; disturbances in the gonadotropic function of the pituitary gland were identified in the form of insufficient secretion of LH and FSH in the middle of the cycle. Almost 50% of patients from group 3 had a BMI above 40 kg/m2.

Thus, the most pronounced disorders of the pituitary-ovarian function system were found in the third group of patients with PCOS with subclinical Cushingoid, who had a significant decrease in the functional state of the pituitary-gonad, namely a decrease in LH, FSH, estradiol and progesterone in the blood plasma on the 14th day of menstruation cycle against the background of hyperandrogenemia and hypercortisolemia, which was confirmed by ultrasound of the uterus and ovaries by depletion of the ovarian follicular apparatus and anovulation.

Conclusions:

1) The incidence of subclinical Cushingoid among women with PCOS is 6.6%.

2) In all groups, on the 14th day of the cycle, there was a significant decrease in basal values of LH, FSH, IGF-1, progesterone, estradiol against the background of hyperandrogenemia (increased levels of free testosterone.). At the same time, hyperinsulinemia was observed in groups 2 and 3. Only patients in group 3 showed significantly increased values of DHEA, 17 OCS and blood cortisol. The average values of prolactin and AMH were normal.

3) It is necessary to further monitor the dynamics of the likelihood of restoration of fertile function in all groups of patients with PCOS.

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