



## FEATURES OF ULTRASOUND MEASUREMENTS TO HELP SOLVE THE PROBLEM OF INFERTILITY

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<p><b>Received:</b> September 3<sup>rd</sup> 2021 <b>Accepted:</b> October 4<sup>th</sup> 2021 <b>Published:</b> November 28<sup>th</sup> 2021</p>	<p>Today, the role of ultrasound in gynecology is an integral part, and it is one of the main solutions and treatment of such a problem as endocrine infertility. Since folliculometry is a very important part of ovulation induction. The purpose of this study was to determine the criteria for differential prescription of ovulation inducers in the treatment of infertility among women with PCOS. The study included 55 patients of reproductive age with polycystic ovary syndrome accompanied by anovulatory infertility. The patients are divided into three groups. Ovulation induction was carried out by direct and indirect inducers of ovulation according to the groups. The efficiency of treatment of patients with PCOS depends on the complex conservative preparation before the stimulation of ovarian function and differentiated prescription of ovulation inducers depending on the baseline characteristics of patients and characteristics of folliculogenesis and steroidogenesis in the ovaries.</p>
<p><b>Keywords:</b> Polycystic Ovary Syndrome, Ultrasound, Stimulation Of Ovarian Function, Controlled Ovulation Induction.</p>	

Endocrine infertility accompanied by anovulation is the most common form of endocrine disorders in women of reproductive age [3,6,10]. Polycystic ovary syndrome (PCOS), being the most common cause of anovulatory infertility [3, 5], invariably attracts the attention of scientists [1,3,8]. The tactics of managing patients with PCOS is primarily aimed at correcting hyperandrogenism, eliminating anovulation, regulating the rhythm of menstruation and restoring fertility [2, 4].

The development of medical technologies, research in the field of reproductive gynecology served as the basis for the synthesis and clinical use of drugs that stimulate ovulation, and thereby, enable the implementation of fertility. Ovarian stimulation has become a key component of assisted reproductive technology (ART). Over the past 45 years, clomiphene citrate has been the "drug of choice" in the treatment of infertility in anovulatory infertility. Clomiphene citrate acts to increase pituitary FSH secretion by reducing the negative response to estrogens. But the presence of clomiphene-resistant forms of anovulation (30-40%, according to different authors) limits the use of this ovulation inducer [2,9,5]. With the synthesis and use in clinical practice of new ovulation inducers: menopausal gonadotropins (HMG), recombinant gonadotropins (rFSH) [7,8], it became possible to choose a method of treating infertility in anovulation of various origins. At the same time, the criteria for an adequate choice of an ovulation inducer in the

treatment of endocrine infertility without the use of ART are not fully presented in the literature, and the assessment of the effectiveness and side effects of ovulation inducers is sometimes controversial. Therefore, the widespread use of modern and advanced medicines stops the practicing physician because of the cost of these drugs and the variability in the selection of doses. But if we evaluate the ovulation inducer from the position of "the minimum time spent on obtaining the effect - the price of the drug", then the choice of the most adequate, in each specific case, ovulation induction scheme will be relevant and important for clinical practice. This will shorten the treatment time and improve the efficiency of reproductive function restoration in patients with PCOS.

The aim of this study was to determine the criteria for the differential prescription of ovulation inducers in the treatment of infertility in women with PCOS.

### MATERIALS AND RESEARCH METHODS.

It included 55 female patients of reproductive age with infertility. The age range was from 24 to 36 years old. The duration of infertility varied from 3 to 7 years. All patients were examined clinically and laboratory according to the protocols developed by us for the examination of infertile couples to identify the cause of infertility. Clinical analysis of blood, urine, smears for flora, oncocytopology, bacterial culture for



flora and antibiotic sensitivity, biochemical blood test, blood serum glucose - no pathology was found. In these patients, RW, ELISA HBsAg, ELISA HIV were negative. All patients were examined for the group of TORCH infections. The hormonal status of patients was determined by ELISA (FSH, LH, prolactin, estradiol, progesterone, 17-OH-progesterone, testosterone, DHEAS, cortisol, TSH, T4, antibodies to TG, antibodies to TPO - according to the phases of the cycle in accordance with the examination protocols) ... We also performed an echography of the thyroid gland, mammary glands on days 5-7 of the menstrual cycle, with the study of the structure and presence of pathological foci. Ultrasound examination of the pelvic organs included determination of the size of the uterus, the state of the endometrium, ovaries and folliculometry. The length, width, anteroposterior size of the uterus, as well as the length, width and thickness of the ovaries were assessed. Patients and their sexual partners were examined for sexually transmitted infections (STIs) (chlamydia, mycoplasma, ureaplasma) by PCR. All women underwent diagnostics of the patency of the fallopian tubes. All patients were consulted by a therapist in order to exclude pathology that is a contraindication for pregnancy. In order to exclude the male factor of infertility, sexual partners were examined (spermogram) - no pathology was found. All patients underwent a post-coital test - positive. In terms of forms of infertility, the criteria for inclusion in the study were: established diagnosis of PCOS, absence of ovulation, FSH <15 IU / L, estradiol <50 pg / ml; endometrial thickness <5 mm, body mass index 18-35. Exclusion criteria: the presence of tumor-like formations of any localization, inflammatory diseases of the pelvic organs of one or both spouses, the presence of sexually transmitted infections, obstruction of the fallopian tubes, sperm infertility. Patients, depending on the chosen method of stimulation, were divided into three groups: group 1 included patients with PCOS (16 people), whose ovulation was induced by recombinant follicle-stimulating hormone (rFSH); Group 2 - patients with PCOS (11 people), induction of ovulation was carried out by human menopausal gonadotropin (menopur) containing FSH and LH in a 1: 1 ratio; Group 3 included women with PCOS (28 people), in whom ovulation was induced by clomiphene citrate (CC). Statistical analysis of the research results was carried out using the Student's t-criteria STATISTICA 6.0. In Patients, the diagnosis of PCOS was established on the basis of generally accepted criteria characterizing this syndrome. Violation of the menstrual cycle with menarche was observed in 100% of patients, of which 95.2% were of the oligomenorrhea type. Anovulation

was confirmed by functional diagnostic tests and the determination of the progesterone content in the putative luteal phase of the menstrual cycle.

Table 1 Induction by various doses of clomiphene citrate in women with PCOS

Parameter	CC 50 mg N = 25	CC 100 mg N = 15	CC 150 mg N = 10
Number of ovulatory cycles	18 (24,6%)	10 (13,6%)	35 (63,6%)
The number of preovulatory follicles in 1 patient	1,5±0,6	3,8±0,5	3,4±0,6
Endometrial thickness	7,2±0,8	8,8±0,5	6,7±0,4

BMI of 67.6% of patients - 28, hirsutism - in 56.2%, hyperandrogenism - in 94.2%, an increase in the LH / FSH ratio - in 85.7%, the concentration of LH in all patients was  $16.7 \pm 0.4$  Honey / l. Ultrasound signs of polycystic ovaries were recorded in most patients: an increase in ovarian volume - in 88%, an increase in ovarian-uterine index - in 80%, a small cystic ovarian structure - in 98%, of which 24% had a peripheral location of cystic follicles. Subsequently, each patient underwent folliculometry in a cycle of controlled induction of ovulation. Basal ultrasound was performed on the 3rd day of the menstrual cycle. Folliculometry was performed 3-5 days after the start of the administration of ovulation inducers, and then from the 7-8th day of the cycle every day to adjust the dose of the administered drugs and record the dynamics of the growth of the dominant follicle. In order to diagnose pregnancy, a serum b-cG test was performed on the 14th day and an ultrasound scan on the 20-21st day after the ovulation trigger was administered. Results and discussion 1 group of patients with the aim of inducing ovulation was administered the drug rFSH Gonal-F (Merck Serono), 75 units. from 3-5 days of the menstrual cycle according to individually selected doses. The total dose of the drug was 450-525 units, the drug Pregnyl was used as a trigger of ovulation at a dose of 5000 units. Group 2 of patients for the induction of ovulation was injected with the drug Menopur HMG 75 units. in accordance with the instructions for use. The total amount of the drug was 525-1025 units. As a trigger of ovulation, the drug Pregnil was used at a dose of 5000 units. Group 3 was prescribed Clomiphene citrate (CC; Egis Pharmaceuticals, Hungary) was prescribed from the 5th to the 9th day of the menstrual cycle



(MC) at doses of 50-100-100 mg per day per os for 3 months. Pregnyl 5000 - 10000 units were used as a trigger for ovulation. At the first stage of the work, 25 women of group 3 were prescribed clomiphene citrate 50 mg, but in the first cycle of ovulation induction it turned out that 5 women did not have an ovarian response to the selected dosage of the drug. In these women, the growth of follicles more than 10 mm was not recorded, therefore, these patients, in the next menstrual cycle, were prescribed Gonal-F and, therefore, they were included in group 1. In the further study, 15 women remained in group 3. In order to support the luteal phase of the cycle, we used the endogenous micronized progesterone Utrozhestan, at a dosage of 200 mg 2 times a day. Marked in all women taking clomiphene citrate, insufficient transformation of the endometrium at the time of ovulation. A snapshot of an ultrasound examination of the uterus in a patient on the 13th day of the stimulated cycle is shown in Fig. 1. The endometrial line is marked with a triangle marker. Of 25 women in this group, 5 (24.6%) were clomiphene-resistant, which was the reason for changing the drug and including them in another group. A comparison was made of a group of clomiphene-sensitive and clomiphene-resistant women in terms of clinical and laboratory parameters: age, duration of menstrual irregularities, body mass index (BMI), T, LH, E2 levels, and ovarian size. Analysis of the data obtained showed that older women predominate among clomiphene-resistant patients, there were no significant differences in LH levels, clomiphene-resistant patients had low E2 levels, and 7 out of 18 women had previously undergone laparoscopic ovarian cauterization. It was also noted that in the group of clomiphene-resistant patients there were women in whom pregnancy was previously achieved using CC, but it was not developing. This fact may serve as confirmation that clomiphene-resistance is most likely not an initial condition, but is formed in the process of long-term unsuccessful infertility treatment. At the next stage of work in groups 1 and 2, ovulation was induced by direct ovulation inducers. The results of the ovulation induction by HMG and rFSH did not differ significantly in many parameters, possibly due to the small number of patients in the groups. But the results were significantly different from the induction of ovulation by clomiphene citrate. The size of the leading follicle against the background of drug administration was  $20.1 \pm 0.3$  mm, the thickness of the endometrium was  $9.9 \pm 0.4$  mm. Upon reaching a dominant follicle of 18 mm and an endometrial thickness of at least 8 mm, ovulation triggers were prescribed (hCG - Pregnyl at a dosage of 5000 IU. Ovulation was diagnosed in 100%

of cases after  $2 \pm 1$  days. Moreover, in cycles with rFSH induction, ovulation occurred spontaneously in 3 cases, which made it possible not to inject Pregnyl. In order to support the luteal phase of the cycle, the secretory transformation of the proliferative endometrium, the secretion of proteins, the preparation of the endometrium for the invasion of the trophoblast, the rest of the uterus by reducing prostaglandins and oxytocin, we used endogenous micronized progesterone Utrozhestan, the chemical structure of which is 100% identical to endogenous progesterone. Gestagen was administered vaginally at a dosage of 200 mg 2 times a day. In the middle of the luteal phase, ultrasound was performed: the size of the corpus luteum was  $17.4 \pm 0.6$  mm.

Table 2 Induction by various doses of clomiphene citrate in women with PCOS

Parameter	1st group N = 17	2nd group N = 10
Number of ovulatory cycles	100%	100%
Number of preovulatory follicles	$2,5 \pm 0,5$	$2,2 \pm 0,5$
Duration of drug administration per cycle, days	$8 \pm 2$	$10 \pm 2$
Spontaneous ovulation	3(10%)	0
Pregnancy rate	2 (10%)	1(5%)
Prolonged pregnancies	2 (10%)	1(5%)

rFSH can be recommended for women with a history of hyperstimulation syndrome (OHSS), as well as for patients with high blood LH levels and women at risk of developing OHSS. After the second stage of the study, a group of patients was identified (16) in whom the induction of ovulation by direct and indirect inductors was ineffective for the restoration of reproductive function: absence of ovulation, insufficiently prepared endometrium for implantation of the ovum, lack of growth of the dominant follicle in the ovaries during induction of ovulation with normal ovarian reserve. In addition, endoscopic ovarian surgery, previously performed in 10 of the patients, and IVF methods in 2 patients, were ineffective. These patients were regarded as the most difficult for reproductive rehabilitation. Thus, the presented results indicate the need for further study of the effectiveness of conservative treatment of infertility in PCOS under the condition of comprehensive preliminary



preparation before the induction of ovulation and the differentiated use of ovulation inducers, taking into account the clinical and anamnestic characteristics of patients, the results of laboratory examination and analysis of the ovarian response.

### CONCLUSIONS.

The success of the treatment of patients with PCOS depends on a comprehensive conservative preparation before stimulating ovarian function and the differential prescription of ovulation inducers, depending on the initial characteristics of patients and the characteristics of folliculo- and steroidogenesis in the ovaries. According to our study, about a third of patients (24.6%) with PCOS are clomiphene-resistant. Predictive criteria for clomiphene resistance may be older age of patients (over 30 years), increased body mass index, increased size of the ovaries with peripheral cysts, surgical treatment of PCOS, increased LH levels ( $> 15$  IU / L) in combination with serum E2 concentration. blood below 150 pmol / l. Considering the rather high percentage of women with PCOS who are not sensitive to clomiphene citrate, it is necessary to recommend this category of patients to prescribe recombinant gonadotropins as the first ovulation inducer. The preference for using rFSH over HMG as ovulation inducers in women with PCOS remains controversial and requires further comprehensive study.

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