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A NEW APPROACH TO THE COMBINATION THERAPY OF POLYCYSTIC OVARY SYNDROME

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The article presents the results of hormonal parameters and metabolic homeostasis in women with polycystic ovary syndrome (PCOS) and a treatment method developed on this basis. 67 women with PCOS (main group) and 50 healthy women (control group) were under the supervision. The results showed that in women with PCOS hormonal and metabolic disorders are significant, among which a prominent place is occupied by disorders of central regulation of ovarian function, hyperandrogenism, hypoprogesteronemia, insulin resistance on the background of impaired adrenal response to change. Taking into account the pathophysiological multifactority of PCOS and in order to avoid polypharmacy, patients with PCOS were offered a combined drug based on myo-inositol in combination with Lagerstroemia speciosa extract, vitamin D3, methyl folate and chromium. The treatment lasted for 3 months. Clinical evidence of treatment efficacy was spontaneous ovulation (25%) and positive attempts to induce ovulation in resistant patients (40%), probably due to improved ovum quality, hormonal balance, and reduced incidence of insulin resistance. As a result of treatment, 64% (43/67) of patients with PCOS had a menstrual cycle improvement. 33% (22/67) of women reported a reduction in hyperandrogenic dermopathy. No side effects were observed during treatment.

Key words: polycystic ovary syndrome, myo-inositol, treatment.

The study is a fragment of the research project "Improving the monitoring of obstetric care in idiopathic miscarriage", state registration No. 0117U001080.

Polycystic ovary syndrome (PCOS), which incidence reaches 15% in women of reproductive age, is the most common cause of menstrual disorders, ovarian dysfunction and infertility [1]. The course of the disease is associated with insulin resistance (IR) and compensatory hyperinsulinemia (HI), which are central complications of PCOS. HI plays a leading pathogenetic role in hyperandrogenism (HA) and nonovulation in PCOS in both obese and slim women [11]. According to some provisions, patients with PCOS have a high risk of developing diabetes [9] and increased risk of cardiovascular profile: hypertension, dyslipidemia, subclinical inflammation and atherosclerosis [13].

Due to the specific pathophysiological role of insulin in the treatment of PCOS, sensitizers such as metformin, pioglitazone, and troglitazone were prominent. However, metformin, used in therapeutic doses, showed some side effects: in particular, diarrhea, flatulence, nausea. Because of this, a number of patients can not apply this method of treatment for a long time. Therefore, in recent years there has been an active search for other therapeutic corrections for IR and HI [8]. Recent studies have shown that one of the mechanisms of insulin deficiency is provoked by a mediator such as inositol phosphoglycan, and that a lack of myo-inositol in inositol phosphoglycans causes IR [4,5]. For these reasons, application of inositol-containing drugs in the treatment of metabolic disorders is appropriate.

The purpose of the study was to determine the effectiveness of hormonal and metabolic disorders correction in women with PCOS, taking into account the complex pathophysiology of the disease.

Materials and methods. 67 women with PCOS (main group) and 50 healthy women (control group) were under the supervision. PCOS was diagnosed according to the Rotterdam (ESHRE/ASRM) criteria (2003) [1]. The age of patients in both groups ranged from 23 to 29 years. Ultrasonographic examination was performed using the Aloka SSD-2000 apparatus. The presence of hirsutism was assessed on the Ferriman-Gallwey scale.

Determination of estradiol (E_2), progesterone (Pg), free testosterone (T_f), total testosterone (T_t), androstenedione (A), free androgen index (FAI), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), insulin, cortisol (C), anti-mullerian hormone (AMH), inhibin B was performed by "ECLIA" electrochemiluminescence assay using automatic analyzers and reagents Cobas 6000 of "Roche Diagnostics" company (Switzerland). Venous blood glucose was determined by enzyme-linked immunosorbent assay using a Cobas 6000 analyzer and test system from Roche Diagnostics (Switzerland). Surrogate indices were calculated to assess IR, β-cell function, and insulin sensitivity [1]. The conclusion on IR was made on the HOMA index (>3.0): fasting glucose (mmol/l) × fasting immunoreactive insulin (mcU/ml)/22.5 and Caro: fasting glucose (mg/dL)/fasting immunoreactive insulin (mcU/ml). To determine the metabolic characteristics, patients of control (n = 50)

and PCOS groups (n = 67) were divided into subgroups depending on body mass index (BMI): I – BMI less than 25 kg/m^2, II – BMI more than 25 kg/m^2 [1].

Patients with PCOS were treated with the combined drug myoxin oro (PharmaSuisse Lab. Str., Italy) based on the activating substances of myo-inositol 2000 mg, methylfolate 400 µg, banaba extract (Lagerstroemia speciosa) 48 mg, vitamin D_3 1000 IU and 40 µg of chromium. The drug was prescribed for 1 sachet twice a day for three months. Examination of patients was performed before treatment and after three months, evaluated complaints, hyperandrogenic dermopathy, metabolic and hormonal parameters, changes in menstrual and reproductive functions.

The study provided for measures to ensure human health, human dignity and moral and ethical standards in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and relevant laws of Ukraine (conclusion of the Danylo Halytsky LNMU Commission on Bioethics).

Statistical processing of the obtained data was performed using standard methods of descriptive and categorical statistics and a package of certified programs Statistica for Windows 13.0 (Statsoft Inc., USA).

Results of the study and their discussion. Clinically, the combination of ovulation disorders and HA was the most typical for women with PCOS: oligo-/amenorrhea – in all patients, 100% (67/67), hirsutism – in 74% (50/67), infertility – in 100% (67/67).

Hormonal examination of women with PCOS showed a significant increase of LH in peripheral blood (p=0.0001), ovarian androgens, including the biologically active fraction of free androgens (p = 0.00001), a tendency to decrease the level of E_2 (p = 0.016) and insufficient content of Pg (p = 0.0053) (table 1).

Table 1

The state of hormonal balance in the examined women

Index	Control group (n=50)	PCOS (n=67)
LH, mIU/ml	3.3±0.7	11.7±1.7* p=0.0001
FSH, mIU/ml	4.7±1.3	5.5±2.1
PRL, ng/ml	10.1±2.7	9.87±0.73
DHEA-S, mcg/ml	177.2±18.7	237.6±22.3
E_2, pmol/l	163.0±17.9	91.7±17.6* p=0.016
SHBG, nmol/l	97.8±13.2	33.1±8.5* p=0.0001
T, nmol/l	1.3±0.1	3.7±0.3* p=0.00001
FAI	1.3±0.2	11.2±2.5* p=0.0001
Pg, nmol/l	65.0±16.4	18.4±3.5 * p=0.0053
C, nmol/l	253.0±65.8	280.1±71.7
17-OHP, ng/ml	0.50±0.16	1.61±0.67
A, nmol/l	2.6±0.40	14.1±4.41* p=0.009
AMH, ng/ml	2.1±0.3	7.6±1.7* p=0.0012
Inhibin B, ng/ml	113.0±13.0	129.0±21.7

Note. * – the difference is significant compared to the control group.

According to our data, HA in PCOS was 76% (51/67), subnormal level of T_f was detected in 58% (39/67) of patients, T_t – in 34% (23/67), and DHEA-S – in 33% (22/67). Simultaneous increase of all three hormones was observed in 18% (12/67) of patients. AMH levels in the control group and in patients with PCOS differed significantly (p = 0.0012).

The results of metabolic studies revealed HI in 41% (16/39) of patients with PCOS and normal body weight and in 78% (22/28) of patients with PCOS and obesity (Table 2).

Table 2

Surrogate indices of fasting IR, M ± m

Indices	Control group		Main group	
	I, n = 28	II, n = 22	I, n = 39	II, n = 28
CARO	10.98±0.91	15.72±5.49	13.84±2.15	8.34±0.90 p_1=0.0375 p_3=0.0168
HOMA	1.28±0.09	4.29±1.36 p_1=0.0278	1.70±0.81	7.46±1.37 p_1=0.0001 p_3=0.0003
IR-HOMA	1.53±0.11	5.13±1.65 p_1=0.0293	2.04±0.14	4.13±0.95 p_1=0.0067 p_3=0.0293

Note. p_1 – reliability of the difference compared with subgroup I of the control group; p_2 – reliability of the difference compared with the subgroup II of the control group; p_3 – reliability index of the difference compared with subgroup I of the main group.

IR was more common in overweight patients due to the synergistic effect of HI inherent in obesity and PCOS. IR was more typical for patients with the male type of adipose tissue distribution at a value of WHR>0.85. Such a clinical sign as "acanthosis nigricans" was observed only in patients with IR and male obesity – in 39% (11/28).

According to the results of metabolic examinations, it should be said that the clinical phenotype of PCOS with excess body weight was characterized by fasting IR on the background of reduced insulin sensitivity, and the clinical phenotype of PCOS with normal body weight was characterized by a tendency to abdominal fat accumulation in the absence of excess body weight. These changes are possible risk factors for the formation of cardiovascular disease in women with PCOS, type II diabetes, and gestational diabetes during pregnancy [13].

Studies after treatment in patients of the main group showed a decrease in the content of LH ($p = 0.0078$), LH/FSH, T_t, ($p = 0.0014$), FAI ($p = 0.0477$), A ($p = 0.0257$), AMH ($p = 0.008$), IR ($p = 0.0150$), HOMA index ($p = 0.0455$) and CARO ($p = 0.0105$) (table 3).

Table 3

Hormonal balance in women with PCOS before and after treatment, n = 67

Index	Before treatment	After treatment
LH, mIU/ml	11.7±1.7	6.1±1.3, p =0.0078
FSH, mIU/ml	5.5±2.1	4.9±1.8
PRL, ng/ml	9.87±0.73	8.03±0.43, p =0.0285
DHEA-S, mcg/ml	237.6±22.3	205.1±18.7
E_2, pmol/l	91.7±27.6	104.9±11.5
SHBG, nmol/l	33.1±8.5	43.0±7.6
T, nmol/l	3.7±0.3	2.1±0.4, p =0.0014
FAI	11.2±2.5	5.7±1.2, p =0.0477
Pg, nmol/l	18.4±3.5	23.3±2.7
C, nmol/l	280.1±71.7	271.0±80.1
17-OHP, ng/ml	1.61±0.67	1.03±0.52
A, nmol/l	14.1±3.41	6.2±1.01, p =0.0257
AMH, ng/ml	7.6±0.9	5.0±0.4, p = 0.008
HOMA	5.72±1.11	3.04±0.75, p =0.0455
CARO	11.09 ±1.15	7.14 ±1.03, p=0.0105

Note: p –reliability of the difference in indices before and after treatment.

In 25% (17/67) of patients with PCOS who received myo-inositol-containing combination drug, spontaneous ovulation was restored, but any spontaneous pregnancies did not occur during the observation. During ovulation induction in the first cycle, 40% (27/67) of patients became pregnant (previously clomiphene-resistant), and 28% (19/67) of women continued to attempt reproductive function. 31% (21/67) of women had no reproductive intentions at the time of observation. As a result of treatment, 64% (43/67) of patients with PCOS had a menstrual cycle correction. 33% (22/67) of women reported a reduction in the manifestations of hyperandrogenic dermopathy. Thus, myo-inositol is not only an effective but also a safe alternative in the treatment of patients with PCOS, as no side effects have been observed. The obtained positive effect can be explained by recalling the basics of clinical biochemistry of the drug components.

Myo-inositol plays an important role in the signaling pathways of cells [15]. Recent studies have shown that the effect of myo-inositol in PCOS may be associated with improved insulin sensitivity and a subsequent increase in intracellular glucose uptake [12]. According to the authors, during the preparation of patients with PCOS for in vitro fertilization, it was found that the use of myo-inositol and folic acid can increase the ovum number from 29 to 68.1% [14].

The problem of folic acid deficiency is relevant for our country, as it is necessary for the division and growth of new cells in the body, for the synthesis of melatonin and the metabolism of several important amino acids, is involved in cell DNA replication [3] and is necessary for patients with reproductive intentions. Corosolic acid, which is part of Lagerstroemia speciosa, effectively reduces the glucose content in human blood [10]. Ellaginanin in Lagerstroemia speciosa (Lagerstremin) served as an insulin receptor agonist [6]. It was proposed that vitamin D status be associated with an androgenic profile in women with PCOS [7]. Pub Med, SCOPUS, and Google Scholar reported on six clinical trials involving 183 participants aged 18-41. Vitamin D supplementation has been shown to significantly reduce total testosterone, but did not affect free testosterone or SHBG levels [2]. The biological role of chromium, which is to regulate carbohydrate metabolism and blood glucose levels, is important since chromium is a component of low molecular weight organic complex – a glucose tolerance factor. Chromium normalizes the permeability of cell membranes to glucose, the processes of its application by cells and deposition, and in this regard functions together with insulin. It is believed that chromium forms a complex with insulin that regulates blood glucose levels. Chromium increases the sensitivity of cellular tissue receptors to insulin, facilitating their interaction and reducing the organism's need for insulin. High chromium deficiency can cause a diabetic condition [8].

Given that the PCOS pathophysiology is multicomponent, the disease is not limited to reproductive pathology and health problems in patients with age are exacerbated, hormonal drugs for them have limited administration, the application of myo-inositol in combination with methyl folate, Lagerstroemia speciosa, vitamin D_3 and chromium may be an alternative therapeutic option.

Conclusions

1. In women with PCOS hormonal and metabolic disorders are significant, among which a prominent place is occupied by disorders of central regulation of ovarian function, hyperandrogenism, hypoprogesteronemia, insulin resistance on the background of impaired adrenal response to change.

2. Taking into account the pathophysiological multifactority of PCOS and in order to avoid polypharmacy, patients with PCOS were offered a combined drug based on myo-inositol.

3. Clinical evidence of treatment efficacy with a drug based on myo-inositol in combination with Lagerstroemia speciosa extract, vitamin D_3, methylfolate and chromium is a reduction in the manifestations of hyperandrogenic dermopathy, spontaneous ovulation (25%) and positive attempts to induce ovulation in resistant patients (40%), probably due to improved ovum quality, hormonal balance, and reduced incidence of insulin resistance.

Prospects for further research will concern the comparison of the effectiveness of the proposed treatment of PCOS with other therapeutic regimens.

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Реферати

НОВИЙ ПІДХІД ДО КОМПЛЕКСНОГО ЛІКУВАННЯ СИНДРОМУ ПОЛІКІСТОЗНИХ ЯЄЧНИКІВ

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У статті представлені результати обстеження гормональних параметрів та обмінно-метаболічного гомеостазу у жінок з синдромом полікістозних яєчників (СПКЯ) та розроблений на цій підставі метод лікування. Під спостереженням знаходилось 67 жінок з СПКЯ (основна група) та 50 здорових жінок (контрольна група). Результати показали, що у жінок з СПКЯ гормональні та обмінно-метаболічні порушення є вагомими, серед яких чільне місце посідають порушення центральної регуляції функції яєчників, гіперандрогенія, гіпопрогестеронемія, інсулінорезистентність на тлі порушеної адреналової реакції на зміни. Приймаючи до уваги багатофакторність патофізіології СПКЯ з метою уникнення фармакологічної поліпрагмазії пацієнткам з

НОВЫЙ ПОДХОД К КОМПЛЕКСНОМУ ЛЕЧЕНИЮ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ

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В статье представлены результаты обследования гормональных параметров и обменно-метаболического гомеостаза у женщин с синдромом поликистозных яичников (СПКЯ) и разработан на этом основании метод лечения. Под наблюдением находилось 67 женщин с СПКЯ и 50 здоровых женщин. Результаты показали, что у женщин с СПКЯ гормональные и метаболические нарушения весомые, среди которых главными есть нарушения центральной регуляции функции яичников, гиперандрогения, гипопрогестеронемия и инсулинорезистентность на фоне нарушенной адреналовой реакции на изменения. Принимая во внимание многофакторность патфизиологии СПКЯ с целью предупреждения фармакологической полипрагмазии

СПКЯ було запропоновано комбінований препарат на основі міо-інозитолу в комбінації з екстрактом Lagerstroemia speciosa, вітаміном D3, метілфолатом і хромом. Лікування тривало упродовж 3 місяців. Клінічним підтвердженням ефективності лікування є самостійні овуляції (25%) та позитивні спроби індукції овуляції у резистентних пацієнток (40%), ймовірно, за рахунок покращання якості яйцеклітин, гормонального балансу та зменшення частоти інсулінорезистентності. У результаті лікування у 64%(43/67) пацієнток з СПКЯ відбулось врегулювання менструального циклу. 33% (22/67) жінок повідомили про зменшення проявів гіперандрогенної дермопатії. Побічних ефектів у ході лікування не спостерігали.

Ключові слова: синдром полікістозних яєчників, міо-інозитол, лікування.

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пациентки с СПКЯ был предложен комбинированный препарат, содержащий мио-инозитол, экстракт Lagerstroemia speciosa, витамин D_3, метилфолат и хромю Лечение продолжалось в течении трёх месяцев. Клиническим подтверждением эффективности лечения были самостоятельные овуляции (25%), положительные результаты индукции овуляции у резистентных в прошлом пациенток (40%), вероятно, за счет улучшения качества яйцеклеток, гормонального баланса и уменьшения частоты инсулинорезистентности. В результате лечения у 64% (43/67) пациенток с СПКЯ произошло урегулирование менструального цикла. 33% (22/67) женщин сообщили об уменьшении проявлений гиперандрогенной дермопатии. Побочных эффектов в ходе лечения не наблюдалось.

Ключевые слова: синдром поликистозных яичников, мио-инозитол, лечение.

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STATE OF THE PALATE TISSUES REPARATIVE REGENERATION IN CHILDREN AFTER RADICAL URANOSTAPHYLOPLASTY

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The purpose of the work was to study the state of the soft palate tissues reparative regeneration after radical uranostaphyloplasty by assessing the clinical situation and morphological structure of the palatine mucosal periosteal flaps. A sophisticated complex of interrelated homeostasis disorders, which occurs after uranostaphyloplasty, significantly affects the process of scar formation and the nature of wound healing. The study of reparative regeneration processes in soft palate tissues on the 13-14th and 29-30th days after radical uranostaphyplasty permits to predict the probability of forming a dense scar at early stages and to influence this process using the individual plan of treatment and prevention and rehabilitation measures for this category of patients.

Key words: palate, soft tissues, children, uranostaphyloplasty, reparative regeneration.

The work is a fragment of the research project «Integrative-differentiated substantiation for the selection of optimal methods for surgical interventions and volume of medical measures in surgical pathology of maxillofacial area», state registration No. 0116U003821.

Labial cleft and fissured palate remain widespread forms of congenital defects, and surgery is an integral part of their treatment comprehensive support. Surgical treatment of congenital clefts is accompanied by significant blood loss and intense nociceptive stimulation, which is largely due to traumatic surgery, profuse vascularization and a high concentration of nerve endings in this area. A complex set of interrelated homeostasis disorders that occurs after uranostaphyloplasty significantly affects the process of scar formation and the nature of wound healing [1, 2, 4].

Data reported in the literature indicate that the formation and reorganization of the scar lasts for a long time after scarring and epithelialization of the wound tissue surface, and therefore, in the short term after the wound epithelialization, the scar cannot be considered a complete physiological formation [7].

It is proved that the mechanism of sequential scar remodeling is based on a stable balance between the processes of the formed collagen destruction under the action of collagenase and the new collagen synthesis. When the intensity of collagenosynthesis prevails over collagenolysis, the normal process of scar formation is disturbed and it acquires hypertrophic properties, enlarges in volume and protrudes over the surface of the tissues surrounding it. Such scars cause various secondary deformations and functional disorders [5, 9].

Some scientists believe that one of the reasons for such scars formation after surgery is the presence of disturbances in the histological structures architectonics of the mucous membrane tissues in the area of the operating field. The leading role in the pathogenesis of pathological scarring is played by the disruption of close corporate links between tissue basophils, monocytes, and fibroblasts against the background of general and local autosensitization. Information about the recovery of the epithelium in the area of the postoperative wound healing is questionable, the period of 10 to 25 days is reported [8].

Recent studies have shown that the regeneration of tissues injured after uranostaphyloplasty, and then the function of the palatine-pharyngeal complex, is directly influenced by the state of the muscle