FEATURES OF REPRODUCTIVE FUNCTION AND SOME IMMUNOLOGICAL PARAMETERS IN WOMEN WITH CHRONIC ENDOMETRITIS

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RELEVANCE

The problem of inflammatory diseases of the pelvic organs in women, in particular endometritis, remains one of the most important problems of gynecological theory and practice for a long time. Currently, this problem has not lost its relevance due to the increase in the frequency of endometritis due to the expansion of various intrauterine manipulations, the increase in the number of abortions, the use of intrauterine contraception, as well as due to the increased frequency of sexually transmitted diseases. We should not also forget about the antibiotic resistance of most microorganism stamps, which leads to the absence of the expected results of treatment.

The particular importance of endometritis is associated with their influence on the reproductive system of women. The role of chronic endometritis (CE) as a cause of infertility, ectopic pregnancy, miscarriage and habitual pregnancy loss is known. Numerous studies have been carried out to study the state of the endometrium in women with a failed abortion, with abnormal uterine bleeding against the background of chronic endometritis. Despite the large number of such works, the problem of effective therapy for ChE and associated reproductive disorders is far from being solved. The frequency of reproductive disorders in women with ChE remains high. So, according to A.L. Frolova et al. the incidence of gynecological inflammatory morbidity has doubled, and the incidence of missed pregnancies annually increases by 7% and even more. This may be due to the fact that the immunological resistance of women with inflammatory diseases of the genitals, the state of the hemostasis system in chronic inflammatory diseases, and the need for their correction in this contingent of patients are still insufficiently studied.

In particular, it was found that one of the main reasons for the failed implantation in IVF programs is a violation of the hemostasis system associated with CE [Rudakova E.B. et al. Pathology of the hemostasis system and chronic endometritis as the cause of IVF failures // Materials of the XVIII annual international conference of RAHR, Samara, September 4-6, 2008]. Pathology of the hemostatic system, which causes defective implantation and impaired placentation, can play a decisive role in predicting reproductive function in patients with ChE.

New diagnostic and therapeutic approaches in the management of women with chronic endometritis and their justification are a reserve for restoring reproductive function and reducing reproductive losses in this contingent of patients.

Purpose of the study: To study the reproductive function, the state of the hemostasis system and some indicators of humoral immunity in patients with chronic endometritis.
I. MATERIAL AND METHODS.

A total of 120 women of reproductive age with impaired reproductive function were examined with a morphologically established diagnosis of chronic endometritis. All patients were divided into 3 groups:

I - main - 40 women with an established diagnosis of ChE and a history of pregnancy loss, who, against the background of conventional therapy, underwent instillation of the uterine cavity with a bacteriophage

II (A) - comparison group - 40 women with an established diagnosis of ChE and a history of pregnancy loss, who received only conventional therapy

II (B) - comparison group - 40 women without a morphologically confirmed diagnosis of CE and a history of pregnancy loss.

The control group consisted of 35 somatically and gynecologically healthy women of reproductive age who applied for the introduction of an IUD.

In order to make the study transparent, inclusion and exclusion criteria were developed.

Inclusion criteria were: reproductive age, history of pregnancy loss. Loss of pregnancy was defined as "chronic" problems of miscarriage, leading to the death of the fetus at different times for the following factors:

• Three or more miscarriages before 8 weeks of pregnancy

• One or more non-developing pregnancies, miscarriage in the period of 10 or more weeks

• Neonatal death of a morphologically normal fetus in preterm labor or pre-eclampsia

• Intrauterine fetal death

The exclusion criteria were: age 45 and older, the presence of somatic and gynecological pathology that could lead to the loss of pregnancy (obesity, thyroid disease, APS, uterine myoma, endometriosis, endometrial hyperplastic processes).

When examining the patients, they paid attention to their age, studied the complaints presented, the peculiarities of the formation of menstrual function, the peculiarities of the menstrual function after the diagnosis of chronic endometritis, sexual behavior, studied the possibilities and use of various methods of contraception, paid attention to the history of sexually transmitted diseases, and methods of their treatment. Close attention was paid to reproductive function and its disorders, as well as the presence of concomitant somatic pathology, methods and effectiveness of their treatment.

The generally accepted gynecological research methods included examination of the external genital organs, examination of the vaginal part of the cervix using Cuzco mirrors, during the bimanual examination, the position of the uterus, its size and consistency, mobility, soreness were noted, as well as the state of the uterine appendages area - the presence of poly , formations, heaviness, seals.

The studies were carried out in the Central Research Laboratory of the Andijan State Institute (Head Prof. Aleinik A.) In the blood and scrapings from the uterine cavity before and after treatment with bacteriophage, the indicators of interleukins were determined: proinflammatory - interleukin-1β (IL-1β), tumor necrosis factor -α (TNF-α), and anti-inflammatory - interleukin-10 (IL-10), as well as secretory immunoglobulins A (sIgA) by ELISA using test systems of ZAO "Vector-Best" (Russia), as well as transforming growth factor -β1 (TGF-β1) by ELISA using test systems "DRG" (Germany).

In the same laboratory, some hemostasiological parameters were determined. To assess the state of the hemostasis system in our study, we used modern methods and tests that characterize the main processes in the most important links of this system - procoagulant, platelet, fibrinolytic and blood coagulation inhibitors. Blood was taken from the cubital vein into a test tube with an anticoagulant in a ratio of 9: 1. Anticoagulant - 3.8%
solution of trisodium citrate. When centrifuged at 1500 rpm for 7 min, platelet-rich plasma was obtained. When centrifuged at 3000 rpm for 10 min, platelet-free plasma was obtained.

A) To assess the procoagulant link of the hemostasis system, the concentration of fibrinogen in the blood plasma was determined; activated partial thromboplastin time (APTT), which characterizes the total activity of blood coagulation factors (except VII, XIII) under conditions of standard activation of contact factors - XI, XII; prothrombin time and index, which characterize the total activity of factors that make up the external mechanism of blood coagulation. In modern conditions, in order to more accurately characterize the prothrombin time and index, the INR is determined - the international normalized ratio or. INR was calculated by the formula:

\[ \text{INR} = \frac{(\text{PV patient})}{(\text{PV control})} \times \text{MIC} \]

Where INR is the international normalized ratio;

PV patient - patient's prothrombin time

PT control - prothrombin time is normal

MIC - international index of sensitivity, an indicator of the sensitivity of thromboplastin relative to the international standard

B) The platelet link of the hemostasis system was studied by measuring the number of platelets in the peripheral blood. The platelet aggregation activity was studied using an automatic two-channel aggregometer ALAT-2 230-2LA (Russia) by the Born photometric method with collagen stimulation. The aggregometer has a built-in microprocessor and is controlled from a computer via a USB port. The program was run on a Windows XP PC.

C) D-dimer was investigated to exclude / confirm the presence of signs of intravascular coagulation. D-dimer is a product of fibrin degradation, i.e. this indicator is a specific marker of the breakdown / degradation of fibrin clots and fibrinolysis. It is known that in pregnant women, the level of D-dimer gradually increases, reaching a maximum during childbirth, but from the third day after childbirth, it begins to decline and returns to normal at the end of the postpartum period.

D) The link of blood coagulation inhibitors was investigated by determining the activity of antithrombin III. Antithrombin III (AT-III) is the main component of the blood anticoagulation system, i.e. natural anticoagulant. Formed in the liver. Due to the formation of the heparin-AT-III complex, it neutralizes thrombin and some activated blood coagulation factors, thus preventing thrombus formation. The determination of AT-III was carried out on an automatic analyzer of hemostasis parameters APG2-02-P (Russia) by the method of kinetic colometry using a chromogenic substrate.

II. RESULTS.

The average age of the examined women with chronic endometritis (there were 80 of them in the study) was 27.2 ± 1.8 years, with fluctuations from 25 to 35 years. The data on the reproductive function of these patients by history are presented in Table 1.
As can be seen from this table, the history of the examined patients had both childbirth and artificial termination of pregnancy, which could not but affect the development of ChE. Despite the fact that, on average, for every woman with ChE there were more than 3 pregnancies, 22.5% of them had infertility. At the same time, 4 patients (5%) suffered from primary infertility, and 14 (17.5%), respectively. It should be noted that there were no complaints of infertility in the comparison group, as well as in the history of the patients in the comparison group there was no ectopic pregnancy and cystic drift. Although the average age at the onset of sexual activity in both groups did not differ significantly, nevertheless, the patients with ChE showed a slightly earlier onset of sexual relations.

With the same frequency in both groups there was anemia, 22.5% each. Also in both groups there were chronic foci of infection with the same frequency: chronic respiratory diseases - 11.3% and 10%, respectively; urinary tract infections - 10% in each group; oral cavity infections - carious teeth, gingivitis - 10% and 12.5%, respectively. Thus, we did not reveal significant differences in the frequency of somatic pathology in patients with ChE and in the comparison group.

Table 2 presents data on the transferred gynecological diseases (according to the anamnesis).

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Groups I, IIA n = 80 (abs.,%)</th>
<th>Group II B n = 40 (abs.,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VZOMT</td>
<td>57 (%)</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Vaginal infections:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td>49 (%)</td>
<td>five (%)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>17 (%)</td>
<td>-</td>
</tr>
<tr>
<td>Tank . In aginosis</td>
<td>21 (%)</td>
<td>five (%)</td>
</tr>
<tr>
<td>Benign diseases of the cervix</td>
<td>27 (%)</td>
<td>6 (%)</td>
</tr>
<tr>
<td>Myoma of the uterus</td>
<td>-</td>
<td>2 (%)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>-</td>
<td>five (%)</td>
</tr>
<tr>
<td>Cysts and cystoma ovaries</td>
<td>fourteen (%)</td>
<td>2 (%)</td>
</tr>
</tbody>
</table>

During an objective examination of patients with somatic pathology, which could lead to impaired reproductive function, we did not find (this was one of the conditions for inclusion in the study), the condition of all patients was assessed as satisfactory.

Gynecological examination (outside of pregnancy) revealed the following abnormalities: in 30 % of patients (24 patients) in the main group , pain in the uterus was found when moving. In the comparison group, we did not observe such a symptom in any case. Limited mobility of the uterus was found in 7 women of the main group, which amounted to 8.8%. Also, this symptom was not observed in the comparison group. Severity in the area of the uterine appendages on one or both sides, tenderness to palpation was detected only in 6 patients of the main group, which amounted to 7.5% . At the first examination, we observed pathological leucorrhoea from the genital tract in almost all women in the main group (78 - 97.5%), versus 11 patients in the comparison group (27.5%). At the same time, in the main group, leucorrhoea had the character of pus-like and cloudy-mucous, flowing out in 62 women out of 78 (79.5%) from the cervical canal. In contrast, in comparison abnormal leucorrhoea group were mainly in the form of vaginal secretions cheesy (y 7 women - 17.5%) and white abundant (diagnosed tank . in aginooz - in 4 patients that was 19% with respect to all surveyed in this group).

Diseases of the cervix were found in both groups of patients - in 30 (37.5%) and 6 (15%), respectively. All these patients underwent extended colposcopy and PAP tests. The structure of cervical diseases is shown in Figure 1 .

Rice. 1 . The structure of cervical diseases in the examined women.

( with making a diagram)

The main group ( n = 80): cervical erosion 8 (10%); polyp of the cervical canal - 5 (6.3%); endocervicitis - 10 (8%); CIN I - II - 7 (8.8%)
Comparison group (n = 40): cervical erosion 2 (5%); polyp of the cervical canal -1 (2.5%); CIN I - 3 (7.5%).

The data in Figure 1 allow us to conclude that both background and precancerous diseases of the cervix are significantly more common in patients with chronic endometritis. This allows them to be attributed to the risk group for the development of precancerous and oncological diseases of the cervix.

As a result of immunological studies of blood in women with reproductive dysfunction compared with healthy women (control group) it was found that the rate of secretory immunoglobulin (sIgA) in the control group was 7.1 ± 0.9 mg / l. At the same time the rate in women with reproductive dysfunction, without chronic endometritis, was not significantly lower than in healthy women and is equal to 6.5 ± 0.5 mg / l. In this study of sIgA in women with reproductive dysfunction and chronic endometritis to standard treatment was 3.6 ± 0.3 mg / L, which was significantly lower than in healthy women. After standard treatment this figure with respect to those before the standard treatment was at level 4.0 ± 0.40 mg / l, which was not significantly higher with respect to performance of the standard treatment. Nevertheless, in women with impaired reproductive function and chronic endometritis, before intrauterine treatment with a bacteriophage, the sIgA index was 3.9 ± 0.32 mg / l, and after treatment with a bacteriophage it significantly increased compared to the indicators before the proposed treatment and was equal to 5.3 ± 0.45 mg / l (Table 3).

Table 3. Changes in blood immunological parameters in women with reproductive dysfunction

<table>
<thead>
<tr>
<th>groups surveyed</th>
<th>Fence procedure</th>
<th>sIgA (mg / l)</th>
<th>TNF-α (pg / ml)</th>
<th>IL-1β (pg / ml)</th>
<th>IL-10 (pg / ml)</th>
<th>TFR-β1 (ng / ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>I fence</td>
<td>7.1 ± 0.9</td>
<td>4.9 ± 0.6</td>
<td>2.2 ± 0.3</td>
<td>4.1 ± 0.5</td>
<td>224.2 ± 27.4</td>
</tr>
<tr>
<td>Comparison group (II B)</td>
<td>I fence</td>
<td>6.5 ± 0.54</td>
<td>5.6 ± 0.49</td>
<td>3.1 ± 0.32</td>
<td>3.3 ± 0.34</td>
<td>196.3 ± 21.2</td>
</tr>
<tr>
<td>Subgroup II A</td>
<td>I fence</td>
<td>3.6 ± 0.32 *</td>
<td>8.81 ± 1.09 *</td>
<td>4.5 ± 0.51 *</td>
<td>1.7 ± 0.22 *</td>
<td>131.7 ± 12.3 *</td>
</tr>
<tr>
<td></td>
<td>II fence</td>
<td>4.4 ± 0.4</td>
<td>7.28 ± 0.9</td>
<td>3.7 ± 0.41</td>
<td>2.3 ± 0.26</td>
<td>148.0 ± 15.3</td>
</tr>
<tr>
<td>Main group</td>
<td>I fence</td>
<td>3.9 ± 0.32 *</td>
<td>9.4 ± 1.08 *</td>
<td>4.7 ± 0.44 *</td>
<td>1.6 ± 0.2 *</td>
<td>120.6 ± 11.1 *</td>
</tr>
<tr>
<td></td>
<td>II fence</td>
<td>5.3 ± 0.45 **</td>
<td>6.2 ± 0.68 **</td>
<td>3.3 ± 0.36 **</td>
<td>2.8 ± 0.31 **</td>
<td>178.3 ± 18.7 **</td>
</tr>
</tbody>
</table>

* - significantly different values in relation to healthy women.

** - significantly different values in relation to I blood sampling - before treatment.

The data in Table 3 indicate the following. When studying the indicator of pro-inflammatory interleukin, tumor necrosis factor d - α (TNF-α), in healthy women in the blood it was at the level of 4.0 ± 0.5 pg / ml. And in women with reproductive dysfunction, without chronic endometritis, PhH α was not significantly higher than in healthy and was 5.6 ± 0.49 pg / ml. At the same time, in women with impaired reproductive function and chronic endometritis, before standard treatment, this indicator was significantly higher than in healthy women and was at the level of 8.1 ± 0.91 pg / ml. After standard treatment, the FN O-α index in relation to similar results before standard treatment was slightly lower and amounted to 7.28 ± 0.9 pg / ml. At the same time, women with reproductive dysfunction and chronic endometritis before intrauterine processing bacteriophage FN O-α was 9.4 ± 1.08 pg / ml, and after treatment with bacteriophage significantly decreased relative to that of before the treatment and amounted to 6.2 ± 0.68 mg / l.

A similar trend in the change in indicators was noted in the study of proinflammatory interleukin-1 β (IL-1β) in the blood, which manifested itself in a slight increase in this indicator in women with impaired reproductive function, without chronic endometritis in relation to healthy women. Also, IL-1β did not significantly decrease in women with impaired reproductive function and chronic endometritis after standard treatment, in relation to similar results before standard treatment. As for women with impaired reproductive function and chronic endometritis, after treatment with bacteriophage, IL-1β significantly decreased in relation to indicators before standard treatment.

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From these research results antiinflammatory interleukin 10 ( IL-10) in the blood, it was found that in healthy women it was $4, 1 \pm 0, 5 \text{ pg} / \text{ml}$. And in women with reproductive dysfunction, without chronic endometritis, it was at a level of $3, 3 \pm 0, 34 \text{ pg} / \text{ml}$, which is slightly lower than in healthy women. At the same time in women with reproductive dysfunction and chronic endometritis, to the standard treatment, the IL-10 was $1, 7 \pm 0, 22 \text{ pg} / \text{ml}$, which was significantly lower than in healthy women. After the standard treatment, this indicator was $2, 3 \pm 2, 6 \text{ pg} / \text{ml}$, which did not differ significantly from similar results before the standard treatment. Thus, women with reproductive dysfunction and chronic endometritis before intrauterine processing bacteriophage display IL-10 in blood was equal to $1, 6 \pm 0, 2 \text{ pg} / \text{ml}$, and after treatment with bacteriophage was $2, 8 \pm 0, 31 \text{ mg} / \text{L}$, it was significantly more significant in relation to the parameters before treatment with the bacteriophage.

The index of transforming growth factor-β1 ( TGF-β1) of the blood underwent the direction of changes similar to IL-10. There was no significant decrease in TGF-β1 in women with impaired reproductive function, without chronic endometritis in relation to healthy women. Some, but not significant, increase in this indicator took place in women with reproductive dysfunction and chronic endometritis after standard treatment, compared with similar results before standard treatment. After bacteriophage treatment, women with reproductive dysfunction and chronic endometritis showed a significant increase in TGF-β1 in relation to those of women with standard treatment.

According to the results of the study and changes in the immunological parameters of scraping from the uterine cavity, a unidirectional change in the studied parameters, similar to changes in the blood, was established. In women with impaired reproductive function without chronic endometritis, the sIgA value was not significantly lower than in healthy women. The same indicator in women with impaired reproductive function and chronic endometritis, after standard treatment, was not significantly higher in relation to similar results before standard treatment. At the same time, women with the same disorders after treatment with bacteriophage had significantly higher sIgA index in relation to those before treatment. Data on the immunological parameters of the discharge from the uterine cavity are presented in Table 4.

Table 4 Changes in the immunological parameters of aspirate from the uterine cavity in women with impaired reproductive function

<table>
<thead>
<tr>
<th>groups surveyed</th>
<th>Fence procedure</th>
<th>sIgA (mg/l)</th>
<th>TNF-α (pg/ml)</th>
<th>IL-1β (pg/ml)</th>
<th>IL-10 (pg/ml)</th>
<th>TFR-β1 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>I fence</td>
<td>51.5 ± 5.7</td>
<td>36.4 ± 4.1</td>
<td>152.6 ± 16.8</td>
<td>28.1 ± 3.1</td>
<td>1033.7 ± 120.3</td>
</tr>
<tr>
<td>Subgroup II B</td>
<td>I fence</td>
<td>44.3 ± 3.9</td>
<td>42.6 ± 4.3</td>
<td>175.6 ± 16.5</td>
<td>25.3 ± 2.4</td>
<td>911.4 ± 98.5</td>
</tr>
<tr>
<td>Subgroup II A</td>
<td>I fence</td>
<td>29.2 ± 3.1</td>
<td>68.1 ± 7.4</td>
<td>257.4 ± 26.9</td>
<td>11.9 ± 1.4</td>
<td>402.8 ± 43.3</td>
</tr>
<tr>
<td></td>
<td>II fence</td>
<td>35.2 ± 3.7</td>
<td>59.6 ± 6.3</td>
<td>219.3 ± 23.1</td>
<td>16.3 ± 1.8</td>
<td>535.3 ± 58.6</td>
</tr>
<tr>
<td>Main group</td>
<td>I fence</td>
<td>26.9 ± 2.6</td>
<td>79.8 ± 8.2</td>
<td>282.8 ± 26.4</td>
<td>13.5 ± 1.5</td>
<td>455.8 ± 47.9</td>
</tr>
<tr>
<td></td>
<td>II fence</td>
<td>39.4 ± 3.5</td>
<td>49.0 ± 4.8</td>
<td>169.8 ± 18.5</td>
<td>22.3 ± 2.5</td>
<td>770.8 ± 80.5</td>
</tr>
</tbody>
</table>

* - significantly different values in relation to healthy women.

** - significantly different values in relation to the indicators before treatment (I blood sampling).

The change in the FN O-α index of aspirate from the uterine cavity was manifested in a higher, but not significant value in women with reproductive disorders without chronic endometritis, compared with the results of healthy women. In addition, in an insignificant decrease in FN O-α after standard treatment of women with impaired reproductive function and chronic endometritis, in relation to similar results before standard treatment. In women, the aspirate from the uterine cavity after treatment with bacteriophage showed significantly lower FN O-α values in relation to similar indicators before treatment.

Similar changes were observed in women with impaired reproductive function and without chronic endometritis, when examined in aspirates from the uterine cavity of IL-1β, which were expressed in an insignificant increase.
in this indicator in relation to healthy women. Also, IL-1β decreased slightly in women with impaired reproductive function and chronic endometritis after standard treatment, in relation to similar results before standard treatment. After treatment with a bacteriophage, women with impaired reproductive function and chronic endometritis showed a significant decrease in IL-1β in aspirates from the uterine cavity in relation to those before treatment.

The results of the study of the immunological parameters of IL-1 0 in the composition of the aspirate from the uterine cavity showed that in women with impaired reproductive function, without chronic endometritis, this indicator was slightly lower than in healthy women. At the same time, in women with impaired reproductive function and chronic endometritis after standard treatment, there was a slight, but not significant increase in IL-1 0 in aspirate from the uterine cavity, in relation to similar results before standard treatment. However, after treatment with bacteriophage in women with reproductive dysfunction and chronic endometritis there was a significant increase in IL-1 0 in scraping x from the uterus with respect to indices before treatment.

In the composition of the aspirate from the uterine cavity, the TGF-β1 indices in women with impaired reproductive function, without chronic endometritis, practically did not differ from those in healthy women. In women with impaired reproductive function and chronic endometritis after standard treatment, there was an increase in TGF-β1 in the composition of scrapings from the uterine cavity compared to similar results before standard treatment, but these data were not reliable. And in women with impaired reproductive function and chronic endometritis after treatment with bacteriophage, a significant increase in TGF-β1 was observed in relation to the indicators before treatment.

III. CONCLUSION.

The study allows us to conclude that in the presence of ChE, the patients can be attributed to the risk group for the development of reproductive dysfunctions. These disorders are manifested by primary and secondary infertility, miscarriage (premature birth, spontaneous abortion, undeveloped pregnancy), ectopic pregnancy and trophoblastic diseases. In this case, there is a decrease in the function of the main links of humoral immunity. The inclusion of intrauterine administration of staphylococcal toxoid into the complex of treatment led to an improvement in the parameters of immunity. The influence of this method of treatment on the reproductive function of women with ChE requires further study.

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