

The State of the Hemostasis System in Women with Impaired Reproductive Function against the Background of Chronic Endometritis

Nigmatshaeva Aziza Ravshanovna

Department of Obstetrics and Gynecology, Andijan State Medical Institute, Andijan, Uzbekistan

Abstract The problem of chronic inflammatory diseases of the small (CIDS) of the pelvis is an actual problem of modern science and gynecological practice. This is due to an increase in sexually transmitted infections, an increase in the number of diagnostic and therapeutic intrauterine manipulations, artificial and spontaneous abortions, as well as the antibiotic resistance of most of the antimicrobial drugs used in the treatment of CIDS, found in recent years. In this case, chronic endometritis (CE) is of particular importance due to the difficulties in diagnosis and treatment, and frequent relapses. Undoubtedly, CE has a significant effect on a woman's reproductive function, leading to habitual loss of pregnancy, miscarriage, ectopic pregnancy, infertility, as well as menstrual dysfunction. It was found that due to CE, the frequency of missed pregnancies increases by 7% every year.

Keywords Hemostasis system, Reproductive function, Gynecology, Chronic endometritis, Pregnancy prevention

1. Introduction

At the same time, it was found that one of the main reasons for 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 CE. New diagnostic and therapeutic approaches based on the study of the hemostasis system 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 state of the hemostasis system and determine the possibilities of its correction in the management of patients with reproductive dysfunction against the background of chronic endometritis.

2. 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 CE 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 intrauterine contraceptive.

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).

During the examination, the patients 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 a 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.

All patients underwent sonographic examination of the pelvic organs and morphological examination of the endometrium, as the "gold standard" for the diagnosis of CE. According to the sonography data, a significant tendency to an increase in the size of the ovaries in the main group of patients was established, which may be an indirect sign of the inflammatory process. However, there were no significant differences in the M-echo value in the main group compared with healthy women. Among other ultrasound signs of chronic endometritis, diffuse changes in the myometrium should be noted, found in 62 (77.5%) patients with chronic endometritis and only in two patients of the control group (5.7%) ($p < 0.01$). This sign with great reliability can also be defined as a sign of the inflammatory process. Such general criteria for the inflammatory process of the pelvic organs as vasodilation of the parametrium and the presence of foci of calcification in the myometrium (in our study, they took place in 29 -36.3% of women with chronic endometritis and impaired reproductive function and were not found in healthy women). attributed to the diagnostic and prognostic criteria of CE ($p < 0.01$).

As for the ultrasound "findings" in the course of the study, the following concomitant diseases of the pelvic organs were found: functional ovarian cysts - 17 (21.3%) examined with CE and 4 (11.4%) in the control group; ovarian cystomas - 2 (2.5%) in women with CE and were not observed in the control group; intramural uterine myoma - 5 (6.3%) and 1 (2.9%) in both groups, respectively. Thus, long-term anti-inflammatory treatment, changes in hormonal levels were predictive factors for the risk of developing benign tumors of the uterus and uterine appendages, as well as functional ovarian cysts in patients with impaired reproductive function against the background of chronic endometritis.

The study of the hemostasis system was carried out in the Central Research Laboratory of the Andijan State Medical Institute (head of the laboratory - prof. V. Oleinik).

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. 1500 by centrifugation on / min 7 min to give a plasma rich in platelets. 3000 by centrifugation on / min for 10 minutes, was prepared bestrombotsitnuyu plasma.

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:

$$\text{INR} = (\text{PV}_{\text{patient}}) : (\text{PV}_{\text{control}}) \times \text{MI},$$

Where INR is the international normalized ratio;

PT_{patient} - prothrombin time of the patient

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-2 230-2 LA (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 (A T - III) - the main component anticoagulative system of blood, i.e., natural anticoagulant. Formed in the liver. Due to the complex formation heparin A T - III neutralizes thrombin and certain activated clotting factors, thus prevents thrombus formation. Definition A T - III were performed on an automated analyzer hemostasis APG2-02-II (Russia) kinetic method kolometrii using a chromogenic substrate.

3. Results

The average age of the surveyed 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. Data on the reproductive function of these patients by history are presented in Table 1.

Table 1. Reproductive function of patients with ChE

Index	Groups I, IIA n = 80 (M ± m)	Group II B n = 40 (M ± m)
Age	27.2 ± 1.8	26.1 ± 2.0
Average age of sexual debut	19.2 ± 1.4	20.1 ± 0.5
Duration of infertility	2.5 ± 1.5 years	-
Number of pregnancies	3.1 ± 1.6	2.2 ± 1.1
Number of births	0.91 ± 0.4	2.1 ± 0.7
Number of premature births	0.71 ± 0.6	0.22 ± 0.3
Number of spontaneous abortions	3.11 ± 1.1	1.2 ± 0.8
Number of induced abortions	0.23 ± 0.55	0.3 ± 0.2
Ectopic pregnancy (abs,%)	4 (5%)	-
Trophoblastic disease (abs,%)	1 (1.25%)	-

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 CE. 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 CE showed a slightly earlier onset of sexual relations.

The state of the hemostasis system in the examined women.

The data of the hemostatic system in patients with ChE

were compared with those of healthy women of childbearing age.

When analyzing the procoagulant link of the hemostatic system (Table 2) before treatment, there was a significant shortening of APTT (20.1 ± 0.2 sec, $p < 0.01$), an increase in INR ($p < 0.01$), which convincingly indicated an increase in activity of procoagulants (clotting factors). At the same time, the concentration of fibrinogen did not differ significantly from that of healthy women ($p > 0.05$).

When analyzing the state of the platelet link of the hemostasis system in patients with CE before treatment, there was an increase in the intensity of maximum collagen aggregation by 18% ($p < 0.05$), which indicates an increase in platelet aggregation activity in patients with CE. At the same time, the number of platelets did not differ significantly from the values of this indicator in healthy women ($p > 0.05$).

In the study of the natural anticoagulant cofactor heparin - antithrombin III - about a significant decrease in its activity (AtIII - 51%, $p < 0.05$), indicating a significant decrease in overall anticoagulant potential of the blood in patients with chronic treatment of endometritis.

Assessment of the level of D - dimer, gives an indication of the concentration of fibrin degradation products, showed that the rate is more, than 4 times higher than in healthy women.

As seen from the table in women with reproductive dysfunction and without chronic endometritis D - dimer was N and level indicators healthy women ($163, 5 \pm 13, 5$ ng / m l), i.e. there were no significant differences. After standard treatment this figure ($320, 5 \pm 20, 7$ ng / m l) in women with reproductive dysfunction and chronic endometritis significantly decreased with respect to similar results to the standard treatment ($368, 5 \pm 14, 5$ ng / m L)... At the same moment women with reproductive dysfunction and chronic endometritis after treatment bacteriophage significant lowering of D - dimer ($291 \pm 17, 4$ ng / m L) relative to that of ($374 \pm 25, 3$ ng / m L) to the proposed treatment... It follows from this that a more radical and effective treatment of CE leads to an improvement in the main indicators of blood coagulation.

Table 2. Changes in hemostasis indicators in women with CE and reproductive dysfunction

groups surveyed	Fence procedure	INR (fe)	D dimer (ng / ml)	Max.T rombotsitov (mm ³)	APTT (Seconds)	F and brinogen (g / l)	Antithrombin 3 (%)
The control	I fence	0.98 ± 0.032	$163, 5 \pm 13, 5$	281 ± 9.0	35.4 ± 0.6	$2, 37 \pm 0, 12$	94.2 ± 8.8
II B	I fence	0.91 ± 0.026	162 ± 11.5	284 ± 7.5	32 ± 1.1	5.1 ± 0.17	88 ± 2.8
II A	I fence	$6, 0 \pm 0.034 *$	$368 \pm 14.5 *$	$177 \pm 5.1 *$	$25 \pm 0.7 *$	$6.9 \pm 0.18 *$	$52 \pm 1.5 *$
	II fence	$3, 84 \pm 0, 024 *$	$320 \pm 20.7 *$	$191 \pm 6.4 *$	$27 \pm 0.9 *$	$6.5 \pm 0.22 *$	$56 \pm 1.9 *$
The main	I fence	$8.5 \pm 0.033 *$	$374 \pm 25.3 *$	$278.4 \pm 6.8 *$	$26 \pm 0.8 *$	$7.1 \pm 0.23 *$	$54 \pm 1.7 *$
	II fence	$1, 87 \pm 0, 030 *$	$291 \pm 17.4 **$	$198 \pm 6.1 **$	$29 \pm 0.9 **$	$6.3 \pm 0.19 **$	$61 \pm 2.0 **$

* - significantly different values in relation to healthy women

** - significantly different values in relation to the indicators before treatment.

In women with reproductive dysfunction without chronic endometritis in the study of fibrinogen blood, it has been found that these values ($5,1 \pm 0,17$ g/l) were not significantly higher with respect to healthy women ($4,2 \pm 0,13$ g/l). At the same moment women with reproductive dysfunction and chronic endometritis after standard treatments, this result ($6,5 \pm 0,22$ g/l) was not significantly lower in relation to such data to the standard treatment ($6,9 \pm 0,18$ g/l). And after the proposed complex treatment in women with impaired reproductive function and chronic endometritis, a significant decrease in fibrinogen ($6,3 \pm 0,19$ g/l) was observed in comparison with the results ($7,1 \pm 0,23$ g/l) before treatment.

Pri study atitrombina 3 in the blood of women with reproductive dysfunction without chronic endometritis showed a significant decrease of this indicator ($84 \pm 2,8\%$) with respect to healthy women ($109 \pm 3,4\%$). In this case, after standard treatment in women with reproductive dysfunction and chronic endometritis, this indicator ($56 \pm 1,9\%$) was not significantly higher with respect to such data to the standard treatment ($52 \pm 1,5\%$). However, in women with reproductive dysfunction and chronic endometritis conducted after the proposed treatment there was a significant increase in antithrombin 3 ($61 \pm 2,0\%$) relative to its parameters ($54 \pm 1,7\%$) before treatment.

Thus, in patients with impaired reproductive function against the background of chronic endometritis, there is an increase in the activity of blood coagulation factors and some hypercoagulation in the plasma link against the background of a low anticoagulant potential of blood, as well as an increase in the functional activity of platelets. The appearance of high concentrations of D - dimer convincingly indicates the presence of a thrombophilic state in these patients. All this served as the basis for the appointment of low doses of low molecular weight heparin (LMWH) - rivaroxaban (Xarelto Bayer, Germany) - 10 mg / day for 14 days before the expected conception.

Rivaroxaban is a highly selective direct inhibitor of coagulation factor X_a , which has a very high bioavailability. The formation of active factor X_{and} due to external and internal pathways of blood coagulation plays a major role in triggering the coagulation cascade. That factor X_{and} promotes the conversion of prothrombin to thrombin, thereby forming a fibrin clot, and activates platelets function due to thrombin. Rivaroxaban blocks the formation of thrombin by suppressing the formation of factor X_a , and also indirectly activates antithrombin III. In the presence of LMWH, the fibrinogen-thrombin reaction leads to the formation of a fibrin clot with an altered structure, which

facilitates its subsequent lysis. The use of LMWH in small doses does not require constant laboratory monitoring and can be carried out on an outpatient basis. We did not observe any complications associated with the use of LMWH in the form of allergic reactions, bleeding, hemorrhagic complications, increased bleeding during menstruation or intrauterine manipulations.

It was the appointment of LMWH that promoted a more rapid relief of disorders in the hemostasis system in patients with CE.

4. Conclusions

1. Reproductive dysfunctions in patients with CE lead to tense functioning of the hemostasis system, which manifests itself in an increase in the anticoagulant potential of the blood, an increase in the function of the procoagulant link of the hemostasis system and an increase in the aggregation function of platelets.
2. The inclusion of low-molecular-weight heparin in the comprehensive treatment program for such patients contributes to the normalization of the hemostasis system, which can be a good prognostic factor for the further realization of the reproductive function.

REFERENCES

- [1] Manukhin I.B., Sementsova N.A., Mitrofanova Yu., Livshits L.Yu. Chronic endometritis and miscarriage // Medical Council, 2018, No. 1, pp. 33-38.
- [2] 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 the RAHR, Samara, September 4-6, 2008.
- [3] Radzinsky V.E., Petrov Yuri Alekseevich, Polina M.L. Chronic endometritis: modern aspects // Kuban Scientific Medical Bulletin, 2017, No. 3, pp. 19-24.
- [4] Tapilskaya H. And., A Savicheva. M., Shalepo K. In. Kopylova A. A. Experience in the treatment of chronic endometritis // Gynecology, 2020. Available <https://doi.org/10.26442/20795696.2020.4.200312>.
- [5] McQueen DB, Bernardi LA, Stephenson MD. Chronic endometritis in women with recurrent pregnancy loss and / or fetal demise. Fertil Steril 2014; 101 (4): 1026-30.
- [6] Sweet RL Pelvic Inflammatory Disease: Current Concepts of Diagnosis and Management // Curr. Infect. Dis. Rep. 2012. Vol. 2.