

# Clinical Prediction of the Development of Infertility in Women with Polycystic Ovary Syndrome

Shokirova Sadokathon Muhammatsolievna

Andijan State Medical Institute, Andijan, Uzbekistan

**Abstract** In this study, women with non-endocrine factors of infertility (tube - peritoneal and endometriosis) without tumor-like formations or functional ovarian cysts, with PCOS (Polycystic Ovarian Syndrome) background and complaining of infertility against PCOS background were studied being divided into groups. The age gradation of the examined women was significant in the groups. Anamnestic data showed that the age of menarche in all groups of women corresponds to the indicators of a healthy population. In women with PCOS, menstrual disorder in the oligomeric type was found, and the duration of the menstrual cycle was from 36 to 240 days. According to the results of hormonal and ultrasound examination, anovulation was noted in these patients. The obtained results allow predicting the development of infertility in patients with PCOS. Risk factors for the development of infertility in women with PCOS: age older than 30 years, history of infertility, no ovarian surgery, high body mass index (obesity), ovarian volume less than 3 cubic cm, antral follicular number less than 5, PI in ovarian stromal arteries and Low IR indicators were found.

**Keywords** Infertility, Endocrine system, Endometriosis, Polycystic ovary syndrome, Age gradation, Menstrual cycle, dopplerometry, Antral follicular, Stromal artery, Tumorous ovary, Hyperandrogenism syndrome, Prospective analysis, Ovarian cysts, Gonadotropins, Sex steroids, Ovulation, Oligomenorrhea, Amenorrhea, Anovulation, Gastogens, Spontaneous menstruation

## 1. Introduction

All over the world, women are one of the main branches of the chain of life. Because women play a major role in the continuation of the human race. A woman becomes pregnant and gives birth to a child one or more times based on the complex structure and uniqueness of her body. Millions of women around the world become mothers every year, but there are women in society who are deprived of such happiness. There are various causes and factors of female infertility. They can be external and internal influences, unfortunate events that happened during life. Among such causes and factors, the most important are various hereditary and acquired diseases. In our research, we have studied several diseases and factors that cause female infertility. We have obtained a number of results mainly by analyzing women's gynecological diseases and studying them in depth, as well as conducting observations and examinations. On the basis of our results, we developed criteria for clinical prediction of the causes of infertility in women directly related to the ovaries, that is, ovarian diseases. We conducted our research mainly by studying the medical history of

several women who were treated for infertility with polycystic ovary syndrome and obtaining analysis from them.

Polycystic ovary syndrome is an endocrine pathology of the female body, which is characterized by a violation of the menstrual cycle with the absence of ovulation and, as a result, an increase in the level of male sex hormones - androgens [8,9,5,7,10,11]. The disease is also called Stein-Leventhal syndrome or non-tumor ovarian hyperandrogenism syndrome. According to international medical statistics, the prevalence of polycystic ovary syndrome varies between 2.5-8%, and the incidence among teenagers is 3 times less than that of girls and women aged 20-45. The highest incidence was observed in women aged 25-30.

## 2. Materials and Methods

We conducted a prospective analysis among 208 women with infertility in order to achieve the research goal and objectives. The age range was from 20 to 40 years, with a mean age of  $29.9 \pm 0.5$  years, that is, all examined women were of active reproductive age. During the examination, women diagnosed with infertility were divided into 3 groups:

Group 1 - 64 women with non-endocrine factors of infertility (tube - peritoneal and endometriosis) without tumor-like formations or functional ovarian cysts;

\* Corresponding author:

shokirova.sadoqat@mail.ru (Shokirova Sadokathon Muhammatsolievna)

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Group 2 – 48 pregnant women with PCOS (Polycystic Ovarian Syndrome);

Group 3 - 96 women diagnosed with infertility on the background of PCOS.

Patients in groups 1 and 2 had a regular ovulatory menstrual cycle against the background of normal indicators of gonadotropins and sex steroids.

All women in group 3 had oligomenorrhoea or amenorrhoea, menstrual cycle disorder of chronic anovulation type, primary or secondary infertility in pregnancy anamnesis. All patients underwent a traditional clinical examination, including anamnesis data, the nature of the menstrual cycle, reproductive function, and a general and gynecological examination. During spontaneous menstruation or when the menstrual cycle was induced with progestogens or COCs, on days 2–4 of the menstrual response, ultrasound examination was performed using a 6.5 mHz transvaginal transducer on the Sonolme Sienmo (Siemens, Germany) machine. The following parameters were determined for each ovary: ovarian volume, number of antral follicles with a diameter of 2-10 mm, dopplermetric indicators of intraovarian blood flow. At the time of examination, all women complained of not becoming pregnant during regular sexual intercourse without using contraceptives for at least 12 months. Age gradation of the examined women did not have significant differences in groups, the average age in group 1 was  $26.7 \pm 0.4$  years, in group 2 -  $28.5 \pm 0.3$  years, and in group 3 -  $26.5 \pm 0.5$  years. The duration of infertility in group 1 is  $2.2 \pm 0.3$  years, in group 2 -  $2.8 \pm 0.4$  years, in group 3 -  $2.6 \pm 0.3$  years. Anamnestic data showed that the age of menarche in all groups of women corresponded to the indicators of a healthy population and averaged  $13.7 \pm 0.3$  years in group 1,  $14.3 \pm 0.2$  years in group 2, and  $14.3 \pm 0.2$  in group 3, 2 years old.  $13.9 \pm 0.3$  years ( $r > 0.05$ ) (Table 1).

When the characteristics of the menstrual cycle were studied, it was found that oligomeric type of menstrual cycle disorder was found in women with PCOS, and the duration of the menstrual cycle ranged from 36 to 240 days ( $139.6 \pm 1.5$  days). According to the results of hormonal and ultrasound examination, anovulation was noted in these patients. Obstetric anamnesis indicators showed that the number of women with first births was similar in all groups.

Women with PCOS had a history of severe gestational complications (pre-eclampsia in previous births) and perinatal losses. Infertility was primary in 69% of women in groups 2 and 3 and in 53% of women in group 2. Among the women of groups 1 and 2, the causes of infertility were distributed as follows, the tube-peritoneal factor and endometriosis prevailed, in the 3rd group, in most cases, anovulation was the only cause of infertility, the coexistence of tube-peritoneal factor with anovulation was detected in women who had previously undergone an operation on the ovary. Prior to this study, 47% of women in group 1 and 54% of women in groups 2 and 3 were screened and treated, respectively. The main reasons for previous surgical interventions on the ovaries in women of group 2: endometrioid ovarian cysts - 62.5% (60 women) and retention derivatives (follicular cysts, corpus luteum cysts) - 27.1% (26 women), as well as other good-quality ovarian tumors derivatives (fibroma, teratoma, cystadenoma) - 10.4% (10 women). The size of the removed ovarian cysts ranged from 1 to 5 cm (average  $2.4 \pm 0.2$  cm). Enucleation of ovarian cysts was performed in 20 cases, resection of ovaries in 28 cases. Bilateral ovarian surgery was performed in 26 (54.2%) women, unilateral - in 22 (45.8%) women. In the 3rd group of women with PCOS, ovarian surgery was performed in 22 (22.9%) women, laparoscopic surgery was used in all cases. The performed operations did not lead to the restoration of menstruation and reproductive functions. In the study of accompanying pathology in the examined women, we found that 14.1% of women (9 out of 64) were overweight, in group 2 - 39.6% (19 out of 48 women), and in group 3 this percentage was significantly higher. 3.2 times and was 47.9% (46 out of 94). The resulting data is presented in Chart 1 below.

### 3. Result and Discussion

As material, a total of 208 cases of women treated with infertility and surgical removal of the ovary were obtained, who underwent outpatient examination at the biopsy department of the Republic of Uzbekistan Center for Pathological Anatomy and the gynecology department of the 2nd maternity complex of Andijan city, and were examined in the MODUS private laboratory.

**Table 1.** Distribution of women in the compared groups by age of menarche (% of the number of examined)

| Women groups       | Average age of menarche | Up to the age 14 |          | Age 15-16 |          | Older than age 17 |         |
|--------------------|-------------------------|------------------|----------|-----------|----------|-------------------|---------|
|                    |                         | N                | %        | N         | %        | N                 | %       |
| Group 1<br>(n= 64) | 13,7±0,3                | 45               | 70,3±4,9 | 16        | 20,0±4,8 | 3                 | 4,7±1,6 |
| Group 2<br>(n= 48) | 14,3±0,2                | 33               | 68,8±5,8 | 12        | 25,0±6,1 | 3                 | 6,3±2,2 |
| Group 2<br>(n= 96) | 13,9±0,3                | 68               | 70,8±4,7 | 24        | 25,0±3,8 | 4                 | 4,2±1,6 |

**Table 2.** Somatic condition of the examined women

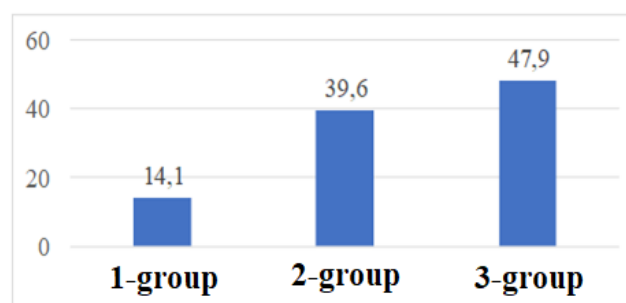
| Indicators                             | Group 1<br>(n= 64) |      | Group 2<br>(n= 48) |       | Group 3<br>(n= 96) |       |
|--|--------------------|------|--------------------|-------|--------------------|-------|
|  | abc.               | %    | abc.               | %     | abc.               | %     |
| Insulin resistance                     | 5                  | 7.8  | 8                  | 16,7* | 19                 | 19,8* |
| Type 2 diabetes (compensation phase)   | 0                  | 0    | 1                  | 1.6   | 3                  | 3.1^  |
| Functional hyperprolactinemia          | 0                  | 0    | 1                  | 2.1   | 4                  | 4.2^  |
| Hypothyroidism                         | 1                  | 1.6  | 1                  | 2.1   | 4                  | 4,2*  |
| Diseases of the cardiovascular system  | 5                  | 7.8  | 17                 | 35,4* | 49                 | 51,0* |
| Diseases of the gastrointestinal tract | 10                 | 15.6 | 12                 | 25.0  | 27                 | 28,1* |
| Anemia                                 | 7                  | 10.9 | 11                 | 22,9* | 23                 | 24,0* |
| Diseases of the urinary system         | 6                  | 9.4  | 9                  | 18,8* | 23                 | 24,0* |
| Respiratory diseases                   | 4                  | 6.3  | 7                  | 14,6* | 20                 | 20,8* |

Note: \* - reliability of data compared to group 1 ( $R < 0.05$ ); ^ - reliability of data between groups 2 and 3 ( $R < 0.05$ )

All patients underwent a traditional clinical examination, including anamnesis data, the nature of the menstrual cycle, reproductive function, and a general and gynecological examination. During spontaneous menstruation or when the menstrual cycle was induced with progestogens or COCs, on days 2-4 of the menstrual reaction, an ultrasound examination was performed using a 6.5 mHz transvaginal probe on the Sonolme Sienmo (Siemens, Germany) machine. The following parameters were determined for each ovary: ovarian volume, number of antral follicles with a diameter of 2-10 mm, dopplermetric indicators of intraovarian blood flow. At the time of examination, all women complained of not becoming pregnant during regular sexual intercourse without using contraceptives for at least 12 months. Age gradation of the examined women did not have significant differences in groups, the average age in group 1 was  $26.7 \pm 0.4$  years, in group 2 -  $28.5 \pm 0.3$  years, and in group 3 -  $26.5 \pm 0.5$  years. The duration of infertility in group 1 is  $2.2 \pm 0.3$  years, in group 2 -  $2.8 \pm 0.4$  years, in group 3 -  $2.6 \pm 0.3$  years. When the characteristics of the menstrual cycle were studied, it was found that oligomeric type of menstrual cycle disorder was found in women with PCOS, and the duration of the menstrual cycle ranged from 36 to 240 days ( $139.6 \pm 1.5$  days). According to the results of hormonal and ultrasound examination, anovulation was noted in these patients. Obstetric anamnesis indicators showed that the number of women with first births was similar in all groups. Women with PCOS had a history of severe gestational complications (pre-eclampsia in previous births) and perinatal losses. Infertility was primary in 69% of women in groups 1 and 3 and in 53% of women in group 2. Among the women of groups 1 and 2, the causes of infertility were distributed as follows, the tube-peritoneal factor and endometriosis prevailed, in the 3rd group, in most cases, anovulation was the only cause of infertility, the coexistence of tube-peritoneal factor with anovulation was detected in women who had previously undergone an operation on the ovary.

The main reasons for previous surgical interventions on the ovaries in 2 groups of women: endometrioid ovarian cysts - 62.5% (60 women) and retention formations (follicular cysts,

corpus luteum cysts) - 27.1% (26 women), as well as other benign ovarian formations (fibroma, teratoma, cystadenoma) - 10.4% (10 women). The size of the removed ovarian cysts ranged from 1 to 5 cm (average  $2.4 \pm 0.2$  cm). Enucleation of ovarian cysts was performed in 20 cases, resection of ovaries in 28 cases. Bilateral ovarian surgery was performed in 26 (54.2%) women, unilateral - in 22 (45.8%) women. In the 3rd group of women with PCOS, ovarian surgery was performed in 22 (22.9%) women, laparoscopic surgery was used in all cases. The performed operations did not lead to the restoration of menstruation and reproductive functions. In the study of accompanying pathology in the examined women, we found that 14.1% of women (9 out of 64) were overweight, in group 2 - 39.6% (19 out of 48 women), and in group 3 this percentage was significantly higher. 3.2 times and was 47.9% (46 out of 94). 1 – diagram

**Diagram 1**

High body mass index indicators are one of the factors that have a negative impact on the course of the disease. The average BMI in group 1 was  $25.1 \pm 1.3$  kg, in group 2 -  $28.9 \pm 1.8$  kg, in group 3 -  $31.2 \pm 2.1$  kg. When comparing TVI indicators, it was proved to be significantly higher in women of groups 2 and 3 ( $R < 0.05$ - $0.01$ , respectively). It can be noted that during the interview, women in group 3 did not record positive results when trying to reduce their weight. The somatic condition of the examined women is characterized by the presence of diseases of the cardiovascular system, which are significantly more frequent in groups 2 and 3 ( $R < 0.05$ ). Gastrointestinal diseases are also significantly

[illegible]

In addition to the prognostic table, based on the obtained set of factors, we determined the range of possible quantities for the development of infertility in patients with PCOS. The possible risk range was determined as follows. In the prognostic table, we find the minimum quantities of the prognostic coefficient (X) for each factor and summarize them. This value is the initial quantity of the risk of this pathology. For example, for a comprehensive evaluation of the development of infertility in patients with PCOS, table 5 shows the minimum and maximum quantities of prognostic indices (X) for all factors: the minimum quantity is 28.2; the maximum quantity is 50.4. In this case, the range of development of infertility in patients with PCOS is in the range of 28.2-50.4. It follows that the higher the quantity of the standard integrated indicator due to the influence of the set of factors under study, the higher the probability of infertility in patients with PCOS and the more reason to include it in the risk group. In this regard, we determined the range of possible risk (28.2-50.4), as well as sub-ranges: weak (28.2-33.2), medium (33.3-43.3) and high (43.4 -50.4) risk of developing infertility in patients. with PCOS. Thus, the threshold quantities of the final prognostic coefficients and the risk group for the occurrence of an unfavorable reproductive prognosis were determined (Table 5).

**Table 5.** Quantity of lower ranges and groups of individual forecasts of the risk of adverse reproductive prognosis

| Under the range     | Sub-range size | Groups of risk |
|---------------------|----------------|----------------|
| Weak probability    | 28.2-33.2      | Low risk       |
| Average probability | 33.3-43.3      | Attention      |
| High probability    | 43.4-50.4      | High risk      |

To determine the diagnostic value of the model for evaluating the development of infertility in patients with PCOS, the following were calculated: diagnostic specificity (DS), diagnostic efficiency (DE), diagnostic sensitivity (DSN), negative predictive quantity (NPQ), predictive quantity according to positive formulas (PQAPF):

$$DS = d/(d + b) \times 100\%,$$

$$DE = (DSN + DE\%) / 2,$$

$$DSN = a / (a + c) \times 100\%,$$

$$NPQ = d/(c + d) \times 100\%,$$

$$PQAPF = a/(a + b) \times 100\%,$$

where a is a real positive result,

b - false positive result;

c - false negative result;

d - a true negative result.

We analyzed data from 144 women with PCOS to test a prognostic matrix for comprehensive assessment of complication risk. Thus, when calculating the size of the lower range, 46 women were assigned to the favorable prognosis group, 35 to the focus group, and 65 to the unfavorable prognosis group. In the observation dynamics, in the group with a favorable prognosis, infertility developed in 3 women (6.5%) - a false negative result, pregnancy occurred in 43 women (93.5%) - a true negative result; in the

group of high-risk women, 5 (7.7%) women recorded pregnancy - a false positive result, 63 women (92.3%) suffered from infertility - a true positive result 6 - in the table.

**Table 6.** Diagnostic quantity to ensure the safety of recommendations for developing infertility in patients with PCOS

| Operational characteristics | Indicators            |
|-----------------------------|-----------------------|
| DS= d/(d+ b)× 100%,         | 43 /(3+43)×100%=93,5  |
| DE = (DSN + DE %) / 2,      | (93,5+92,6)/2=93,1    |
| DSN = a / (a + c) × 100%,   | 63 /(63+5) ×100%=92,6 |
| NPQ=d/(c+ d)× 100%,         | 43 /(3+43)×100%=93,5  |
| PQAPF =a/(a+ b)× 100%,      | 63/(63+5)×100%=92,6   |

According to the obtained data, shown in Table 6, DS is 93.5%, DSN - 92.6% and DE - 93.1%. Thus, one of the important components of an effective strategy for predicting the development of infertility should be an algorithm for comprehensive identification of clinical signs of this pathology in patients with PCOS. Identification of risk factors suggested in patients with PCOS implies greater clinical severity and higher risk of infertility. Also, one of the important components of an effective strategy for predicting the development of infertility should be an algorithm for comprehensive identification of clinical signs of this pathology in patients with PCOS. Identification of risk factors suggested in patients with PCOS implies greater clinical severity and higher risk of infertility.

In conclusion, 45% of patients with infertility problems underwent surgery for benign ovarian cysts (endometrioid cysts, functional cysts, teratomas, etc.), and 63% of them underwent resection of both ovaries mainly laparoscopically.

The results obtained from our studies allow us to predict the development of infertility in patients with PCOS. Risk factors for the development of infertility in women with PCOS: age older than 30 years, history of infertility, no ovarian surgery, high body mass index (obesity), ovarian volume less than 3 cubic cm, antral follicular number less than 5, PI in ovarian stromal arteries and Low IR indicators were found.

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