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FEATURES OF THE BEHAVIOR OF MOLECULAR BIOLOGICAL MARKERS IN POLYCYSTIC OVARIAN DISEASE DEPENDING ON CLINICAL MANIFESTATIONS IN WOMEN WITH INFERTILITY

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Abstract
Despite the fact that there is an active search for new universal diagnostic, therapeutic and/or prognostic molecular biological markers for polycystic ovary syndrome, the problem of full diagnosis and tactics for choosing targeted therapy has not yet been solved.
However, molecular biology research opens up new ways to understand genetic disorders and makes it possible to apply the information obtained in clinical practice. Thus, the study of molecular genetic disorders will allow the development of new targeted drugs, which will contribute to the further development of individualization of therapy for each patient. Of course, the basis for making decisions on treatment tactics will be molecular diagnostics, which, along with the clinical features of the pathological process, will gain more and more knowledge and experience and will contribute to early diagnosis and monitoring of the disease, as well as improved treatment results.
Keyword: polycystic disease, endometriosis, ovary, apoptosis, estradiol, testosterone.

INTRODUCTION

It is known that p53 is a protein that is the product of the TP53 gene. It is involved in the regulation of basic cell functions, such as cell movement through the cell cycle, cell death, differentiation, DNA repair, and blood vessel formation. For its many important functions, it has been called the "guardian of the genome." P53 activates the P21 TS gene, which prevents the transition from phase 01 to phase S of the cell cycle. There are many reports of TP53 mutations in various types of cancer. Due to disruption of the mechanisms of apoptosis, which is controlled by the P53 protein, conditions are created for various cell transformations. [1, 2].

Genetic instability due to disruption of P53-mediated DNA repair contributes to the occurrence of genetic abnormalities leading to chronicity of the pathological process and its consequences. TP53 mutation profiles differ depending on the histological picture of the pathological process, including polycystic ovary syndrome. Based on the above, we conducted research and analysis to study the state of molecular markers depending on the clinical course of polycystic ovary syndrome in women of different groups. The above chapters showed the clinical signs of the women examined quite well. This chapter is devoted to the analysis of the state of molecular markers of polycystic ovary syndrome in women with infertility, depending on the clinical course of polycystic ovary syndrome with consequences [3, 4, 5].

The women in our study were divided into 3 large groups: Group 1 – 64 women with non-endocrine factors of infertility (tubal-peritoneal and endometriosis) with the absence of tumor-like formations or functional ovarian cysts; Group 2 – 48 women with PCOS who became pregnant after treatment and Group 3 – 96 women with infertility due to PCOS. All groups became comparison groups with each other and were collected to comparatively characterize the behavior of molecular markers involved in the pathogenesis of polycystic ovary syndrome. Moreover, it should be noted that women with polycystic disease had concomitant obesity. It should be noted that in recent years, all practical medicine, especially gynecology and endocrinology for the treatment of infertility, is based on already known values that play an important role in achieving the effectiveness of therapy [6].

Thus, polycystic ovary syndrome (PCOS), according to our data and world literature, is based on certain molecular changes. It was shown above in the chapter that proliferative changes in the reproductive organs are of great importance. We examined several molecular markers in stages depending on the different groups. As shown above, first we present data on the study of the expression of the proliferative activity of the Ki-67 antigen, normal and mutant p53 [7, 8].

Purpose of the study:

Analysis of clinical and anamnestic data of primary infertility and clarification of the morphogenesis and specific pathomorphological signs of pathological conditions observed in the ovaries.

MATERIALS AND METHODS

To achieve the aim and objectives of the study, we conducted a prospective analysis among 208 women with infertility. The age range was from 20 to 38 years, the average age was 28.9±0.5 years, that is, all the women examined 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 (tubal-peritoneal and endometriosis) without tumor-like formations and functional ovarian cysts;
Group 2 – 48 pregnant women with PCOS (polycystic ovary syndrome);
Group 3 - 96 women diagnosed with infertility due to TPKS.
Patients of groups 1 and 2 had a regular ovulatory menstrual cycle against the background of normal levels of gonadotropins and sex steroids.
All women in group 3 had a history of pregnancy with oligomenorrhea or amenorrhea, menstrual irregularities such as chronic anovulation, and primary or secondary infertility [10].
All patients underwent a traditional clinical examination, including medical history, the nature of the menstrual cycle, reproductive function, as well as a general and gynecological examination.
In case of spontaneous menstruation or when the menstrual cycle is induced by gestagens or COCs, on the 2-4th day of the menstrual reaction, an ultrasound examination was performed using a 6.5 MHz transvaginal probe on the Sonolme device Sienmo (Siemens , Germany).

RESULTS AND DISCUSSION

An important aspect and great significance in infertility were women with obesity, or rather with metabolic syndrome. It should be noted that in this group of women, obesity was observed in 14% of cases. It is known that metabolic syndrome is one of the factors in the unfavorable course of the disease. Thus, the average BMI values in the first group described were 25.1±1.3 kg/m2. Also, insulin resistance occurred in 7.8% of cases, hypothyroidism in 1 case. As for obese women, which occurred in 14% of cases, we see that these women were characterized by slightly different hyperplastic activity of the ovaries. Thus, molecular studies have shown that high p53 expression was detected in 3% of cases, moderate expression in 44% of cases, and negative expression in 53% of cases. This shows moderate activity of the hyperplastic reaction in obese women. At the same time, Ki -67 expression was detected as moderate expression, which once again confirms a slight hyperplastic reaction; high expression was not detected in this group. Moreover, the 1st group of women was characterized by concomitant diseases, such as cardiovascular system - 8%, gastrointestinal - 16%, anemia - 11%, urinary system - 9%, respiratory diseases - 6% .
As for gynecological diseases, in this group, against the background of unexpressed hyperplasia, the following diseases occur, such as polyps - 8%, pathology of the fallopian tubes - 33%, adhesions in the pelvic area - 3%. With regard to ovarian reserve, the first group had the lowest levels of LH, FSH, estradiol, testosterone, prolactin and progesterone when compared with the data of the other two groups.
The following presents the data from the analysis of women from group 3; these were women with infertility due to polycystic ovary syndrome. Molecular studies have shown that immunohistochemically , during this course of the proliferative process, there is high expression of p53 in 25% of cases, moderate expression of proliferative activity of p53 in 42% of cases, and negative expression in 33% of cases. As can be seen, with this proliferative process there is a high frequency of proliferation activity compared to moderate and negative expression, which explains the pronounced hyperplastic process in women with clinically significant polycystic ovary syndrome.
Thus, moderate expression of Ki -67 in the third group of women is observed in 45% of women, high in 49% of women, and negative in 6% of cases. This marker is a marker of proliferation and is expressed in almost all phases of the mitotic cycle, and reflects the size of the proliferative pool, which proves a more pronounced predominance of proliferative processes in polycystic ovary syndrome in this group of women with polycystic ovary syndrome.
Table 1 presents the results of an immunohistochemical study of polycystic ovary syndrome tissue samples from women in various groups.

Table 1.
Frequency of occurrence of molecular biological markers and their expression in polycystic ovary syndrome (high expression - more than 50% of cells)

Marker	1 group	2 group	3 group
mtp 53	0	14%	25%
Ki -67	18%	31%	49%

As for the second group of patients, which included 48 women with PCOS and who became pregnant after treatment, in this group of women there is still not such pronounced proliferation as in the third group.

Table 2.
Frequency of occurrence of molecular biological markers and their expression in polycystic ovary syndrome (moderate expression - from 10-50% of cells)

Marker	1 group	2 group	3 group
mtp 53	32 %	36%	42%
Ki -67	68%	51%	45%

Table 3.
Frequency of occurrence of molecular biological markers and their expression in polycystic ovary syndrome (negative expression - less than 10% of cells)

Marker	1 group	2 group	3 group
mtp 53	67 %	50%	33%
Ki -67	21%	18%	6%

Clinical studies showed that in the third group of women, compared to the second group, a significantly increased frequency of insulin resistance was revealed (19.8%) compared to 16.7% in the second group, and diabetes mellitus as a diagnosis was identified in women in the third group, almost 3%. cases, further analysis showed that in the third group hyperprolactinemia was detected in 4% of cases, hypothyroidism in 4.2% of cases. And they also have cardiovascular diseases, which occur in 51% of cases, while in the second group - in 35% of cases, diseases of the gastrointestinal tract in the third group occur in 28% of cases, anemia - in 24%, diseases of the urinary system - in 24 % of cases, respiratory diseases - in 21% of cases.
As can be seen from the data presented, the third group of women with polycystic ovary syndrome turned out to be the most complex with concomitant diseases, with a pronounced picture of proliferation and hyperplasia. The analysis showed significant differences between the groups, especially between the second and third groups of women [10, 11].

From the above data, characteristic pronounced clinical and molecular signs of polycystic ovary syndrome have been established, which turned out to be characteristic of women with this pathology. These signs also include the characteristics of the ovarian reserve, where a significant increase in LH levels was observed in women of groups 2 and 3 ($p < 0.05$). In women of the third group, a significant increase in LH values was recorded in relation to the second group ($p < 0.05$). The level of total testosterone in women of the third group was significantly increased when compared with the first and second groups of women ($p < 0.05$).

In the third group of women with PCOS, the average volume of the ovaries and the number of antral follicles turned out to be significantly higher compared to the data of women. All this is explained by pronounced proliferation, that is, ovarian hyperplasia, which can be substantiated by the identified elevated proliferation markers.

Consequently, statistically significant differences were found between the studied groups in such indicators as ovarian volume and the number of antral follicles. From our data it follows that the higher the proliferation and pronounced values of hyperplasia, the higher the likelihood of developing infertility in patients with PCOS.

It was in the third group of women that the highest BMI indicators were observed, which adversely affected the course of the disease in 48% of cases ($p < 0.05$-0.01). It should be noted that when surveyed, women in the third group did not report positive results when trying to reduce their weight. Immunohistochemical studies showed that pronounced hyperplastic activity of the ovaries was detected, which showed the following picture: high p53 expression was detected in 16% of cases, moderate in 57% of cases, and negative in 27% of cases. Thus, high activity of p53+ expression was more common than in groups 1 and 2 of women. Moreover, the expression of Ki -67 was also more common in this group of women than in the first and second groups and amounted to a high expression of 24% of occurrence, which confirms a pronounced hyperplastic reaction.

The second group was characterized by the following immunohistochemical picture: high p53 expression in 14% of cases, moderate expression of p53 proliferative activity in 36% of cases, and negative expression in 50% of cases. Moderate expression of Ki -67 in the third group of women is observed in 51% of women, high in 31% of women, and negative in 18% of cases.

Thus, when comparing clinical, laboratory and molecular data, we emerge a picture of proliferation, which is characterized by three main types of expression, which we can characterize and present in the form of a logically complex picture. Thus, it turned out that high and moderate expression was most characteristic of the 3rd group of women with a severe clinical picture. And for the 1st group of women, a pronounced moderate pattern of proliferation with negative expression of p53 was most characteristic [12, 13].

As shown by the above immunohistochemical studies of the material in combination with clinical and laboratory data, all this allows us to obtain a morphological description of the process, an assessment of the level of proliferation , an assessment of the level of expression of various receptors, which gives an accurate assessment of the further development and prognosis of the pathological process. It should also be noted that IHC studies significantly increase the diagnostic capabilities of morphological studies and are used to identify the exact histogenesis, which makes it possible to objectify the diagnosis, differential diagnosis of neoplasms and hyperplastic and proliferative processes that have morphological similarities [14].

Thus, according to the literature and our data, a promising marker of proliferation is the Ki -67 antigen, which is expressed in almost all phases of the mitotic cycle and, accordingly, reflects the size of the proliferative pool. Thus, we conducted an IHC study aimed at determining the activity of ovarian hyperplasia. During the IHC study, specially synthesized labeled antibodies were added to ovarian tissue samples containing cells with Ki -67 antigens. During the reaction, “antigen-antibody” complexes were formed, which demonstrate the number of cells in the active phase of division, then the index of proliferative activity was calculated, which was indicated as a percentage. It is known that Ki-67 is present in cell nuclei throughout the cell life cycle, except for G0 and G1. The presence of this gene in cells in all phases of the mitotic cycle, the absence during the transition to the resting period and during DNA repair, allows us to consider Ki -67 an ideal marker of proliferation, especially when assessing the activity of the proliferative process, the growth of a tumor or pathological tissue, which has an important role for characteristics of the oncological essence of the tumor and its aggressiveness, in which this indicator can be selected as one of the decisive prognosis factors.

Thus, the detected increased expression of Ki -67 in this study is an independent factor in the proliferative process. A diagnostic and prognostic sign of hyperplasia is the overexpression of the mutant protein mtp 53. A set of signs is often used that allows the properties of the hyperplastic process under study to be clarified as much as possible.

Below we will present the results of studies on immunohistochemical studies of ovarian tissue samples from women with polycystic disease, depending on the three groups of women examined. Thus, it is presented above that all examined women with infertility were divided into 3 groups: group 1 – 64 women with non-endocrine factors of infertility (tubal- peritoneal and endometriosis) with the absence of tumor-like formations or functional ovarian cysts; Group 2 – 48 pregnant women with PCOS; Group 3 – 96 women with infertility due to PCOS. We also adhered to this division into groups and described the state of molecular biological markers depending on different groups of women.

The analysis performed is presented in Table 4. Thus, it is clear that the study of the main CD - markers of lymphocyte differentiation - CD 3+ in women of the first group was not detected in any tissue sample, which indicates that mature lymphocytes with the CD 3+ marker were not identified .

A study of CD 20+ expression in ovarian tissue revealed high, moderate and negative expression in ovarian tissue samples. Thus, high expression of CD 20+ was identified in 25.6% of cases in tissue samples, moderate expression in 28.4% of cases and negative expression in 46%.

Therefore, we can say that the studies did not reveal lymphoid infiltration based on the expression of the CD 3+ marker, which is responsible for lymphoid proliferation. Against this background, a slight lymphoid infiltration of CD 20+ can be traced in samples of women with polycystic ovary syndrome due to infertility, although the bulk of the expression was negative and amounted to 46% of cases.

Further, it is clear that in this group of women there is high interstitial expression of CD 4+ in 27% of cases, moderate in 35% of cases and negative in 38% of cases. This picture indicates the presence of proliferative activity of cells in the ovarian tissue, but to an insignificant extent. That is, we see insignificant production of proliferation mediators, which are

restrained by opportunistic mediators. One of them is CD 8+ expression in ovarian tissue samples, high expression of which was detected in this group of women in 49% of cases, moderate expression in 26% of cases and negative expression in 25% of cases.

It is known from the literature that interstitial expression of CD 8+ is a sign of severe inflammation, this marker indicates a cytotoxic lytic function in the tissue, which is also a pro-inflammatory sign with the production of pro-inflammatory cytokines that will lead to adhesions and scarring.

Consequently, in the first group of women, a predominance of C D 8+ expression over C D 4+ expression was revealed in the ovarian tissue by 1.8 times, which is a sign of a chronic inflammatory process. Moreover, there are women with high expression of CD 20+ in 25.6%, which indicates the presence of proliferative activity characteristic of this group of women. The obtained data are presented in Table 4.

CD4+ Th cells are central organizers of pro-inflammatory and anti-inflammatory immune responses. This inflammatory response within the ovaries leads to the accumulation of numerous follicles without ovulation and PCOS patients experience high levels of estrogen. Thus, it has been confirmed that a significant difference in the Th17/Th2 ratio with a bias towards Th17 is common among patients with PCOS [4,8,72,89]. Consequently, the accumulation of Th1 and Th17 cells leads to immune hyperactivity, which can often lead to the formation of autoimmune inflammation.

Table 4. Features of the expression of molecular biological markers in polycystic ovary syndrome in women with infertility in group 1

Molecular Biology Marker	High expression in more than 50% of cells	Moderate expression from 10% to 50% of cells	Negative expression in less than 10% of cells
CD3 +	0	0	60/100%
CD20 +	25.6%	28.4%	46%
CD4 +	27%	35%	38%
CD 8+	49%	26%	25%

The picture presented above is typical for women of the first group with polycystic ovary syndrome.

Below will be presented the results of women included in the second group of women with polycystic ovary syndrome. The obtained data are presented in Table 5.

As for C D 8+ cells, they are the primary effector cells of the cellular immune system. They cause cytotoxic processes aimed at destroying infected or malignantly transformed cells. As stated above, most often their increased expression leads to inflammatory diseases.

Table 5. Study of molecular biological markers of lymphocytes in polycystic ovary syndrome in women in group 2

Molecular Biology Marker	High expression in more than 50% of cells	Moderate expression from 10% to 50% of cells	Negative expression in less than 10% of cells
CD3 +	16%	15%	69%
CD20 +	44%	35%	21%
CD4 +	37%	21%	42%
CD 8+	34%	49%	17%

Thus, a study of the expression of the main CD - markers of lymphocyte differentiation - CD 3+ in women of the second group revealed the following changes. Thus, high expression of CD 3+ mature lymphocyte markers was identified in 16% of women, moderate expression in 15% of cases and negative expression in 69% of cases.

A study of CD 20+ expression in ovarian tissue revealed high expression in 44% of cases, moderate expression in 35% of cases, and negative expression in 21% of cases. Thus, high expression of CD 20+ was identified in 44% of cases in tissue samples, this is a fairly high value. Moreover, the high expression of CD 20+ was 2.8 times higher than the expression of CD 3+, which once again indicates proliferative activity in the ovarian tissue. Therefore, we can say that the studies revealed lymphoid infiltration by the slight expression of the CD 3+ and CD 20+ marker , which is responsible for lymphoid proliferation within the ovarian tissue against the background of polycystic disease. Moreover, it should be noted that CD 20+ lymphoid infiltration in samples of women with polycystic ovary syndrome against the background of infertility was high, a higher percentage than moderate and negative.

Next, the interstitial expression of CD 4+ was studied, which showed that high expression was detected in 37% of cases, moderate in 21% of cases and negative in 42% of cases. As can be seen, proliferation is observed, which is expressed in the production of the main pro-inflammatory proliferative cytokines.

One of the interesting and important markers of inflammation and proliferation is precisely the imbalance in the expression of CD 8+ in ovarian tissue samples. Thus, high expression of this marker was detected in the second group of women in 34% of cases, moderate expression in 49% of cases and negative expression in 17% of cases.

It is known from the literature that interstitial expression of CD 8+ is a sign of severe inflammation, moreover, chronic inflammation. Consequently, in the second group of women, a predominance of C D 4+ expression over C D 8+ expression was revealed in the ovarian tissue by 1.2 times. Although this is not a big difference, lymphoid proliferation is still visible.

It is known from the literature that the presence of high and moderate expression of CD 4+ indicates the proliferative activity of cells, i.e. in the production of proliferation mediators, which explains the increased proliferation activity against the

background of polycystic ovary syndrome. According to our data, there is a predominance of high expression of C D 4+ over expression of C D 8+, which indicates a proliferative process.
Further, the results obtained from studying the expression of CD - markers of lymphocyte differentiation in the third group of women will be described below. The results obtained are presented in Table 6. Thus, the analysis showed that high expression of CD 3+ in women of the third group was detected in 28% of cases, moderate expression in 40% of cases and negative expression in 32% of cases. Thus, it was shown that the high expression of this marker was insignificant, but turned out to be functional enough to enhance proliferative activity. The obtained research results are presented in Table 6.

Table 6. Study of molecular biological markers of lymphocytes in polycystic ovary syndrome in women in group 3

Molecular Biology Marker	High expression in more than 50% of cells	Moderate expression from 10% to 50% of cells	Negative expression in less than 10% of cells
CD3 +	28%	40%	32%
CD20 +	54%	42%	4%
CD4 +	46%	32%	14%
CD 8+	23%	18%	59%

A study of high expression of CD 20+ in ovarian tissue showed that it was found in 54% of cases, moderate in 42% of cases and negative in 4% of cases. Thus, the high expression of CD 20+ identified in ovarian tissue turned out to be quite significant for increased proliferative activity in this group of women.
From the data obtained it is clear that high expression of CD 20+ prevailed over high expression in frequency of occurrence among women in this group by 2 times higher than the frequency of high expression of CD 3+. Consequently, high expression of CD 20+ occurred 2 times more often in this group, which indicates lymphoid proliferation within the ovarian tissue against the background of polycystic disease and the production of pro-inflammatory cytokines, which reflect pronounced proliferation.
Next, the interstitial expression of CD 4+ was studied, which showed that high expression was detected in 46% of cases, moderate in 32% of cases and negative in 14% of cases. As can be seen, proliferation is observed, which is expressed in the production of the main pro-inflammatory proliferative cytokines due to the frequent occurrence of high expression of CD 4+ among women in this group.
A study of the inflammatory marker CD 8+ in ovarian tissue samples showed that high expression of CD 8+ was found in 23% of cases, moderate expression in 18% of cases, and negative expression in 59% of cases. It is known from the literature that interstitial expression of CD 8+ is a sign of severe inflammation, moreover, chronic inflammation. From our data it follows that the presence of more negative expression of CD 8+ indicates a proliferative process rather than an inflammatory process. Consequently, in the third group of women, a predominance of high expression of C D 4+ over the expression of general C D 8+ was revealed in the ovarian tissue by 2 times, which indicates that there is a pronounced high proliferation in the expression of CD 20+ and CD 3+ in the tissue ovaries.
Above, we were able to analyze the behavior of such molecular patterns as receptors of cells of the adaptive immune system, which consists of T cells and B cells, that is, lymphocytes, especially in the ovarian tissue itself. T lymphocytes are known to participate in the cell-mediated immune response, whereas B lymphocytes primarily mediate the humoral immune response.
We know that the balance of these cells is an important mechanism for maintaining interstitial homeostasis in the ovary. Also, it should be noted that T lymphocytes such as CD 3+, CD 4+ and CD 8+ play a critical role in mediating inflammation by secreting pro-inflammatory cytokines in various metabolic organs and stimulating follicle formation by releasing specific chemokines and growth factors, which promote the development of granule cells and the selection of ovarian follicles, and also send cytotoxic signals.
The results we obtained from studying the behavior of individual populations and subpopulations in ovarian tissue can serve as a diagnostic and prognostic criterion in the diagnosis and understanding of the pathogenesis of proliferative processes, in particular in developing polycystic ovary syndrome. It is also known that IHC markers reflect the functional state of proliferative interstitial cells, which is important in assessing the characteristics of the course and outcome of the pathological process. It should be noted that CD 20+ and CD 4+ turned out to be the most pronounced proliferative marker, which is responsible for the proliferation of cells in the tissue, as well as for the production of proliferative inflammatory mediators that support the active proliferative process. Moreover, concomitant obesity is one of the leading factors determining the frequency and nature of various forms of ovarian proliferative processes. Visceral obesity is important. In this regard, diagnosis and treatment of women with polycystic ovary syndrome should be comprehensive and combine components of hormonal and metabolic therapy.
Next, we tried to identify the characteristic behavior of molecular markers of CD among women with polycystic ovary syndrome depending on different clinical groups. Thus, we carried out a comparative analysis between three groups of women. Thus, our studies have shown that when compared between groups, the following changes are observed.
Thus, for women of group 1, compared with groups 2 and 3, it was characteristic: the absence of CD 3+ expression at all.
CD 20+: high expression occurred 1.7 times less often than in group 2 and 2 times less than in group 3 of women. Moderate expression occurred 1.2 times less often than in group 2 and 1.5 times less often than in group 3. Negative expression occurred 2.2 times more often than in group 2 and 11.5 times more often than in group 3.
CD 4+: high expression occurred 1.4 times less frequently than in group 2 and 1.7 times less often than in group 3 of women. Moderate expression occurred equally with group 2 and 1.2 times less frequently than in group 3. Negative expression was the same as in group 2 and 2.7 times more frequent than in group 3.
CD 8+: high expression occurred 1.4 times more often than in group 2 and 2 times more often than in group 3 of women. Moderate expression occurred 1.8 times less often than in group 2 and 1.4 times more often than in group 3. Negative expression

occurred 1.5 times more often than in group 2 and 2.4 times less often than in group 3.
For women of group 2 it is typical compared to group 3:
High expression of CD 3+ was 1.8 times less common than in group 3. But almost 2 times more often than in group 1. Moderate expression – 2.7 times less common than in group 3. Negative expression is 2.2 times more common than in group 3.
CD 20+: high expression was 1.3 times less common than in group 3. Moderate expression occurred 1.2 times less frequently than in group 3. Negative expression occurred 5.3 times more often than in group 3.
CD 4+: high expression was 1.3 times less common than in group 3 of women. Moderate expression occurred 1.5 times less frequently than in group 3. Negative expression is 3 times more common than in group 3.
CD 8+: high expression was 1.5 times more common than in group 3 of women. Moderate expression occurred 2.7 times more often in group 3. Negative expression was 3.5 times less common than in group 3.
Thus, the comparative analysis of the markers presented above allowed us to identify the following patterns:
The molecular risk factors for the development of infertility in women with PCOS were for 1 group of women: against the background of the absence of CD 3+ expression in the ovarian tissue, high and moderate expression of CD 20+ in 26% and 28.4% of cases, respectively, high and moderate expression of CD 4+ in 27% and 35% of cases, as well as high and moderate expression of CD 8+ in 49% and 26% of cases.
The molecular risk factors for the development of infertility in women with PCOS were for 2 groups of women: against the background of high and moderate expression of CD 3+ in 16% and 15% of cases, high and moderate expression of CD 20+ in 44% and 35% of cases, respectively, high and moderate CD 4+ expression in 37% and 21% of cases, and high and moderate CD 8+ expression in 34% and 49% of cases.
The molecular risk factors for the development of infertility in women with PCOS were for the 3rd group of women: against the background of high and moderate expression of CD 3+ in 28% and 40% of cases, high and moderate expression of CD 20+ in 54% and 42% of cases, respectively, high and moderate CD 4+ expression in 46% and 32% of cases, and high and moderate CD 8+ expression in 23% and 18% of cases.
As you can see, the following molecular signs were characteristic of women with infertility against the background of PCOS, which were manifested by the fact that in group 1 of women, in the foreground there were inflammatory changes, which were accompanied by a slight expression of CD 20+, CD 4+ against the background of pronounced expression of CD 8+ in 49% and 26% of cases, which further confirms our assumption of a chronic inflammatory process.
Women with PCOS and infertility in group 2 were characterized by insignificant expression of CD 3+, often detected expression of CD 20+ and CD 4+ against the background of moderate expression of CD 8+.
For women of group 3 with PCOS, it was detected against the background of pronounced expression of CD 3+ in 28% and 40% of cases, significant expression of CD 20+ in 54% and 42% of cases, and CD 4+ in 46% and 32% of cases, insignificant expression of CD 8 is observed + in 23% and 18% of cases.
Thus, drawing conclusions from the material presented in this chapter, immunohistochemical studies showed that women in group 1 were characterized by: moderate expression of p53 proliferative activity in 32% of cases , negative – in 67% of cases, high – no cases. Moderate expression of Ki-67 is observed in 68% of female cases, high in 18% of female cases, and negative in 21%. This marker is a marker of proliferation and is expressed in almost all phases of the mitotic cycle, and reflects the size of the proliferative pool, which proves the predominance of proliferative processes in polycystic ovary syndrome, all this proves the presence of endometrial hyperplastic processes and metabolic changes. Consequently, there is a predominance of moderate expression of Ki -67 in 68% of cases over high and moderate expression of p53 and Ki -67, indicating little significant hyperplasia and proliferation.
In all groups, women with obesity, or rather with metabolic syndrome, were identified. Molecular studies have shown that high p53 expression was detected in 3% of cases, moderate expression in 44% of cases, and negative expression in 53%. This shows moderate activity of the hyperplastic reaction in obese women. At the same time, the expression of Ki-67 was detected as moderate expression, which once again confirms a slight hyperplastic reaction; high expression was not detected in this group.
Women in group 3 were characterized by: high expression of p53 in 25% of cases, moderate expression of proliferative activity of p53 in 42% of cases, and negative expression in 33% of cases. Moderate expression of Ki-67 in the third group of women is observed in 45% of women, high in 49% of women, and negative in 6% of cases. Consequently, there is a predominance of high and moderate expression of Ki -67 in 49% and 45% of cases over high and moderate expression of p53, which indicates more pronounced hyperplasia and proliferation in the ovarian tissue.
Women in group 2 were characterized by: high expression of p53 in 14% of cases, moderate expression of proliferative activity of p53 in 36% of cases, and negative expression in 50% of cases. Moderate expression of Ki-67 in the third group of women is observed in 51% of women, high in 31% of women, and negative in 18% of cases. Consequently, there is a predominance of moderate expression of Ki -67 in 51% of cases over high and moderate expression of p53, which indicates significantly pronounced hyperplasia and proliferation in the ovarian tissue.
The molecular risk factors for the development of infertility in women with PCOS were for 1 group of women: against the background of the absence of CD3+ expression in the ovarian tissue, high and moderate expression of CD20+ in 26% and 28.4% of cases, respectively, high and moderate expression of CD4+ in 27% and 35% cases, as well as high and moderate CD8+ expression in 49% and 26% of cases.
The molecular risk factors for the development of infertility in women with PCOS were for 2 groups of women: against the background of high and moderate expression of CD3+ in 16% and 15% of cases, high and moderate expression of CD20+ in 44% and 35% of cases, respectively, high and moderate expression of CD4+ in 37% and 21% of cases, as well as high and moderate CD8+ expression in 34% and 49% of cases.
The molecular risk factors for the development of infertility in women with PCOS were for the 3rd group of women: against the background of high and moderate expression of CD3+ in 28% and 40% of cases, high and moderate expression of CD20+ in 54% and 42% of cases, respectively, high and moderate expression of CD4+ in 46% and 32% of cases, as well as high and moderate CD8+ expression in 23% and 18% of cases.
As you can see, the following molecular signs were characteristic of women with infertility against the background of PCOS, which were manifested by the fact that in group 1 of women, in the foreground there were inflammatory changes, which were accompanied by a slight expression of CD20+,

CD4+ against the background of pronounced expression of CD8+ in 49% and 26% cases, which further confirms our assumption of a chronic inflammatory process.
Women with PCOS and infertility in group 2 were characterized by insignificant expression of CD3+, often detected expression of CD20+ and CD4+ against the background of moderate expression of CD8+.
As for women of group 3, it was detected against the background of pronounced expression of CD3+ in 28% and 40% of cases, significant expression of CD20+ in 54% and 42% of cases, and CD4+ in 46% and 32% of cases; insignificant expression of CD8+ was observed in 23% and 18% of cases. cases.

CONCLUSION

In polycystic ovary syndrome, it has been proven that the interstitial tissue of the ovaries degenerates, fibrous tissue grows instead of theca cells, the follicular epithelium around the primordial eggs is highly hyperplastic , numerous cysts appear, this leads to hyperandrogenemia and anovulation , and infertility develops.
In polycystic ovary syndrome , immunohistochemical studies of ovarian tissue showed that the CD3 marker is always negative, CD20 is moderately expressed in half of the cases, negative in half of the cases, CD4 is high in 27%, 32% is moderately expressed, CD8 is highly expressed in 25% , 44% were moderately expressed. The proliferation marker Ki-67 was expressed at a high 18%, average 67.7% and negative 21% level, the apoptosis gene was expressed at an average 33% and negative 67%.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript. The research did not receive specific funding but was performed as part of the employment of the authors (Andijan State Medical Institute, Andijan, Uzbekistan).

Conflicts of Interest

The authors declare no conflicts of interest

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