Modern possibilities for expanding complex therapy of postpartum septic complications.

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ABSTRACT

In modern obstetrics, the medical and social significance of infections is due to their significant contribution to the formation of maternal morbidity and mortality rates [1–3]. Despite significant advances in diagnosis and antimicrobial therapy, according to the conclusions of WHO experts [4], the share of postpartum sepsis in the structure of maternal mortality in the world is quite high.

Keywords:

A certain contribution to the indicator is made by the high frequency of cesarean section, alimentary obesity, chronic diseases, the use of assisted reproductive technologies, multiple births, preeclampsia with premature placental abruption and pathological obstetric blood loss. Endometritis after cesarean section is one of the most common septic complications. Treatment of patients with this complication is difficult due to the large wound surface and the diversity of pathogenic microflora of the birth canal. Postpartum endometritis often occurs in a mild form and ends with recovery. Nevertheless, a severe course, accompanied by purulent-resorptive fever and the possibility of generalization of infection, is noted in 25% of cases [2]. It is known that the development of endometritis is largely due to the initial compromised state of the mother's immune system [6] and is accompanied by progressive disturbances in the state of cellular and humoral immunity. We hypothesized that the use of drugs that normalize cellular and humoral immunity can significantly improve the results of therapy for patients with postpartum endometritis. In particular, such drugs include one of the safest effective drugs of natural origin, the flavonoid, Proteflazid. A consequence of the inability of the immune system and nonspecific defenses of the body (complement system, phagocytosis) to completely eliminate the infectious agent is bacterial and viral colonization of the endometrium. In this connection, we additionally used the drug Valavir as an antiviral therapy in the complex treatment of postpartum septic complications. As the pathological process develops, its spread appears to be limited due to the activation of T-lymphocytes (T-helper cells, natural killer cells) and macrophages. In all of these cases, persistence of microorganisms occurs, which is accompanied by the attraction of mononuclear phagocytes, natural killer cells, and T-helper cells that synthesize cytokines to the site of

inflammation. According to modern information, when exposed to specific antigens in endometrial tissue, T-helper cells differentiate into two subpopulations: T-helper cells of classes I and II (Th1 and Th2), specialized in the synthesis of certain cytokines. Th1 synthesizes predominantly pro-inflammatory cytokines: interleukin-1 (IL-1), interferon -γ (IFN- γ), tumor necrosis factors α and β, which are involved in the growth and differentiation of T-, B-lymphocytes, natural killer cells, antiviral and antibacterial protection. It has been established that in septic diseases, including endometritis, hypercoagulation develops [8, 13]. It is known that drugs that affect the immune system reduce the intensity of intravascular coagulation [8–11].

Thus, along with the impact on the pathogen and the inflammatory process, an important place in the treatment of endometritis should be occupied by the identification of structural and functional disorders in the immune system and their correction. On the other hand, one of the pressing problems of obstetrics is the development of drug resistance in pathogens of both community- and nosocomial infections to antibiotics, which served as an additional justification for the use of immunomodulators in patients with purulent-inflammatory diseases in puerperia in order to increase the effectiveness of treatment. It is known that the elimination of most infectious agents is carried out precisely by the cells of the phagocytic system, therefore immunomodulators acting on the cells of the monocyte-macrophage system are the optimal choice for activating anti-infective immunity [9–11].

In the presence of a characteristic symptom complex, the diagnosis of postpartum endometritis was verified by hysteroscopic examination and confirmed histologically [3]. Of the group of postoperative endometritis, 25 received standard therapy (ST), including infusion and antibacterial therapy, taking into account the sensitivity of the microflora obtained from the cervical canal [3]; 32 postpartum women were additionally given immunocorrective therapy: Proteflazide suppositories were prescribed vaginally, 2 times a day for 5 days. Valavir was prescribed from the first day of diagnosis at a dosage of 500 mg 2 times a day for 5 days. When used vaginally, due to the high concentration of the drug at the site of infection and

its fixation on mucosal cells, a local antiviral, antibacterial and antiproliferative effect is manifested. In the groups of patients before and after therapy, indicators of immune status were assessed: the content of leukocytes was determined by the chamber method, the number of lymphocytes was counted in a blood smear, and lymphocyte subpopulations. In the study groups (the main group and those receiving immunomodulators), the initial indicators of immune status and hemostasis before treatment did not have statistically significant differences. In the immunograms of postpartum women with a complicated course of puerperia endometritis, leukocytosis was observed, a decrease in the absolute number of lymphocytes and CD3+, CD4+ and CD22+ cells, a decrease in the concentration of IgG, which indicates a change in helper activity and insufficient function of humoral immunity (*Table 1*).

Table No. 1

	Healthy postpartum women	Postpartum women with endometritis	Standard treatment	Treatment with the addition of P+B complex
Leukocytes, in 1 μl	7143 ± 817	9300 ± 5621*2*	9400 ± 7401*2*	6780 ± 674
Lymph., %	34.0 ± 3.7	20.2 ± 2.81*2*	19.4 ± 2.11*2*	31.1 ± 3.2
Lymph., in 1 μl	2429 ± 207	1860 ± 2241*	1786 ± 2121*2*	2109 ± 2331*

CD3+, %	55.0 ± 2.4	46.2 ± 2.81*2*	40.5 ± 2.71*2*	57.0 ± 2.7
CD3+, in 1 µl	1336 ± 161	855 ± 541*2*	714 ± 421*2*	1202 ± 142
CD4+, %	44.3 ± 2.0	21.2 ± 1.31*2*	22.5 ± 2.21*2*	62.6 ± 1.31*
CD4+, in 1 µl	592 ± 54	391 ± 651*2*	393 ± 541*2*	752 ± 741*
CD22+, %	35.0 ± 2.6	28.2 ± 2.41*2*	28.5 ± 2.61*2*	18.0 ± 2.81*
CD22+, in 1 µl	850 ± 87	539 ± 431*2*	504 ± 501*2*	381 ± 411*
IgA, g/l	3.6 ± 0.6	5.3 ± 0.61*2*	5.7 ± 1.01*2*	2.1 ± 0.81*
IgM, g/l	1.1 ± 0.2	2.6 ± 0.31*2*	2.4 ± 0.21*2*	1.9 ± 0.31*
IgG, g/l	13.2 ± 1.2	7.1 ± 0.61*	9.1 ± 0.41*3*	8.6 ± 0.71*

Significant differences ($p<0.05$) between: 1* – current column and 1st; 2* – current column and 2nd; 3* – current column and 3rd; 4* – current column and 4th; 5* – current

As is known, during the entire period of gestation, the first 5–6 days of puerperia and ten days after cesarean section, patients experience systemic and local immunodeficiency, which determines the increased sensitivity of pregnant and postpartum women to bacterial infection. The hemostatic system plays an important role in the pathogenesis of postpartum diseases [13]. With the initial symptoms of endometritis in healthy postpartum women, an increase in intravascular coagulation was detected in the postoperative period, as evidenced by the abbreviation a decrease in blood clotting time and plasma recalcification, kaolin time and activated partial thromboplastin time (APTT), an increase in the level of fibrinogen and the concentration of fibrinogen/fibrin degradation products (FDP), as well as a decrease in the activity of antithrombin III (AT-III). At the same time, inhibition of total and Hageman-dependent fibrinolysis was noted in patients. As clinical symptoms worsened in patients with postpartum endometritis, these changes intensified, which was manifested by the progression of hypercoagulation, hyperfibrinogenemia, a decrease in the level of AT-III and an increase in the concentration of PDF. In postpartum women with postoperative endometritis, using standard therapy, clinical improvement was observed with the elimination of the inflammatory process, but changes in indicators of immune status and hemostasis persisted. Due to the generalization of the infectious process, two patients (8%) in this group (n = 25) underwent re-entry into the abdominal cavity with removal of the source of infection (hysterectomy). In 3 postpartum women, partial divergence of the sutures on the anterior abdominal wall was detected. Upon completion of the course of standard therapy, the number of leukocytes in the blood of the examined patients decreased, but did not reach the levels characteristic of healthy postpartum women, while the number of T- and B-lymphocytes still remained reduced, and the concentrations of the studied immunoglobulins remained virtually unchanged. In this group of patients, hemostasis indices only approximated the norm of blood clotting time. Other tests characterizing the state of the hemostatic system did not change (*Table 2*). With the use of a complex of antiviral immunomodulatory therapy, the absolute and relative number of lymphocytes increased, the number of T- and B-lymphocytes increased, and the concentration of IgG also increased (Table *1)*. At the same time, the patients' fibrinogen and PDP levels decreased, the number of positive reactions to ethanol decreased, and the concentration of AT-III, an indicator of the time of total euglobulin and Hageman-dependent fibrinolysis, approached the lower limit of normal.

Table No. 2

	Healthy postpartum women	Postpartum women with endometritis	Standard treatment	Treatment with the addition of Proteflazid
clotting time, s	442.2 ± 35.4	394.4 ± 44.71*2*	314.1 ± 34.61*2*	375.2 ± 42.41*3*
recalcification time, s	178.4 ± 8.2	150.7 ± 7.91*	132.3 ± 8.51*2*	142.3 ± 11.21*
Kaolin time, s	70.2 ± 6.7	51.4 ± 4.51*	52.4 ± 6.91*	62.3 ± 5.2
APTT, s	56.5 ± 3.5	50.1 ± 3.7	41.2 ± 3.81*	46.9 ± 3.71*
INR	1.02 ± 0.12	0.9 ± 0.151*	0.85 ± 0.171*	0.88 ± 0.19
Thrombin time, s	16.8 ± 1.5	13.4 ± 1.7	14.9 ± 1.1	15.4 ± 1.2
Antithrombin-III, %	100.0 ± 1.1	83.6 ± 6.41*	82.2 ± 5.21*	78.9 ± 5.51*
Fibrinogen, g/l	2.8 ± 0.5	3.9 ± 0.4	5.4 ± 0.41*2*	5.0 ± 0.71*2*
PDF, μg/ml	10.9 ± 2.6	16.1 ± 1.31*	37.9 ± 2.31*2*	29.3 ± 1.71*2*3*
Fibrinolysis euglobulin, min.	317.3 ± 15.4	344.4 ± 17.51*	385.5 ± 10.41*2*	373.2 ± 12.61*2*
Hageman-dependent fibrinolysis, min.	11.1 ± 1.2	10.2 ± 1.4	25.1 ± 4.61*2*	24.4 ± 4.31*2*
Ethanol test (% positive reactions)	-	61*	611*2*	521*2*3*

In the standard therapy group, improvement in well-being was observed on days 5–7, normalization of body temperature on days 3–7, reduction in pain on days 3–4, and disappearance of signs of inflammation on days 10–12. day. Tissue healing in such patients proceeded by secondary intention with the formation of a keloid scar (2 cases) (Table *3)*. The reasons for the formation of a keloid scar depend on both the characteristics of the female body and the collagen content, also the type of connective tissue, the migration of endothelial cells supported by VLA-3 and α 6 β 4 integrins. This mechanism is essential for the repair of the edges of a postoperative wound.
When using the proposed combination of an immunomodulator and an antiviral drug, clinical symptoms of recovery in patients with postoperative endometritis were detected significantly faster - on the 3rd–4th day, an improvement in well-being, and normalization of body temperature was observed on the 2nd–3rd day from the start of therapy. A decrease in pain was observed on the first or second day. Signs of inflammation disappeared on the 8th day. Along with this, during drug therapy, the duration of healing time on the anterior abdominal wall of the postoperative suture was reduced, and a normal postoperative scar was formed (Table *3)*.

The obtained effects are indirect, indirect and are determined by the beneficial effects of the drugs used on immunity, hemostasis and tissue regeneration in postpartum women with endometritis after cesarean section. The favorable course of the disease against the background of effective immunomodulatory therapy led to a reduction in hospitalization time by 1.7–1.9 times. (Table *3)*.
In the treatment of postpartum women with endometritis after cesarean section, when choosing a prescribed immunotropic drug, attention should be paid to the features of its use, possible adverse reactions and patient compliance. It should be especially noted that in all cases of the use of a complex of antiviral and

immunomodulatory therapy in patients with endometritis after cesarean section, a day later the patients reported an improvement in their well-being, which we regarded as one of the manifestations of the therapeutic effect, which was accompanied by a decrease in abdominal pain and the amount of pathological discharge (lochia) from the genital tract, relieving general and local inflammatory phenomena. In addition, uncomplicated healing of the postoperative suture on the anterior abdominal wall and a reduction in treatment time were noted (Table *3)*.

	Standard treatment	Treatment with the addition of Proteflazid	Healthy postpartum women
Feeling better, days	5–7 days	3–4*	2-3*
Normalization of body temperature, days	3–7 days	3–4*	2-3*
Stopping chills, days	4–5 days	3*	2*
Elimination of tachycardia, days	3–4 days	2–3 *	1–2 *
No pain	3–4 days	1–2 *	1–2 *
Disappearance of signs of inflammation, days	10–12 days	9	8*
Use of antibiotics	Necessarily	limited	limited
Relaparotomy	8% (2)	absence	absence
Condition of the scar on the anterior abdominal wall	hypertrophic, 12% (3)	normotrophic	normotrophic
Length of hospital stay, days	18 ± 4.2 [CI 21–29]	15 ± 1.1 [CI 14–16] *	3 ± 0.9 [CI 12–14]

Thus, at present, there is no doubt about the existence in the body of a single cellular-humoral anti-infective defense system of the body, including immunity and hemostasis. In addition, the use of these immunotropic drugs in patients with endometritis after cesarean section resolves the clinical symptoms of the disease, eliminates signs of immunodeficiency, and normalizes the biological mechanism of postoperative wound healing on the anterior abdominal wall

Conclusions:

1. Postoperative endometritis in patients, realized in puerperia, is accompanied by a decrease in the total number of T- and B-lymphocytes, including T-helper cells (CD4+), a decrease in the level of immunoglobulin G and activation of intravascular coagulation.
2. Standard therapy for postpartum women with endometritis is not accompanied by the elimination of detected inflammatory changes, while the use of immunocorrective drugs Proteflazid and the antiviral drug Valavir is accompanied by normalization of immunity parameters, hemostasis and a more favorable course of the disease with a reduction in hospitalization.

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