

**MODERN POSSIBILITIES OF A DIFFERENTIATED APPROACH TO
THE TREATMENT OF INFERTILITY IN WOMEN WITH POLYCYSTIC
OVARY SYNDROME**

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ABSTRACT

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%. The main complaints of patients are: infertility (35-74%), hirsutism (17-83%). 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 2018-2021. 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. 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: *Antagonists Of Gonadotropin Releasing Factor, Combined Oral Contraceptives (Cocs), Polycystic Ovary Syndrome (PCOS), Normalization Of Body Weight, Correction Of Metabolic Disorders, Stimulation Of Ovulation, In Vitro Fertilization (IVF).*

INTRODUCTION

In recent years, much attention has been paid to the role of endothelial dysfunction as a cause of the development of PCOS [1]. 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 [2]. But others did not find hyperhomocysteinemia in this cohort of patients [3]. The question of the relationship between homocysteine and androgens in patients with PCOS remains controversial [4]. There is evidence of the ability of androgens to increase homocysteine levels [5].

PCOS have a high risk of developing hyperhomocysteinemia at a young age, which, in combination with hyperandrogenism and hypoestrogenia, leads to endothelial dysfunction and requires the identification of hyperhomocysteinemia in order to choose the most effective method of treating PCOS. Andreeva E.N. et al. (2018) showed that folate-containing COCs in patients with PCOS lead to a decrease in testosterone levels and hirsute number, but does not affect the metabolic profile (BMI, waist circumference, insulin level). An increase in homocysteine concentration in patients with PCOS is a reason for a deeper study of its secretion in this contingent of patients in order to improve treatment methods and improve treatment outcomes. [6]

The use of insulinsensitizers is not only indicated in the presence of insulin resistance, but also helps to reduce the risk of developing hyperstimulation syndrome during in vitro fertilization in patients with PCOS [7]. Of the medications for insulin-resistant patients with normal body weight, metformin therapy is recommended at the first stage. A drug from the biguanide class Metformin (Glucophage, Siofor) leads to a decrease in peripheral insulin resistance, improving the utilization of glucose in the liver, muscles and adipose tissue, normalizes the lipid profile of the blood, reducing the level of triglycerides and LDL, without affecting the function of β -cells of the pancreas. The drug is prescribed at 1000-1500 mg / day according to the control of a glucose tolerance test. The duration of therapy is 3-6 months, including against the background of ovulation stimulation. [8]

The advantages of ovulation induction with the use of clomiphene citrate (in comparison with gonadotropins) when trying to naturally restore fertility include a much lower likelihood of ovarian hyperstimulation syndrome, multiple pregnancies (due to the higher frequency of a monofollicular response), as well as the low cost of this drug. Nevertheless, despite the described advantages of stimulating ovulation with the use of CC, gonadotropins are also used in natural fertility recovery programs. Thus, gonadotropin preparations have an absolute indication for the appointment of patients with primary and secondary hypothalamic-pituitary insufficiency (HPH), since at low E₂ values (<100 pmol / l) CC is in principle unable to implement the feedback mechanism with the pituitary gland, increasing the formation of endogenous FSH. This is due to the fact that in a hypoestrogenic state, CC does not manifest itself as an antiestrogenic drug and therefore turns out to be completely useless as an indirect inducer of ovulation. [9]

Materials and methods

The work is approved in our country by the Higher Attestation Commission. As a result of the work, methods of differential diagnosis and treatment of patients diagnosed with PCOS were introduced in the perinatal center and the 1st maternity hospital.

Patients were informed that their medical data would be used for scientific purposes. 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 2018-2021. The age of the examined patients was from 22 to 35 years old, on average 29.8 ± 3.4 years. [10]

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. [11]

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 Cliaplan 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. [12]

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. [13]

During an objective examination of the patients, the following indicators were determined:

1) Height, body weight, waist-to-hip ratio (W / H) to characterize the type of distribution of adipose tissue, body mass index.

2) 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.

3) 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 colpos copy 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). [14]

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. [15]

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. [16]

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. [17]

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. [18]

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. [19]

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. [20]

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. [21]

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 (table 1) depending on the diagnosed phenotypes.

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

TABLE 1. SIGNS OF MAJOR PCOS PHENOTYPES

| | n | Hyperandrogenemia | Anovulation | RMB | AMG | Metabolic traits |
|--------------------|----|-------------------|-------------|-----|--------------------|------------------|
| Phenotype A | 62 | YES | YES | YES | Elevated | YES |
| Phenotype B | 40 | YES | YES | NO | Unknown | YES |
| Phenotype C | 32 | YES | NO | YES | Slightly increased | Slight |
| Phenotype D | 16 | 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). [22]

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. [23]

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. [24]

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%): [25]

- 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. [26]

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). [27]

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. [28]

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 mmindiameter |
| 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. [29]

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 |
| Bloodglucose(mmol/l) | 6,7±1,5* | 6,1±1,9* | 6,5±1,1* | 5,7±1,0* | 4,8±1,0 |
| Glycosylatedhemoglobin(%) | 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 \pm 1,7 * | 25,0 \pm 1,5 * | 20,5 \pm 1,1 * | 22,1 \pm 1,1 * | 18,1 \pm 1, 7 |
|---------------------------------------|---------------------|---------------------|---------------------|---------------------|--------------------|

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

The average level of homocysteine in patients with PCOS was $10.8 \pm 1.4 \mu\text{mol} / \text{L}$, 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 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 / m² and below. [30]

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). [31]

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 canceled 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. [32]

Thus, we achieved natural restoration of fertility in only 133 women with PCOS. 17 patients were referred for IVF.

CONCLUSIONS

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 leads 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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