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Research Article

Immune-Metabolic Therapy of Purulent Inflammatory Diseases

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Abstract

Introduction: Inflammatory diseases of the female genital organs rank among the leading ones in the total number of women of reproductive age. This results from a decrease in immunity, early sexual activity, neglect of personal hygiene, abortions, birth complications, etc.

Materials and Methods: The study included 100 patients suffering from exacerbated chronic salpingo-oophoritis and its combination with bacterial vaginosis. In the study, all the patients were randomly divided into five groups, with 20 patients each. The patients were treated in the prescribed regimens and doses, according to the standards of specialized medical care. An immunomodulator immunomax and an antioxidant hypoxene were chosen as additional treatment options. Clinical and laboratory parameters were measured in all the patients before and after the treatment. The effectiveness of the treatment was evaluated 10-14 days later. In 18 people, the procedure was repeated after 2-3 months.

Results and Discussion: It was found that the standard therapy to treat exacerbated chronic salpingo-oophoritis reduced inflammatory manifestations after 10-14 days; however, the risk of complications and relapse of the disease remained. Immunomax provided satisfactory second-order normalization of the immunological and metabolic parameters, ultimate normalization of pro-inflammatory parameters and absolutely no positive effect on the clinical parameters in patients with chronic salpingo-oophoritis in the acute stage, when compared with the standard treatment. A complex therapy of salpingo-oophoritis with bacterial vaginosis by means of immunomax and hypoxene aimed to normalize most clinical and laboratory parameters was absolutely positive; a moderate level of parameters was revealed only in cellular-humoral immunity.

Conclusion: After 10-14 days, the standard treatment of patients resulted in normalization of the pro-inflammatory and immunological parameters, rather than the clinical and metabolic parameters. The administration of immunomax contributed to the correction of metabolic, immunological and pro-inflammatory markers, and the complex administration of an immunomodulator with an antioxidant favorably affected all the laboratory parameters.

Keywords

immunomax, hypoxene, salpingo-oophoritis, bacterial vaginosis.

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Introduction

Rationale of this study is determined by the fact that most women experience inflammatory diseases of the genital organs (Ditkoff et al. 2018; Kicha et al. 2018; Desai and Brinton 2019). The female reproductive system has structural features that facilitate the rapid spread of infection from the vagina to the internal genital organs (Dumesic et al. 2015). According to scientific data, the main "point of attack" by bacterial infections of women's genitals is the fallopian tubes. In turn, the depth of tissue damage of the fallopian tubes and specific morphological manifestations of the disease are quite variable and largely depend on the etiological factors, the duration of the inflammatory process and the main pathogenetic mechanism of infection of the internal genital organs (Tomassetti and D'Hooghe 2018). To date the degree of involvement of the ovaries in the inflammatory process in purulent-inflammatory diseases of the genitourinary system is till debatable. The high prevalence of chronic purulent-inflammatory diseases is caused by a decrease in immunity, development of antibiotic resistance by causative microflora (Hauser et al. 2016; Bratchikov et al. 2020). Currently, there is a scientific need to develop valid prescribing regimens and evaluate the effectiveness of an immune-pharmacotherapy (Waldmann 2015; Balercia et al. 2017). One of the main vectors of this problem is to study the impact of combined pathology and a complex treatment associated with it on the clinical and laboratory status of patients (Alvarez-Curto and Milligan 2016; Agarkov et al. 2017). New aspects of the pathogenesis of infections – metabolic disorders, targeted pharmacological correction – are understudied nowadays (Majdan 2016; Verwijs et al. 2019). At the same time, the objective consideration of the combined immuno-metabolic genesis of oxidative infectious stress and its potential appears to be poorly studied (Zhang et al. 2018; Pokrovskaya et al. 2020).

The aim of the study was to investigate changes in laboratory parameters of exacerbated chronic salpingo-oophoritis (ECSO) and its combination with bacterial vaginosis (BV) when prescribing a standard treatment and a treatment combined with an immunomodulator – immunomax – or with an antioxidant – hypoxene.

Materials and methods

A clinical trial plan was approved by the Ethics Committee of Voronezh N.N. Burdenko State Medical University of the Ministry of Healthcare of the Russian Federation and complied with the medical ethics requirements of the Declaration of Helsinki.

The study included 100 patients suffering from chronic salpingo-oophoritis in the acute stage. Of these, 60 patients were diagnosed with bacterial vaginosis; 30 healthy individuals of the similar age constituted a comparison group. All the patients included in the study were randomly divided into five groups, 20 patients each. Two groups consisted of the patients with ECSO receiving the standard treatment and its combination with immunomax (Std + Im). Four groups included the women with ESCO + BV, who received the standard treatment, the standard treatment+immunomax and a combination of the standard treatment+immunomax+hypoxene (Hp) (Std, Std +Im, Std +Im+Hp) (Fig. 1). The treatment was performed in the prescribed regimens and doses, according to the standards (Falconi-McCahill 2019; Faught and Reyes 2019). An immunomodulator immunomax and an antioxidant hypoxene were chosen as additional treatment options.

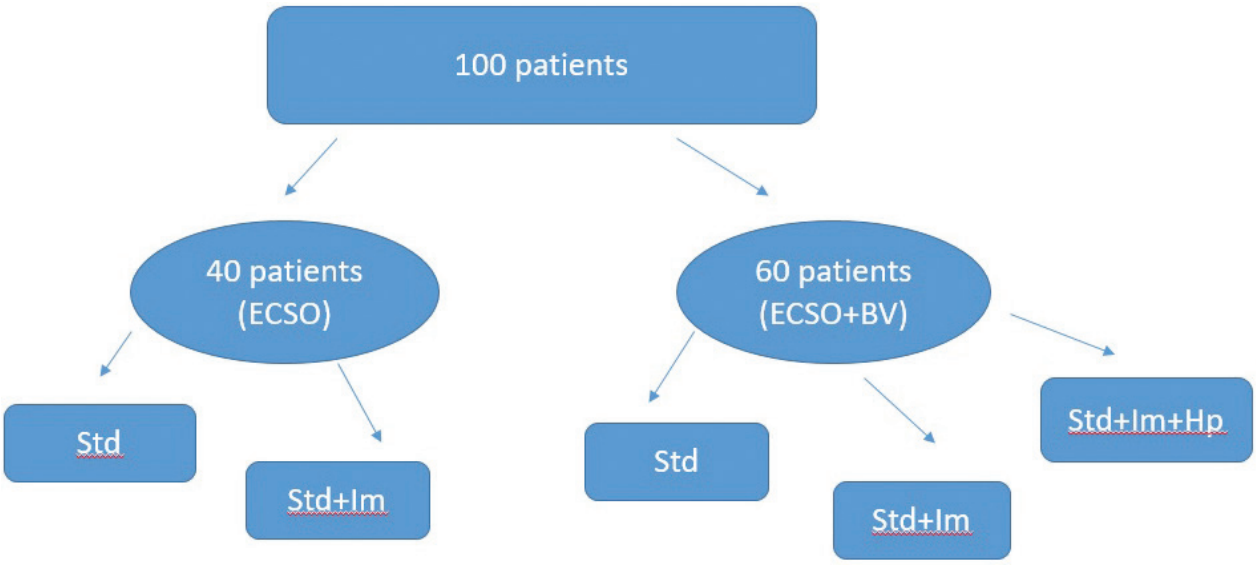

Figure 1. The scheme of differentiated immune pharmacotherapy of chronic salpingo-oophoritis in the acute stage and its combination with bacterial vaginosis.

Notes: ECSO – exacerbated chronic salpingo-oophoritis, BV – bacterial vaginosis, Std – standard treatment, Im – immunomax, Hp – hypoxene.

The laboratory parameters – hematological, biochemical, immunological, bacteriological, metabolic tests – were measured in all the patients before and after the treatment. Clinical and laboratory statuses were also evaluated after 10–14 days. In 18 patients receiving Std+Im and Std+Im+Hp therapies, the procedure was repeated again after 2–3 months.

The analysis of the obtained data included an assessment of the reliability of the studied laboratory parameters through randomization of patients groups by age, severity of the disease, and other signs; determination of the optimal number of patients in the group; use of statistical criteria, for example, Student's or Wilcoxon-Mann-Whitney tests, taking into account the normal distribution of the laboratory findings.

When analyzing immunopathology, the signaling parameters were formalized into standard formulas of the immune system disorders (FISD), including the most significantly changed parameters compared to the norm; immunocorrection targets were identified using the coefficient of diagnostic value (Kj); "proper" immunocorrection targets were identified compared to the standard treatment; the dependence of changes in the components of the immune-laboratory status was specified. When performing a ranking assessment, the percentage of the altered parameters compared to a given level and the following scale – <33, 33–66 > 66% – were used for calculations. The rank of differences was measured on the following scale: insignificant (3rd rank), moderate (2nd rank) and significant (1st rank). Laboratory markers for the selection of medications were detected using an inverse analysis of the composition of the formulas of immunocorrection targets. A five-level assessment of parameters was used when studying the obtained data (Ermishina et al. 2014; Kuzmenko et al. 2019; Zemskov et al. 2019).

Results and discussion

It was found that after 10–14 days the standard therapy of ECSO resulted in a significant reduction of metabolic and immunological markers to a moderate level and pro-inflammatory markers – to the lowest severity level. Complex treatment with the immunomax modulator shows that after 10–14 days there is a decrease in the initial frequency of pathology in terms of the hematological and biochemical parameters from 17.7% to 30.0%, 12.5% to 37.5% almost to trace amounts – 5.0% to 10.0%, which testifies to the successful relief of inflammation in sick women during this period under the influence of complex treatment.

In ECSO complicated by BV, ultimate changes from the norm were registered for all the generalized parameters within 80–100%. Standard therapy administered to female patients from this group had an unsatisfactory effect on the metabolic parameters and a markedly moderate effect on the immunological (51.9%) and pro-inflammatory (35.7%) tests.

Immunomax resulted in satisfactory second-order normalization of the immunological and metabolic parameters, ultimate normalization of the pro-inflammatory parameters of patients suffering from chronic salpingo-oophoritis in the acute stage compared to the standard treatment. The combined therapy by a modulator with an antioxidant hypoxene during this period contributed to the complete normalization of all the studied parameters in the female patients (77.8–100%).

After 2–3 months, the patients with ECSO who had received immunomax in the acute period of the disease in combination with the standard treatment manifested certain preservation of the normalization of the immunological parameters and its complete absence in other pro-inflammatory and clinical parameters.

When inflammation of the uterine appendages was aggravated by BV, the introduction of immunomax contributed to a decrease in isolation of pathogenic microflora from the diagnostic material. However, overall, there was no positive effect of immunotherapy in the grouped pro-inflammatory, immunological, and clinical parameters.

The complex immune-metabolic therapy of women with ECSO+BV was quite active during this period. In the patients, there was completely no significant accumulation of normal blood-biochemical markers of inflammation. On average, clinical manifestations of an exacerbation of the disease in this group were significantly reduced, the fact indicating the sufficient effectiveness of immuno-metabolic therapy.

The effect of the standard treatment alone in patients with ECSO on days 10–14 did not practically affect cellular defense reactions and had a moderate effect on humoral (50%), phagocytic (33%), free-radical-oxidation and antioxidant-system (AOS)-dependent (60–50%) parameters and completely eliminated the pathology of pro-inflammatory hemato-biochemical, cytokine and bacteriological parameters, since their deviation from the norm ranged from 0 to 16.7%.

The effectiveness of the combined standard and immunomax treatment on cellular mechanisms was not significant. In contrast, normalization of the remaining four grouped parameters – bactericidal, cytokine, pro-inflammatory hematological, and biochemical – proved to be significantly absolute in 100% of the cases.

The combined standard, immunomax and hypoxene therapy of salpingo-oophoritis in the acute stage complicated by bacterial vaginosis was absolutely positive in normalizing most laboratory parameters, and moderate only in cellular-humoral immunity.

It was revealed that in the acute period of uncomplicated chronic salpingo-oophoritis, according to FISD, the leading markers of immuno-metabolic disorders were TNF^{+}_{3} IgM^{+}_{2} NKr^{-}_{2} – accumulation of the pro-inflammatory cytokine TNF, hyperimmunoglobulinemia M with a deficiency of NK regulators; and according to FMD – $VitaminE^{+}_{2}$ $Schiff's\ bases^{+}_{1}$ $systemic\ thiols^{-}_{1}$ – excess amounts of vitamin E, Schiff's bases together with insufficient concentration of systemic thiols. The combined formula of immuno-metabolic disorders (FIMD) included the composition of three of the above-mentioned key

Table 1. Correlation of Personalized Immuno-metabolic Parameters in Patients with ECSO and ECSO+BV Before Treatment.

Disorders	Standard formulas	Strong correlations	n
Formula of the immune system disorders (FISD)			
ECSO	**FRIS**-$TNF^{+}_{3}IgM^{+}_{2}NKr^{-}_{2}$	(TNF^{+}_{3}) **+IL10** (IgM^{+}_{2})**+B,+CIC,+MWM** (NKr^{-}_{2})**+Tc,+Ma**	6
Formula of metabolic disorders (FMD)			
ECSO	**FMD**-$VitaminE^{+}_{2}$Schiff's $bases^{+}_{1}$Systemic $thioles^{-}_{2}$	(VE^{+}_{2})**-Diene conjugates,+ceruleoplasmin,+MDA** (Systemic $thioles^{-}_{1}$)**+ketodienes** (Schiff's $bases^{+}_{1}$) **-Catalase**	5
Formula of the immune-metabolic disorders (FIMD)			
ECSO	**FIMD**-TNF^{+}_{3} IgM^{+}_{2} $VitaminE^{+}_{2}$	(TNF^{+}_{3}) **+MDA,+CIC, +β-glob.,+stab neutrophils** **(**IgM^{+}_{2}) **+B,-Catalase, +**α_2 **glob.** **(**VE^{+}_{2}) **+Tc, -Diene conjugates,+ESR**	10
Healthy people	TNF IgM VitaminE	(TNF) **+MWM,+VE,+Catalase,+γ glob,-Ketodienes, +eosinophils (EOS)** (IgM) **+IgG, +β-glob,-Tc, +ESR, +Schiff's bases, +superoxide dismutase** (VitaminE) **+T,+MDA,+Schiff's bases,+C-reactive protein,-Systemic thioles**	17
Formula of the immune system disorders (FISD)			
ECSO+BV	**FISD**-$IgG^{+}_{2}Tc^{+}_{3}NBTac^{-}_{2}$	(IgG^{+}_{2})**-IgA,+Th,-IL10** (Tc^{+}_{3})**+Tac**	4
Formula of metabolic disorders (FMD)			
ECSO+BV	**FMD**-plasma antioxidant $activity^{-}_{3}$Superoxide $dismutase^{-}_{3}MDA^{-}_{3}$	(plasma antioxidant $activity^{-}_{3}$)**+ceruleoplasmin** (Superoxide $dismutase^{-}_{3}$)**+bi-tyrosine linkages** (MDA^{+}_{2})**+ketodienes**	3
Formula of the immune-metabolic disorders (FIMD)			
ECSO+BV	**FIMD**-plasma antioxidant $activity^{-}_{3}$ IgG^{+}_{2} superoxide $dismutase^{-}_{3}$	(plasma antioxidant $activity^{-}_{3}$) **+MDA, +diene conjugates ,+Tc, +γ glob** (IgG**) +Mon** (Superoxide $dismutase^{-}_{3}$)**+ Schiff's bases**	6
Healthy people	Plasma antioxidant activity IgG superoxide $dismutase^{-}$	(plasma antioxidant activity) **+NKr**, **+β-glob,+CIC, +ceruleoplasmin, +Leuc.,+catalase** (IgG**) +B, -Schiff's bases, +ESR, -Diene conjugates, +γglob, +IL8** **(superoxide dismutase) +IL4, -non-protein thioles, +ESR, -MDA, + IgA, +C-reactive protein**	18

Notes: n – number of correlations with a coefficient >0.5; the correlation-related parameters are given in bold; +/- positive/negative bonds, Tc – T-cytotoxic lymphocytes, Tac – T-active lymphocytes, MA – lymphocytes with apoptosis marker, NKt, NKr, NKc – natural thymus-dependent, regulator-, cytotoxic killers; CD – differentiation clusters; B – B cells; Ig – immune globulins of different classes; CIC – circulating immune complexes, MWM – medium weight molecules, PhI, PhN – phagocytic index, phagocytic number; NBTsp , NBTac – nitro-blue tetrazolium test spontaneous/activated; IL – interleukins; TNF – tumor necrosis factor alpha, Ma – carriers of apoptosis marker; ECSO – exacerbated chronic salpingo-oophoritis, BV – bacterial vaginosis.

parameters with the predominance of immunological tests – TNF^{+}_{3} IgM^{+}_{2} $VitaminE^{+}_{2}$.

According to FMD, the key effect of the non-immunotropic treatment alone and a treatment combined with immunomax appeared to be distributed – between either exclusively humoral (IgM^{+}_{3} CIC^{-}_{2} B^{+}_{3}) or a combination of humoral, phagocytic and cytokine parameters (MWM^{-}_{3} PhI^{+}_{2} $IL8^{-}_{2}$).

In turn, treatment options for ECSO – a standard treatment and a complex treatment with immunomax – had a pronounced effect, including that on the components of the metabolic status. According to the standard treatment, (plasma antioxidant $activity^{+}_{2}$ $VitaminE^{-}_{2}$ MDA^{+}_{2}) resulted in the stimulation of the general antioxidant activity of blood, a decrease in the formation of anti-inflammatory vitamin E, which belongs to the antioxidant defense (AOD) system, and the accumulation of malondialdegyde, a leading factor in the free radical oxidation processes. The combination of Std+Im therapy, according to the standard formula (superoxide $dismutase^{+}_{2}$ $ketodienes^{-}_{1}$ plasma antioxidant $activity^{+}_{2}$) resulted in the activation of superoxide dismutase, a decrease in the level of ketodienes and an increase in plasma antioxidant activity. The formula of the immune-metabolic disorders of the combined standard treatment with immunomax included (MWM^{-}_{2} superoxide $dismutase^{+}_{2}$ PhI^{+}_{2}) – a decrease in the number of medium-weight molecules, which are a sign of toxicosis, stimulation of the enzymatic reaction of the antioxidant system – superoxide dismutase and the phagocytic index value.

Crucially different results were obtained in case of the aggravated pathology. In the acute period of chronic salpingo-oophoritis with bacterial vaginosis, the key immunological (IgG^{+}_{2} Tc^{+}_{3} $NBTac^{-}_{2}$) and metabolic parameters (plasma antioxidant $activity^{-}_{3}$ superoxide $dismutase^{-}_{3}$ MDA^{+}_{2}), respectively, appeared to be as follows: one humoral, one cellular, one phagocytic index parameters, two antioxidant system factors and one free radical oxidation parameter. The combined formula of immune-metabolic disorders (plasma antioxidant $activity^{-}_{3}$ IgG^{+}_{2} superoxide $dismutase^{-}_{3}$) contained two antioxidant system parameters and one B-dependent immunological parameter.

The analysis of signaling parameters revealed the following regularities: the complete individuality of the formulas considering the order of location, vector and degree of changes in the basic tests; their stimulating and

suppressing multidirectionality; representation of various types of reactions among the signaling parameters.

For example, anti-inflammatory cytokines IL2, enzymatic and non-enzymatic factors – catalase and plasma antioxidant activity – were determined as part of the combined FIMD of immunomax ($IL2^{+}_{2}Catalase^{+}_{2}$ plasma antioxidant $activity^{+}_{2}$). All the parameters were with a vector of the second degree stimulation.

It should be made clear that the standard formulas of the targets of immunological and pharmacological correction are the result of the combined therapy, including standard medications, a modulator and an antioxidant, administered to female patients; this fact eroding understanding of the target effect of immunotherapy. To identify it, there is a mathematical method by A.M. Zemskova et al. (2008).

It was demonstrated that, in non-aggravated salpingo-oophoritis and salpingo-oophoritis aggravated by BV, 22 and 17 immunological parameters out of the 27 studied parameters were accordingly quantitatively stimulated by immunomax alone. The basic immunological tests ("proper" formula of metabolic disorders) in both cases were the following: $Ig\,A^{+}_{3}$ TNF^{-}_{3} T^{+}_{3} and $IL4^{+}_{3}$ NKt^{+}_{3} $NBTsp^{+}_{3}$ – the maximum accumulation of A immune globulins class, decrease in the concentration of pro-inflammatory TNF, stimulation of the number of T cells and the maximum increase in the content of anti-inflammatory IL4, thymus-dependent natural killer cells and the spontaneous NBT test value.

The above immunological phenomena were combined with the powerful metabolic effect of immunomax, according to the typical "proper" formula of metabolic disorders – (diene $conjugates^{+}_{1}$ plasma antioxidant $activity^{+}_{1}$ systemic $thiols^{+}_{1}$) and (Schiff's $bases^{-}_{2}$ $superoxide\ dismutase^{+}_{2}$ bi-tyrosine $linkages^{-}_{1}$) – activation of one free-radical-oxidation-dependent and two antioxidant-system-dependent factors against accumulation of Schiff's bases, stimulation of superoxide dismutase and decrease in the concentration of free-radical-oxidation-dependent bi-tyrosine linkages in patients with aggravated course of the uterus inflammation.

When female patients with ECSO+BV are administered complex Std+Im+Hp, it produces a multifaceted effect on the immune and metabolic statuses – PhN^{+}_{3} $NBTac^{+}_{2}$ NKc^{-}_{2} and $Catalase^{-}_{2}$ systemic $thiols^{+}_{2}$ plasma antioxidant $activity^{+}_{3}$ – distributed between the absorbing and metabolic abilities of phagocytes, cytotoxic natural killers and catalase, common thiols, and total antioxidant activity of blood.

The correlation analysis revealed the main regularities of the relationship of immunological and metabolic mechanisms – the prevalence of the number of strong correlations of the basic tests in healthy individuals, with their progressive decrease as diseases deteriorate, respectively (from 17 to 10 and from 18 to 6).

Thus, in the control group of healthy individuals compared to the female patients with mono-inflammatory pathology of ECSO, the number of strong associations of FIMD basic tests with immunological parameters constituted – 23.5 and 30.0%, with hematological parameters – 11.8 and 20.0%, biochemical parameters – 17, 6 and 20.0%, and metabolic parameters – 47.1 and 50.0%, respectively. In the patients with ECSO+BV, the number of strong associations of FIMD basic tests with immunological, hematological parameters constituted 11.7 and 16.7%, with biochemical parameters – 16.7 and 16.7%, and with metabolic parameters – 38.8 and 50.0%, respectively.

Therefore, there was established a systemic complex pathology of pro-inflammatory, immunological, metabolic parameters in clinical models of chronic salpingo-oophoritis in the acute stage and its combination with bacterial vaginosis in the acute period. The effectiveness of the standard therapy of ECSO and ECSO+BV after 10–14 days of treatment was incomplete, and in case of the additional administration of immunomax it was significant for ECSO treatment and unsatisfactory for ECSO+BV treatment.

After 2–3 months, the effectiveness of mono-immune-pharmacological therapy wore off completely. The complex of standard treatment for patients suffering from exacerbated chronic salpingo-oophoritis and its combination with bacterial vaginosis with immunomax and hypoxene provided a predominant cure and prevention of the disease after 10–14 days – 2–3 months of treatment. The combination of immunomax with hypoxene completely modified the typical immuno- metabolic targets. It was also demonstrated that oxidative infectious and inflammatory stress had not only a metabolic, but also immune mechanism, with minor participation of hemato-biochemical markers.

Conclusion

Thus, it can be concluded that the standard treatment of patients with salpingo-oophoritis in the acute stage and bacterial vaginosis results in normalization of pro-inflammatory and immunological (64.3–48.0%) parameters 10–14 days later, whereas the metabolic (23.1–38.5%) parameters remain the same. The introduction of immunomax contributes to the correction of metabolic (38.5%), immunological and pro-inflammatory (92.9%) markers, and complex administration of an immunomodulator with an antioxidant favorably affects all the laboratory parameters (88.0–100.0%). Comparative effectiveness of the variants of differentiated immunopharmacotherapy of chronic salpingo-oophoritis in the acute stage and its combination with bacterial vaginosis was analyzed in detail. An additional prescription of immunomax and hypoxene to the standard therapy results in the phenomena of the addition of the effects of drugs and the achievement of a new quality with their combination, which helps to reduce chronicity and recurrence of the process

Conflict of interest

The authors have no conflict of interest to declare.

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