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Modern differentiated approach to the treatment of infertility in women with polycystic ovary syndrome

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Abstract---The article provides data on a differentiated approach to the treatment of patients with PCOS for the natural restoration of fertility. The study examined 150 patients who applied to the gynecological department of the regional Perinatal Center in Samarkand and the gynecological department of clinic No. 1 of the Samarkand State Medical University for infertility in 2017-2019. Fifty patients underwent an attempt to restore fertility without surgery. Endosurgical interventions were performed in 100 patients in order to normalize ovulatory function and treat infertility: in 64 women - drilling or unilateral ovarian resection, in 36 - bilateral ovarian resection. We analyzed the effect of surgical treatment of PCOS, taking into account the volume of surgery, on the levels of homocysteine, AMH, total testosterone, FSH, LH, the ratio of FSH / LH and total estradiol, which were determined before - and three months after the intervention. All patients were divided into 4 subgroups depending on the diagnosed phenotypes. Using the methods of differentiated conservative and surgical treatment of infertility in women with different phenotypes of PCOS based on the study of clinical, laboratory and ultrasound parameters, pregnancy occurs in 75.3% of patients.

Keywords---polycystic ovary syndrome, weight, ovulation, in vitro fertilization, COCs.

Introduction

Polycystic ovary syndrome is one of the most common pathologies in gynecological practice. The frequency of this pathology is approximately 11% among women of fertile age, and in the structure of endocrine infertility it reaches 70% (Savelyeva, G.M. et al. 2018, Ananiev E. V. 2017, Balashova E. O. 2018). Among women with hirsutism, polycystic ovaries are detected in 65-70% of cases (Adamyan L.V. 2013; Beglova A. Yu. et al. 2019). At the same time, being an endocrine-dependent pathology, PCOS with various menstrual irregularities and hirsutism is diagnosed in more than 60% of cases (Agababov R.M. 2012; Andreeva E. N. 2018, Durmanova A.K. et al. 2016). The well-known Stein-Leventhal syndrome was described in 1935 and included clinical signs such as anovulation, hirsutism, obesity, and polycystic ovarian changes. The main complaints of patients are: infertility (35-74%), and hirsutism (17-83%).

However, it should be noted that until now there are no uniform criteria for the diagnosis of PCOS, and this mainly occurs when the diagnosis is made only by one clinical or laboratory research method. In 2003, the European Society for Human Fertility and the American Society for Reproductive Medicine proposed to diagnose PCOS based on the mandatory presence of two of the three proposed criteria: hyperandrogenism, chronic anovulation, and echographic signs of PCOS. In recent years, much attention has been paid to the role of endothelial dysfunction as a cause of the development of PCOS (Akhundova N.E. 2021; Ibragimov B.F. 2019; Khudoyarova D. 2020). One of the factors of endothelial damage is hyperhomocysteinemia, which has a toxic effect on the cells of the inner surface of blood vessels. There is conflicting evidence regarding the level of hyperhomocysteinemia in women with PCOS. Some authors believe that there is an increase in homocysteine levels in women with PCOS compared with healthy women (Ibragimov B. et al. 2021; Mileeva L. V., 2019; Khudoyarova D. 2019). But others did not find hyperhomocysteinemia in this cohort of patients (Kochegurova E. M., et al. 2019; Khudoyarova D. 2019). The question of the relationship between homocysteine and androgens in patients with PCOS remains controversial (Savelyeva G.M. et al. 2018). There is evidence of the ability of androgens to increase homocysteine levels (Ibragimov B.F. et al. 2021).

In the literature, there is no consensus about the methods of treating PCOS. Primary therapy in the treatment of anovulatory infertility in patients with PCOS is weight loss, of course, in cases of overweight. It has been proven that menstrual function is normalized with a loss of 5 to 10% of body weight. Many authors believe that the normalization of body weight leads to the restoration of metabolic and hormonal homeostasis, which contributes not only to the implementation of the generative function, but also to a decrease in health risks, the development of long-term healthy lifestyle habits (Savelyeva, G.M. et al. 2018; Dubrovina S.O. 2016). With the development of obesity, a decrease in body weight of less than 5% of the initial does not lead to the expected effect, 5-10% gives a satisfactory effect and more than 10% leads to a good effect of treatment (Rizaev Zh. A., 2020; Khudoyarova D. 2020). The optimal weight loss is considered to be 0.5-1 kg per week. To introduce the principles of rational nutrition, it is necessary to calculate the calorie content of the daily diet, proposed by the WHO (Beglova A.

Yu. et al. 2019; Khudoyarova D. et al. 2019). To reduce body weight, the resulting caloric content of the daily diet is reduced by 20%.

In recent years, for the treatment of insulin resistance, roglizaton has been used (Gasparov A.S., 2014; Khudoyarova D. et al. 2019), a drug from the group of thiazolidinediones, which is a selective ligand of specific nuclear receptors capable of inducing the synthesis of proteins responsible for glucose transport into the cell. There is a large number of scientific works in the The Cochrane Library database, proving the beneficial effect of COCs on the clinical manifestations of hyperandrogenism (Durmanova A.K. et al. 2016; Matsneva I. A. et al. 2018). Combined oral contraceptives (COCs) are the most commonly used medications in women with PCOS, and are recommended by the Task Force and the Endocrine Society (Akhundova N.E. 2021; Balashova E. O. 2018) as the first line of therapy for hyperandrogenism and restoration of menstrual irregularities. The progestin component of oral contraceptives suppresses LH secretion, thus reducing LH-dependent androgen production. The estrogenic component increases the synthesis of steroid-binding globulin, which reduces the level of free testosterone. COCs also reduce the production of androgens by the adrenal glands (mechanism unknown) and the binding of androgens to their receptors (Ibragimov B. F., 2020; Khudoyarova D. et al. 2019). A minimum of 6 months is required to achieve treatment results for acne and hirsutism. Even though different guidelines do not favor one COC over another (Khudoyarova D. et al. 2019), low-dose contraceptives containing antiandrogenic or neutral progestins are considered the best choice for symptomatic treatment in PCOS.

The widely used practice of prescribing progestins for withdrawal bleeding before ovulation has been stimulated has been shown to have a negative effect on pregnancy and labor rates in PCOS patients (8.4% of pregnancies after progestin administration versus 61.8% after spontaneous menses in stimulated ovulation cycle). This situation may be associated with excessive bleeding and inadequate restoration of the basal layer in the subsequent cycle (Kochegurova E. M., et al. 2019). Clomiphene treatment can be started on days 2, 3, 4, or 5 of the cycles (Ananiev E. V. et al. .2017). About 15–40% of women with PCOS are clomiphene resistant with no follicular development after a 150 mg dose of clomiphene citrate for 5 days (Ibragimov B. F., 2020; Khudoyarova D. et al. 2019). The concept of failure of clomiphene therapy varies, but is most often based on the absence of pregnancy despite ovulation within 6 months. In obese patients with a body mass index of more than 30 kg / m², hyperandrogenism and / or amenorrhea, or in women with a large ovarian volume, the recommended starting dose of clomiphene is 100 mg (Durmanova A.K. et al. 2016). Aromatase inhibitors such as letrozole are formulated to treat breast cancer and work by preventing the conversion of androgens to estrogens. Letrozole has been proposed as an alternative treatment for ovulation induction in PCOS, has been approved for use by the US Food and Drug Administration, but is still off-label in most European countries (i.e. not approved for use). Letrozole inhibits aromatase activity and cytochrome P450-enzyme complex and induces an acute hypoestrogenic status, which stimulates FSH realization. By creating a negative feedback of estrogens with the hypothalamic-pituitary axis, it is an alternative to clomiphene with greater efficiency compared to the latter. It is prescribed from 2.5 mg to a maximum of 7.5 mg / day from the 3rd day of the menstrual cycle for 5 days to 5

cycles. The teratogenic, embryotoxic and fetotoxic effects of letrozole have been shown in an animal model. On the other hand, previous studies in humans have demonstrated the absolute safety of letrozole in relation to offspring health.

In women with PCOS, letrozole is associated with a lower risk of multiple pregnancies compared to clomiphene. Letrozole is indicated in patients with clomiphene resistance or in the presence of vasomotor symptoms, headache, or thin endometrium (Durmanova A.K. et al. 2016; Ibragimov B.F. 2019; Beglova A. Yu., 2018). However, further research is needed to prove the significant benefits of letrozole over clomiphene. In women with clomiphene resistance, the treatment protocol is to include dexamethasone. Laparoscopic ovarian drilling restores ovulation in 50% of cases against the background of normalization of the menstrual cycle. The pregnancy rate after this manipulation is about 50% within 1 year (Ibragimov B.F. 2021; Mileeva L. V., 2019). The mechanism of action of drilling is not clear, but it may be associated with the destruction of cells that secrete androgens both in the follicles and in the interstitial tissue of the ovaries. A decrease in the concentration of androgens and inhibins can increase the secretion of FSH and induce the growth of follicles through negative feedback. Another explanation may be increased blood circulation in the ovaries caused by their damage during this manipulation, which can stimulate the production of a cascade of local growth factors, such as insulin-like growth factor interacting with FSH, and thereby lead to follicular growth (Abashova E.I. et al. 2020; Abdurakhmanova N.F et al. 2019).

It should be emphasized that the above rationale for the use of the CC + gonadotropin regimen to stimulate ovulation in the program of natural restoration of fertility is purely theoretical, since in the available literature until now there has not been any data on the use of such a protocol in the program of natural restoration of fertility. But it is known that the combination of CC + gonadotropins is used in cycles stimulation using artificial insemination and in programs IVF (Adamyan L.V. et al. 2013; Balashova E. O. et al. 2018), and its use provides a decrease in the course dose of gonadotropins. The disadvantage of the CC + gonadotropin protocol in IVF programs is an increase in the frequency of "poor response", which is why most reproductologists prefer regimens with gonadotropins prescribed in combination with GnRH agonists and antagonists (Savelyeva, G.M. et al. 2018; Durmanova A.K. et al. 2016). Of interest is the use of a low-dose protocol with gonadotropins in the "step up" mode and a combination of CC + FSH. It can be expected that the use of such protocols instead of the "traditional regimen" with gonadotropins in clomiphene-resistant patients (constituting a significant proportion of all women with endocrine infertility) will not only minimize the complications typical of any FSH-containing drugs, but also lead to a significant reduction in the cost of treatment for by reducing the course dose of FSH. All of the above, arguing for new approaches to optimizing the tactics of managing infertile patients with PCOS in natural fertility restoration programs, need practical verification, which actually became the incentive for conducting relevant studies, the results of which are presented in this work.

Materials and Methods

The study examined 150 patients who applied to the gynecological department of the regional Perinatal Center in Samarkand and the gynecological department of clinic No. 1 of the Samarkand State Medical University for infertility in 2017-2019. They were diagnosed with PCOS based on the criteria of the Rotterdam Consensus Conference on PCOS. The age of the examined patients was from 22 to 35 years old, on average 29.8 ± 3.4 years. 50 patients underwent an attempt to restore fertility without surgery. Endosurgical interventions were performed in 100 patients in order to normalize ovulatory function and treat infertility: in 64 women - drilling or unilateral ovarian resection, in 36 - bilateral ovarian resection. Surgical interventions on the ovaries included drilling / resection using conventional techniques under endotracheal anesthesia using a laparoscopic approach. The indication for surgery was the lack of effect from conservative stimulation of ovulation with clomiphene-citrate (CC), carried out in at least three cycles, the absence of effect from the appointment of COCs with an antiandrogenic progestin to normalize the menstrual cycle for 6 cycles, the patients were over 30 years old.

The waiting period for spontaneous pregnancy after surgery was one year, provided the menstrual and ovulatory functions were normalized within three months. Ovulation was assessed according to the Claplan test. In the absence of ovulation within three months after the operation, ovulation inducers (clomiphene - citrate and rFSH) were additionally and sequentially used, each no more than three cycles according to generally accepted methods. While maintaining anovulation, the patients were recommended IVF. The IVF procedure was also prescribed to patients with ovulatory function restored against the background of folliculogenesis inducers, but with persisting infertility. We analyzed the effect of surgical treatment of PCOS, taking into account the volume of surgery, on the levels of homocysteine, AMH, total testosterone, FSH, LH, the ratio of FSH / LH and total estradiol, which were determined before - and three months after the intervention.

At the second stage of the work, the effectiveness of the IVF procedure was assessed in 72 patients operated on for infertility with PCOS. The indication for IVF was both the preservation of anovulation after the operation, which was not stopped by the ovulation inducers (CC and rFSH), and the preservation of infertility against the background of confirmed ovulation, restored as a result of the operation or with the additional use of ovulation inducers after the operation. During an objective examination of the patients, the following indicators were determined:

- Height, body weight, waist-to-hip ratio (W / H) to characterize the type of distribution of adipose tissue, body mass index.
- The condition of the skin and integuments (the presence of striae, acanthosis nigroid, acne, hirsutism). With excessive hair growth, the time of its appearance was specified.
- The condition of the mammary glands (degree of development, the presence of discharge from the nipples, masses).

Gynecological examination used bimanual examination, examination of the cervix in mirrors and cytological examination of smears. If necessary, a simple or extended colposcopy was performed. Before surgery, a standard examination was performed: blood type, Rh-affiliation, coagulogram, blood chemistry, general urine analysis, general blood test, blood glucose test. Antibodies to infection were determined in the blood - toxoplasmosis, rubella, cytomegalovirus, herpes. In obese patients, the lipid spectrum of blood was determined (glucose-tolerance test, total cholesterol, HDL, LDL). Of the instrumental methods, a chest X-ray and electrocardiography were used without fail in all patients. The standard preliminary examination also included a therapist's conclusion about the patient's somatic health and the absence of contraindications to pregnancy and childbirth.

The detection of endometrial pathology by ultrasound was an indication for hysteroscopy and histological examination of endometrial scraping. Morphological examination of the endometrium was carried out in the Department of Pathological Anatomy of Clinic No. 1 of the Samarkand State Medical Institute. Ultrasound was also used to monitor the parameters of folliculogenesis and endometrial thickness in the dynamics of ovulation stimulation cycles, as well as to diagnose the alleged pregnancy. In hormonal studies at the initial examination stage, total testosterone (T), free testosterone, dehydroepiandrosterone sulfate (DEA-S), prolactin, basal levels of total estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and the ratio of LH / FSH, studied thyroid hormones (T3, T4, TSH), prolactin. Similar hormonal studies (with the exception of the definitions of DEA-C, prolactin, T3, T4, and TSH) were performed 2-3 months after ovarian surgery. Before the IVF procedure, the level of total testosterone was additionally clarified.

Determination of E2 was also used for hormonal monitoring of the process of ongoing desensitization of the pituitary gland (in a long protocol with GnRH agonists), as well as, along with ultrasound monitoring data, to monitor the effectiveness of the ovulation stimulators used (clomiphene-citrate, rFSH) and calculate the time of administration of the trigger ovulatory dose of CG. ... In comparative studies of the used ovulation stimulation protocols used in IVF programs, the progesterone level was additionally determined on the day of administration of the permissive dose of hCG. A sign of a premature ("parasitic") LH peak was a progesterone concentration > 1 ng / ml. To diagnose pregnancy, the concentration of the β -subunit of hCG was determined: on the 14-16th day after the registration of ovulation in the period of monitoring the results of surgical treatment (supplemented or not with ovulation inducers) or on the 14th day after the transfer of embryos in IVF cycles.

All patients with BMI over 26 were prescribed an appropriate diet with a total caloric value of up to 2000 kcal and dosed physical activity at the first stage of treatment. In parallel, metformin was prescribed 500 mg x 3 times a day. Patients with irregular menstrual cycles were prescribed COCs with drospirenone - Midiana (Gedeon Richter) for 6 menstrual cycles. When diagnosing hyperhomocysteinemia, folate - containing COCs - Yarina + (Bayer) was prescribed. CC was prescribed to patients with preservation of anovulation after surgery for three cycles. The dose of the drug was 100 mg / day for 5 days (from

the 5th day of the cycle). The adequacy of the response of the ovaries to stimulation of CC began to be assessed from the 1st day of its cancellation, by determining the size of the growing follicles and the concentration of E2 in the blood according to the ultrasound data. In the presence of a mature follicle 18-20 mm in size, concentration E2 = 500-2000 pmol / l (depending on the number of mature follicles), an ovulatory dose of hCG of 10,000 units was administered.

In the absence of mature follicles 5-6 days after the withdrawal of CC, the ovulatory dose of pregnyl was not administered. In such cases, gestagens were prescribed for 10 days to detect a menstrual-like reaction, and stimulation was repeated according to the same scheme. If the use of CC in three cycles ensured the restoration of ovulation, but was not accompanied by pregnancy, this was the rationale for the appointment of IVF. Ovulation induction with rFSH (Puregon) was performed from day 3 of the cycle or menstrual-like reaction caused by gestagens. The dose of rFSH was administered from 50 to 75 IU for 5 days, followed by assessment of the adequacy of the dose and duration of drug administration based on generally accepted hormonal and ultrasound criteria.

With controlled stimulation, the response of the ovaries according to ultrasound data was assessed before the start of stimulation, on the 5th day, the introduction of rFSH, then (with an adequate response) - every other day, and upon reaching a dominant follicle of 15 mm in size - daily. E2 measurements were carried out on the 2nd day of the cycle, when a follicle with a diameter of 15 mm appeared, and then according to indications. With adequate growth of follicles, the dose of the drug remained the same, if necessary, it was corrected. When the dominant follicle reached a diameter of 18 mm, hCG (pregnyl) was injected at a dose of 10,000 U. Confirmation of ovulation and management of the luteal phase were carried out in the same way as in cycles with the use of CC. The rFSH protocol was used no more than 3 times, and, with persisting infertility, the patients were referred for IVF.

Results and Discussions

All patients were divided into 4 subgroups depending on the diagnosed phenotypes.

- I A - 62 (41.3%) women with clinical and / or biochemical manifestations of hyperandrogenism in combination with chronic anovulation and PCML
- II B - 40 (26.7%) women with chronic anovulation in combination with clinical and / or biochemical manifestations of hyperandrogenism with normal ovaries
- III C - 32 (21.3%) women with ovulatory cycles, PCML and with clinical and / or biochemical manifestations of hyperandrogenism
- IV D - 16 (10.7%) women with no clinical and / or biochemical signs of androgen excess, but with chronic anovulation and PCML.

Distribution by phenotype was carried out based on the characteristics indicated in Table 1.

Table 1
Signs of major PCOS phenotypes

	Hyperandrogenemia	Anovulation	RMB	AMG	Metabolic traits
Phenotype A	YES	YES	YES	Elevated	YES
Phenotype B	YES	YES	NO	Unknown	YES
Phenotype C	YES	NO	YES	Slightly increased	Slight
Phenotype D	NO	YES	YES	Slightly increased	NO

All patients presented with unsuccessful infertility treatment. In the anamnesis, 138 (92%) have already received treatment aimed at correcting menstrual irregularities using hormonal and non-hormonal agents. But without effect. In order to stimulate ovulation, 87 (58%) patients were prescribed clomiphene citrate in the past (for 3-6 cycles). The study of the hereditary history revealed that the mothers of 61 (40.7%) patients also had menstrual and reproductive disorders. In addition, there was a high frequency of childhood infections (in 81 - 54%) and chronic infectious and inflammatory diseases, such as chronic tonsillitis, chronic pyelonephritis, chronic bronchitis in 29 - 19.3% of those examined during puberty. In most patients, menstrual irregularities manifested themselves as oligomenorrhea (cycle duration 40-90-120 days). The average duration of menstrual irregularities was 10.5 ± 3.2 years and ranged from 1 to 19 years. The average duration of infertility was 7.2 ± 2.9 years and ranged from 1 to 14 years. Primary infertility occurred in 82 patients, secondary - in 68. The distribution of forms of infertility depending on the phenotype of women with PCOS is shown in Table 2.

Table 2
Types of infertility in patients with different phenotypes of PCOS

Phenotype	Primary (abs., %)	Secondary (abs., %)
A(n=62)	59(95,2)	3(4,8)
B(n=40)	20(50)	20(50)
C(n=32)	19(3,1)	31(96,9)
D(n=16)	2(12,5)	14(87,5)

Of the 150 examined patients with PCOS, only 1/5 had urgent labor, another 12 (8%) women had a history of preterm labor. Moreover, only one patient with phenotype C had two children, 25 women with different phenotypes had 1 child each, and patients from the subgroup of phenotype A had no children at all, secondary infertility occurred in three patients after two spontaneous early abortions and one ectopic pregnancy. When clarifying concomitant gynecological diseases according to the anamnesis, it was found that:

- 8 women (5.3%) underwent myomectomy for subserous uterine fibroids;
- 13 women (8.7.1%) previously received conservative hormonal treatment for endometriosis

During gynecological examination and colposcopy, cervical diseases were detected in 25 (16.7%) patients:

- erosion and pseudo-erosion of the cervix - in 18 women (12.0%);
- polyps of the mucous membrane of the cervical canal - in 7 women (4.7%).

81 patients (54%) were prescribed hysteroscopy to exclude uterine infertility and in the presence of abnormal uterine bleeding to exclude pathology of the uterine cavity. In all cases, an additional histological examination of the endometrial scraping was carried out. At the same time, the following pathological conditions were diagnosed in 59 women (39.3%):

- endometrial hyperplasia - in 20 (13.3%) patients;
- endometrial polyps - in 5 (3.3%) patients;
- hypotrophy or atrophy of the endometrium - in 34 (22.7%) patients (similar changes were recorded among patients with secondary amenorrhea and severe oligomenorrhea with delays in menstruation from 3 to 6 months);

- submucous myoma - in 1 (0.7%) patients.
- During laparoscopy performed in 100 (66.7%) patients for the purpose of surgical stimulation of ovulation, the following concomitant factors of infertility were found:
- adhesive process of the 1st degree according to the classification of Hulka J.F - in 9 patients (6%);
- External genital endometriosis I-II degree according to the AFSCE classification in 3 patients (2%);
- subserous uterine myoma - in 4 patients (2.7%);
- ovarian cysts - in 3 patients (2%)

In total, during laparoscopy, these pathological manifestations were found in 19 (12.7%) patients, in 5 (26.3%) of them there was a combination of several types of pathology. Clinical signs of hyperandrogenism were detected with the following frequency:

- obvious hirsutism or borderline values of the hirsut number - in 96 (64%) patients;
- oily skin with acne - in 38 (25.3%) patients.

It should be noted that these were all patients of A, B, C phenotypes, which amounted to 89.3% in relation to all examined patients. At the same time, the most pronounced clinical manifestations of hyperandrogenism were observed in patients with phenotype A. Determination of body mass index (BMI) showed that 75 (50%) patients were overweight. BMI values from 25 to 29.9 (defined as overweight or preobesity with a low risk of metabolic complications) were determined in 35 (23.3%) women; BMI values from 30 to 40 (obesity of I and II degrees with an average risk of metabolic complications) - in 42 (28%) women. Visceral distribution of adipose tissue (OT / OB ratio over 0.83) or waist circumference over 80 cm was observed in 71 (47.3%) women. It was found that if among patients with BMI <26 such patients were about 30% (12 women out of

40), then among patients with overweight their number reached 64% (48 women out of 75).

Nigroid acanthosis was detected in 26 women (17.3%). All patients with this sign had a BMI over 30 and a visceral type of adipose tissue distribution. Most often, this sign was found in patients with phenotype A and B (57.7%). There were no significant differences in the amount of altered hormones among all phenotypes of women with PCOS. A significant difference was observed only when compared with the control group. When performing transvaginal ultrasound (to better visualize the ovaries and accurately count the number of follicles), the characteristics proposed in the Rotterdam Consensus were guided (Table 3). The examination was carried out on days 2-5 of the cycle so that the growing follicle does not cover small antral follicles and / or changes in the volume of the ovaries.

Table 3
Ovarian ultrasound characteristics proposed in the 2003 Rotterdam Consensus for the diagnosis of PCML

	Rotterdam criteria (2003)
Number of follicles	>12 follicles
Follicle sizes	2-9 mm in diameter
Ovary size	>10 ml ³

Patients with PCOS A, B, D phenotypes were characterized by symmetric bilateral enlargement of the ovaries with the formation of small cystic changes in the cortical layer and a significant thickening of the tunica albuginea. The volume of the ovaries in these subgroups reached 10.1-16.8 cm³ (mean value 13.8 cm³), which is much higher than normal values (3-8 cm³). In 110 women with PCOS (73.3%), we identified multiple small cystic formations (up to 10 or more) with a diameter of 2-8 mm, usually located on the periphery, an increased volume of the ovarian stroma and, on average, slightly enlarged ovaries. All these patients were from subgroups of phenotypes A, C, D. In 40 examined subgroups of phenotype B, ultrasound did not reveal any abnormalities in the structure of the ovaries. In the total mass of the examined patients, this amounted to 26.7%. It should be especially noted that during ultrasound examination of patients with PCOS in 39 (26%) the uterus was reduced in size, especially its thickness. The contour of the uterus in all cases was clear, no changes in its internal structure were revealed. The M-echo was most often not detected. Despite the fact that the patients had a normal body weight, they had significant changes in the lipid spectrum of the blood compared to women from the control group.

Table 4
Indicators of carbohydrate metabolism in women of different phenotypes of PCOS

Indicator	Phenotypes				
	A	B	C	D	Control
Blood glucose	6,7±1,5*	6,1±1,9*	6,5±1,1*	5,7±1,0*	4,8±1,0

(mmol/l)					
Glycosylated hemoglobin (%)	7,9±2,0*	6,9±2,7*	6,5±1,0*	5,9±0,1*	6,1±0,4
C-peptide (ng/ml)	3,9±2,2*	3,5±2,9*	2,6±2,0*	2,2±0,2*	1,7±0,9
Insulin (μIU/ml)	24,5±1,7*	25,0±1,5*	20,5±1,1*	22,1±1,1*	18,1±1,7

reliability of differences between the compared indicators with the control group*

The average level of homocysteine in patients with PCOS was $10.8 \pm 1.4 \mu\text{mol/L}$, which is significantly higher than in the control group. In 102 (68%) women with PCOS, hyperhomocysteinemia occurs. At the same time, it should be noted that in women with PCOS phenotypes A, B there is a significant increase in homocysteine, while in patients with PCOS phenotypes C, D there were insignificant non-significant differences from the control group. These findings prove that androgens can increase homocysteine levels. All this was the reason for the appointment of folate-containing COCs with drospirenone to women with PCOS in order to normalize the menstrual cycle and reduce homocysteine levels. However, COCs were prescribed for patients with BMI <30. Forty-two patients with BMI > 30 were initially prescribed appropriate nutrition, dosed exercise, and metformin. COCs were added to metformin when the BMI reached 29.9 kg / m 2 and below.

Using the tactics of reducing body weight to a BMI below 29.9 and prescribing metformin in the first cycle after discontinuation of COCs, we managed to induce ovulatory cycles in 43 (28.7%) patients. However, we observed spontaneous pregnancy only in three women of phenotype C (they had an ovulatory cycle before treatment, but were overweight). In 40% of patients with PCOS, ovulation does not occur after multiple cycles of CC treatment; they are considered resistant (resistant) to CC. In our study, of 47 patients who underwent ovulation stimulation with clomiphene citrate for 6 cycles, 16 women were clomiphene-resistant (34% in relation to the group with this method of treatment, and 10.7% in relation to all examined). Only 1 course of ovulation stimulation with gonadotropins was carried out, as a result of which 15 out of 21 women (71.4%) received ovulatory cycles. However, clinical pregnancy occurred only in 11 patients of this group, which was 7.3% in relation to all examined and 52.4% in this group. All patients with phenotype D (4 women) and 7 patients with phenotype A became pregnant. The protocol was cancelled in 6 women who had more than 3 follicles larger than 16 mm in the middle of the protocol. 10 patients in this group (47.6%) were referred for IVF.

In total, we observed 100 patients with different phenotypes of PCOS who underwent surgical treatment of anovulation. In 64% of cases, LD was performed, in 36 - a typical bilateral wedge resection of the ovaries. All operations were performed under endotracheal anesthesia. We did not observe any surgical and anesthetic complications during the operation or in the postoperative period. In the postoperative period, the patients were observed for three menstrual cycles. Spontaneous clinical pregnancy occurred in 67% of women. These were mainly patients with phenotypes A, C, D - 38%, 20%, 9%, respectively. 33% of patients from this group, after the diagnosis of anovulation 3 months after surgery, were re-prescribed clomiphene citrate for 3 months. As a result, natural conception

was achieved in 8 patients with phenotype B, two patients with phenotype A. In total, 10% of women with PCOS became pregnant after repeated use of clomiphene citrate after surgery. Thus, we achieved natural restoration of fertility in only 133 women with PCOS. 17 patients were referred for IVF.

Conclusion

Using the methods of differentiated conservative and surgical treatment of infertility in women with different phenotypes of PCOS based on the study of clinical, laboratory and ultrasound parameters, pregnancy occurs in 75.3% of patients. The main diagnostic criteria for PCOS phenotypes were: clinical/biochemical manifestations of hyperandrogenism in combination with chronic anovulation (41.3%); chronic anovulation plus hyperandrogenism with normal ovaries (26.7%); ovulatory cycles, PCML and hyperandrogenism (21.3%); chronic anovulation, PCML without hyperandrogenism (10.7%). Fertility varies depending on the specific phenotype of PCOS and comorbidities: with weight loss and hyperhomocysteinemia, spontaneous pregnancy occurs in 2% of women (phenotype C). 12.1% of patients require ART. Low-dose and slow stimulation with gonadotropin lead to pregnancy in 7.3% (phenotypes D, A). After surgical treatment, spontaneous clinical pregnancy occurs in 67% of women. With a combination of surgical treatment with stimulation of ovulation with clomiphene citrate, pregnancy occurs in 10%.

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