СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ РАЗЛИЧНЫХ СХЕМ ИММУНОРЕАБИЛИТАЦИИ ПРИ БЕСПЛОДИИ ТРУБНО-ПЕРИТОНЕАЛЬНОГО ГЕНЕЗА

По О.Б.Ж., Конопля А.А., Медведева И.Н.

ФГБОУ ВО «Курский государственный медицинский университет», г. Курск, Россия

Резюме. Целью исследования явилось сравнение эффективности различных схем фармакотера- пии при бесплодии трубно-перitoneального генеза. Под постоянным наблюдением находились 96 пациенток, направленных в стационар для проведения диагностической лапароскопии по пово- ду бесплодия трубно-перitoneального генеза, разделенных поровну на 4 группы в зависимости от способов фармакологического лечения: 1-я группа получала базовую фармакотерапию (БФТ) после эндоскопического операционного вмешательства (антибактериальная, противогрибковая, витами- нотерапия). Пациентки 2-4-й групп, кроме БФТ, соответственно получали гепон, циклоферон или лавомакс. Контрольная группа была сформирована из 38 гинекологически здоровых женщин. Лабо- раторное обследование осуществляли в течение 24 часов после операции и на 30-е сутки после БФТ. В вагинально-цervикальном смыве и в плазме крови оценивали активность процессов перекисного окисления липидов, состояние антиоксидантной системы, выявляли уровень стабильных метабо- литов оксида азота, неоптерина, C-реактивного белка, цитокинов (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), иммуноглобулинов (IgM, IgG, IgA, sIgA), компонентов системы комплемента (C3, C4, C5, C5A), фагоцитарную и кислородзависимую активность полиморфноядерных лейкоцитов крови. Установлено, что применение в БФТ препаратов с иммуномодулирующей и антивирусной активностью по степени возрастания эффективности в коррекции иммунометаболических параметров на системном и местном уровне при бесплодии трубно-перitoneального генеза представляет собой следующую последовательность: базовая фармакотерапия < базовая фармакоте- рапия + гепон < базовая фармакотерапия + циклоферон < базовая фармакотерапия + лавомакс.

Ключевые слова: бесплодие трубно-перitoneального генеза, фармакологическая коррекция иммунометаболических нарушений

COMPARATIVE EFFECTIVENESS OF VARIOUS SCHEMES OF IMMUNOREHABILITATION IN INFERTILITY OF TUBOPERITONEAL GENESIS

Po O.B.J., Konoplya A.A., Medvedeva I.N.

Kursk State Medical University, Kursk, Russian Federation

Abstract. The study aimed to compare the effectiveness of various pharmacotherapy regimens for infertility of tubo-peritoneal genesis. Under constant supervision were 96 patients referred to the hospital
for diagnostic laparoscopy for infertility of tubo-peritoneal genesis, divided equally into 4 groups depending on the pharmacological treatment methods: the 1st group received basic pharmacotherapy (BPT) after endoscopic surgery (antibacterial, antifungal, vitamin therapy). Patients of groups 2-4, in addition to BPT, received Hepon, Cycloferon or Lavomax, respectively. The control group consisted of 38 gynecologically healthy women. Laboratory examination was performed within 24 hours after the operation and on the 30th day after BPT. Vaginocervical lavage and plasma were assayed for the activity of lipid peroxidation processes, the state of the antioxidant system, the level of stable nitric oxide metabolites, neopterin, C-reactive protein, cytokines (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), immunoglobulins (IgM, IgG, IgA, sIgA), components of the complement system (C3, C4, C5, C5α), phagocytic and oxygen-dependent activity of polymorphonuclear leukocytes. It was established that the use of immunomodulatory and antiviral activity components of the immune system is a trigger factor in the development of PID according to the degree of increasing efficiency in the correction of immunometabolic and endocrine system parameters. The presence of somatic factors, pathogenic microorganism, but also by the state of the microorganism, surgery itself, antibiotic prophylaxis, adverse affects the immune and metabolic status, which leads to inadequate rehabilitation of patients, requires adequate postoperative pharmacological correction [7].

Introduction

The restructuring of the etiological system of infectious and inflammatory diseases of the female reproductive system health that revealed in the last decade indicates the need to change opinions and positions on the influence of conventional-pathogenic bacterial flora in the genesis of this nosology. The realization of microflora pathological potential properties, as well as the majority of viral agents, occurs in the presence of an imbalance, primarily in the link of local immunity of a macroorganism. Microbial associations enhanced the pathogenic characteristics of each individual representative of this association, which in turn leads to increased resistance of microorganisms to external factors, antibiotic therapy is no exception [1, 2].

It is believed that the reason for the development of tubal infertility in 55-85% of cases is untimely therapy of pelvic inflammatory diseases (PID). In addition, the risk of developing an ectopic pregnancy increases by 7-10 times in patients of this category in the anamnesis. Now the pathology of organs located in the pelvis in women is determined by the duration and chronicity of this inflammatory process. This leads to the addition of components of the immune and endocrine systems to this inflammatory process. An integral part is the manifestation of local and somatic pathological symptoms. Most often, the triggering mechanism in the development of PID is the effect of a microbial fact, while the development of the inflammatory process, as well as its course and outcome are determined not only by the nature of the pathogen, but also by the state of the microorganism, environmental conditions, the presence of somatic pathology, including viral etiology, leading to prolonged persistence of viruses and, as a rule, immune changes occurring against this background. In the genesis of all inflammatory diseases of the female reproductive system, especially chronic diseases of the pelvic organs, there is a violation of local immune mechanisms of anti-infection protection with the protective effect of the endometrium and endosalpinx. All this is a trigger factor for the involvement in this process of systemic mechanisms of stabilization of the immune and oxidative homeostasis of the body [6, 9].

In a chronic inflammatory process occurring in the pelvic organs, the highest incidence of adhesions is observed, including due to impaired immune status, which in essence is the cause of secondary infertility. Solving this problem often requires the use of radical invasive surgical correction techniques. The full restoration of the woman’s reproductive function after such treatment, with an average and severe inflammatory adhesion process, varies from 15 to 35%. Diagnostic laparoscopy is the standard for the diagnosis of tuboperitoneal infertility, however, the history of the chronic infectious and inflammatory process of the reproductive spheres, the surgery itself, the presence of anesthetic benefits, antibiotic prophylaxis adversely affect the immune and metabolic status, which leads to inadequate rehabilitation of patients and requires adequate postoperative pharmacological correction [7].

Previous publications presented data on immunometabolic laboratory disorders at the systemic and local levels and methods for their pharmacological correction in infertility of tuboperitoneal genesis [3, 6]. Based on this, the aim of the study was the need to use various statistical methods to compare the effectiveness of the applied pharmacotherapy regimens for this pathology.

Materials and methods

For the period 2010-2018 Under constant supervision in the gynecological department of the Kursk Perinatal Center and City Clinical Hospital No. 4 of Kursk, there were 96 patients referred to the hospital for diagnostic laparoscopy for infertility of tuboperitoneal origin. In order to verify the tuboperitoneal genesis of infertility and exclude ot-
her forms of infertility, all patients underwent a basic clinical and obstetric-gynecological history; infectious screening (microscopic examination of smears from the vagina, cervical canal, and urethra; PCR diagnosis of Chlamydia and Herpes viral infection; screening for Syphilis (RW), Hepatitis B, C (HBsAg, anti HCV antibodies); determination of antibodies of class IgG, IgM to TORCH complex infections), assessment of ovulatory function (Ovulation “ClearPlan” test), and pelvic ultrasound.

The following parameters were determined by the inclusion of criteria:
- age of patients 18-40 years old;
- verified diagnosis – secondary infertility of tuboperitoneal genesis against the background of a chronic infectious and inflammatory process of bacterial-viral etiology, which caused immune disorders that require pharmacological correction;
- presence of bad obstetric and gynecological history (chronic inflammatory diseases of the pelvic organs, a history of infertility, spontaneous miscarriages, miscarriage, abortion);
- availability of indications for the use of medications used in this study;
- medical history up to 10 years;
- absence of severe extragenital pathology;
- negative results on sexually transmitted infections;
- invasive treatment method is applied for the first time;
- signed consent to participate.

Exclusion criteria:
- the general condition of the patient, not allowing to participate in the study;
- persons with a history of surgical treatment;
- the presence of a verified specific sexually transmitted infection;
- persons with uncompensated somatic pathology requiring continuous drug therapy;
- persons with a history of allergies;
- patients who refused to participate in the study.

Randomization was formed according to age, concomitant pathology of the history of the disease.

All the women were divided into 4 groups of 24 patients each, depending on the pharmacological treatment methods: the 1st group received basic pharmacotherapy (BPT) after endoscopic surgery (antibacterial – cefotaxime, antifungal – metronidazole, vitamin therapy – B1, B6). Patients of groups 2-4, besides for BPT, respectively received Hepon (as a solution for oral administration in a volume of 10 mg once a day, for 30 days), Cycloferon (12.5% injection for 2 ml, intramuscularly, 1 time per day according to the basic scheme – on 1, 2, 4, 6, 8, 11, 14, 17, 20, 23, 26, 29 days; course dose – 2.5 g) or Lavomax (in the form of tablets according to 125 mg in the first 2 days at 125 mg, then after 48 hours at 125 mg; course dose – 2.5 g).

The control group was formed in the same period of time, from persons of completely gynecologically healthy women, who came to an outpatient appointment for their annual medical examination and amounted to 38 people.

Laboratory examination was carried out within 24 hours after surgery and on the 30th day after BPT. The activity of lipid peroxidation processes was evaluated by the content of malondialdehyde and acyl hydroperoxides in the vaginal-cervical flushing and plasma, the state of the antioxidant system – by the general antioxidant activity, catalase activity, superoxide dismutase, concentrations of ceruloplasmin. In addition, the level of stable metabolites of nitric oxide, neopterin, C-reactive protein was revealed. All findings were carried out using commercial kits for Enzyme-Linked Immunosorbent Assay (ELISA).

In the blood plasma and vaginal-cervical flushing, cytokines (TNFα, IL-1β, IL-8, IFNγ, IL-18, G-CSF, IL-4, IL-10), immunoglobulins of classes M, G, A (IgM, IgG, IgA), secretory immunoglobulin A (sIgA) was detected by ELISA using the Vector Best kit (Russia), the components of the complement system (C5, C6, C7, C8) using the diagnostic kit "Cytokine Ltd" (Russia). The activity of the C1-inhibitor (C1-inh.) was determined by the chromogenic method with the ability to inhibit C1-esterase. Registration was carried out using a microplate photometer “Sunrise”, Tecan (Austria).

The phagocytic activity of polymorphonuclear blood leukocytes after their isolation from the blood at a density gradient of Ficoll-Urografin (d = 1.077) was evaluated by determining the phagocytic index, phagocytic number and phagocytosis activity index by conventional methods. The activity of oxygen-dependent neutrophil-mediated systems was evaluated on a PD-303S Apel spectrophotometer (Japan) by the reduction reaction of nitro-blue tetrazolium (NBT-test) spontaneous and stimulated by zymosan (NBT-sp., NBT-st.) and a functional neutrophil reserve.

All clinical, instrumental and laboratory studies, pharmacological therapy was carried out with the voluntary informed consent of patients on the use of materials of medical and diagnostic measures related to this disease, exclusively for research purposes.

Statistical and mathematical processing of the research results was carried out according to the criteria of variational-statistical analysis with calculation of average values (M), arithmetic mean errors (m) using the Microsoft Excel 2010 software package. The significance of differences was evaluated by the
U-criterion. Only those differences that corresponded to p < 0.05 were considered statistically significant.

Results and discussion

Comparing the number of total differences in laboratory indicators of immune status at the systemic (peripheral blood plasma) and local (cervical-vaginal swab) levels with normal parameters (healthy women) with tuboperitoneal infertility, it was found that before treatment, such indicators were 100% of the studied. After the BPT, this percentage decreased to 93.3%, while only 6.7% returned to normal, 76.7% of the laboratory parameters studied were corrected, and 16.7% remained at the level of treatment initiation.

The use of Hepon did not affect the total number of altered and normalized indices, but increased the number of corrected ones to 83.3% and reduced the number of laboratory parameters remaining at the beginning of BPT up to 10%. The use of Cycloferon in BPT reduced the number of parameters changed from the norm to 73.3%, changed the level of normalized and corrected indicators to 26.7% and 73.3%, respectively. After the introduction of Lavomax into the BPT, the corresponding indicators are as follows: 63.3%, 36.7% and 63.3%.

The total differences in metabolic indicators at the systemic and local levels compared with the norm amounted to 93.3%. BPT reduced their number to 80.0%, while it was respectively normalized, corrected and remained unchanged 13.3%, 66.7%, and 13.3%. The introduction of Hepon into BPT led to the following distribution of the studied parameters: altered from the norm – 73.3%, normalized 20.0% and corrected 73.3%. The use of Cycloferon: altered from the norm – 60.0%, normalized 33.3%, corrected – 60.0%. The use of Lavomax: altered from the norm – 40.0%, normalized 53.3%, corrected – 40.0%.

It was important to compare the changes in all studied laboratory parameters individually at the systemic and local levels. The total differences in immune and metabolic parameters at the systemic level compared with the norm amounted to 100%. BPT reduced their number to 93.5%, while it was respectively normalized, corrected and remained unchanged at 6.5%, 80.6% and 12.9%. The introduction of Hepon into the BPT led to the following distribution of the studied parameters: 90.3% changed from the norm, 9.7% normalized, 83.9% corrected, remained at the level of BPT – 6.5%. The use of Cycloferon: altered from the norm – 74.2%, normalized 25.8%, corrected – 74.2%. The use of Lavomax: altered from the norm – 58.1%, normalized 41.9%, corrected – 58.1%.

The total differences in immune and metabolic indices at the local level compared with the norm amounted to 92.9%. BPT reduced their number to 84.6%, while it was respectively normalized, corrected and remained unchanged at 15.4%, 61.5% and 23.1%. The introduction of Hepon into BPT changed only the level of corrected parameters – 76.9% and those remaining at the level before BPT – 7.7%. The use of Cycloferon: altered from the norm – 61.5%, normalized 38.5% and corrected – 61.5%. The use of Lavomax: changed from the norm – 53.8%, normalized 46.2%, corrected – 53.8%.

The total differences of all the studied laboratory immune and metabolic indicators at the systemic and local levels compared with the norm amounted to 97.8%. BPT reduced their number to 90.9%, while it was respectively normalized, corrected and remained unchanged 9.1%, 75.0% and 15.9%. The introduction of Hepon into BPT changed the number of parameters studied: differences from the norm – 88.6%, 11.4% normalized, 81.8% corrected, remained at the level of BPT – 6.8%. The use of Cycloferon: altered from the norm – 70.5%, normalized 29.5%, corrected – 70.5%. The use of Lavomax: altered from the norm – 56.8%, normalized 43.2%, corrected – 56.8%.

It was important to find out not only the general quantitative but also the changes in each of the studied laboratory parameters according to the degree of disorder [8, 9].

It was found that with infertility of tuboperitoneal genesis before surgery, 100% of the studied indicators of immune status were changed from the normal values at the systemic (blood plasma) and local (cervical-vaginal swab) levels, while it was found that I degree of disturbances had 16, 7%, and II and III, respectively, 30.0% and 53.3%. It should be noted that with the II-III degree of disturbed laboratory parameters requiring mandatory profile correction [8, 9], 56.7% were found. After BPT, 93.3% of the parameters of the immune status turned out to be altered, and accordingly, I, II and III, the degree of disorders was 20.0%, 23.3%, and 50.0%. After the inclusion of Hepon in the BPT, 93.3% of indicators remained impaired, respectively, I, II and III, the degree of impairment was 26.7%, 20.0%, and 46.7%. The use of Cycloferon reduced the number of violated laboratory parameters to 73.3%, respectively, according to the degree of violation from I to III: 30.0%, 10.0%, and 36.7%. The inclusion of Lavomax in the BPT was the most effective since 63.3% of laboratory parameters remained altered, and I, II, and III degrees of violations had 20.0%, 10.0%, and 30.0% of parameters, respectively, at the systemic and local levels.

In infertility of tube-peritoneal genesis before BPT, 93.3% of the studied metabolic status indicators changed at the systemic (blood plasma) and local (cervical-vaginal swab) levels from normal values, while it was found that I degree of disturbances was 26.7%, and II and III, respectively, 13.3% and 53.3%. After BPT, 80.0% of metabolic parameters turned out to be altered, and accordingly, I, II and III degree of
disturbances were 26.7%, 20.0%, and 33.3%. After the inclusion of Hepon in the BPT, 73.3% of the indicators remained impaired (respectively, I, II and III, the degree of violations was 20.0%, 40.0%, and 13.3%). The use of Cycloferon reduced the number of violated laboratory parameters to 60.0%, respectively, according to the degree of violation from I to III: 20.0%, 26.7%, and 13.3%. The inclusion of Lavomax in BPT was most effective, since 40.0% of metabolic indicators remained altered, and I, II, and III degrees of disorders had 13.3% respectively at the systemic and local levels.

The total differences of all the studied laboratory immune and metabolic indicators at the systemic and local levels compared with the norm amounted to 100% of the metabolic status at the systemic and local levels, while it was revealed that I degree of disturbances were 19.4%, and II and III, respectively 29.0% and 51.6%. After BPT, 93.5% of the immunometabolic parameters turned out to be altered, and accordingly, I, II and III, the degree of disorders was 29.0%, 16.1%, and 48.4%. After the inclusion of Hepon in the BPT, 90.3% of the indicators remained impaired (respectively, I, II and III, the degree of impairment was 32.3%, 22.6%, and 35.5%). The use of Cycloferon reduced the number of violated laboratory parameters to 74.2%, respectively, according to the degree of violation from I to III: 32.3%, 12.9%, and 32.3%. The inclusion of Lavomax in the BPT was most effective, since 58.1% of metabolic indicators remained altered, and I, II, and III degrees of disturbances were 22.6%, 12.9%, and 22.6%, respectively, at the systemic and local levels.

The total differences in immune and metabolic indices at the local level compared with the norm amounted to 92.9%, while it was revealed that I degree of disorders was 21.4%, and II and III, respectively, 14.3% and 57.1%. After BPT or after incorporation of Hepon into it, 84.6% of immunometabolic parameters turned out to be altered; respectively, I, II and III degree of disturbances were 7.1%, 35.7%, and 35.7%. The use of Cycloferon reduced the number of impaired immunometabolic laboratory parameters to 61.5%, respectively, according to the degree of impairment from I to III: 14.3%, 21.4%, and 21.4%. After the inclusion of Lavomax in the BPT, 53.8% of the indicators remained altered, and I, II and III degree of violations were 7.1%, 7.1%, and 21.4%, respectively, at the systemic and local levels.

The total differences of all the studied laboratory immune and metabolic parameters at the systemic and local levels compared with the norm amounted to 97.8%, while it was found that I degree of disorders was 20.0%, and II and III, respectively, 24.4% and 53, 3%. After BPT, 90.9% of the immunometabolic parameters turned out to be altered, and, accordingly, I, II, and III degrees of disturbances were 22.2%, 22.2%, and 44.4%. After the inclusion of Hepon in the BPT, 88.6% of the indicators remained impaired (I, II and III, respectively, had a degree of impairment in 24.4%, 26.7%, and 35.6%). The use of Cycloferon reduced the number of violated laboratory parameters to 70.5%, respectively, according to the degree of violation from I to III: 26.7%, 15.6%, and 28.9%. The introduction of Lavomax into BPT reduced to 56.8% immunometabolic indices altered from the norm, and I, II and III degree of disturbances were 17.8%, 11.1%, and 20.0%, respectively.

When assessing the proper corrective effects of Hepon, Cycloferon, and Lavomax in the correction of laboratory immunometabolic disorders in infertility of tuboperitoneal origin, the following was established.

The introduction of Hepon into BPT, in comparison with it, had a positive effect on improving laboratory parameters of the immune status (19 points), immunometabolic parameters at the systemic and at the combined (systemic and local) level (10 and 6 points, respectively).

The use of Lavomax in the postoperative BPT in patients with tuboperitoneal infertility in assessing their own corrective effects was most effective since the sum of correction indicators was higher compared to Hepon and Cycloferon in the study at all levels: in terms of immune status — 46 points, metabolic status parameters — 50 points, laboratory immunometabolic parameters at the system level — 45 points, immunometabolic indicators at the local level — 60 points and the total immune and metabolic performance at the systemic and local level — 53 points.

The use of Cycloferon in BPT compared with Hepon and Lavomax showed an intermediate result.

References

1. Antimirova E.A., Letyaeva O.I., Dolnikova O.A. The condition of the local immunity of the reproductive system of women with inflammatory diseases accustomed to bacterial-viral infection. Immunologiya, 2016, Vol. 10 (19), no. 3, pp. 214-216. (In Russ.)

2. Buralkina N.A., Katkova A.S., Arutyunova E.E., Zhorova V.E., Batyrova Z.K., Vlasova G.A. Inflammatory diseases of the body of the small basin: pathogenetic aspects, diagnostics, clinic, treatment (literature review). Gynecology, 2018, Vol. 20, no. 3, pp. 12-15. (In Russ.)

3. Konoplya A.A., Gavrish S.A., Gavrilyuk V.P., Konoplya A.I. Immunology of tubal infertility. Scientific Notes of the Oryol State University, 2014, no. 7 (63), pp. 55-56. (In Russ.)
4. Konoplya A.A., Karaulov A.B., Konoplya A.I., Gavrilyuk B.P. Relationship between the correction of immune and oxidative disorders with the structural and functional properties of erythrocytes in chronic salpingo-oophoritis: monograph. Kursk: Kursk State Medical University, 2009. 180 p. (In Russ.)

5. Poh Omasharifa Binti Jamal, Konoplya A.A., Ivanova O.Yu. Immune and metabolic disorders at the systemic and local level with infertility of tuboperitoneal origin. Kursk Scientific and Practical Bulletin “Man and His Health”. Kursk, 2019, no. 3, pp. 63-72. (In Russ.)

6. Snimshchikova I.A., Shmaneva I.A., Akulenko E.O., Snyashchikova M.D., Halilov M.A., Obolenskaya T.I. Secondary immune deficiency on the background of inflammatory diseases of the pelvic organs. Russian Journal of Immunology, 2015, Vol. 9 (18), no. 1 (1), pp. 181-182. (In Russ.)

7. Yakovleva N.V. Surgical treatment of tubular genesis: problems and solutions. Bulletin of New Medical Technologies, 2014, Vol. 21, no. 1, pp. 121-127. (In Russ.) (In Russ.)

8. Zemskov A.M., Zemskov V.M., Chershnev V.A., Reshetnikov S.S., Galimzyanov H.M., Zemskova V.A. Clinical Immunology Guide for Practitioners. Moscow: Triada-X, 2011. 288 p. (In Russ.)

9. Zorina V.N., Likhacheva V.V., Zorina R.M., Bazhenova L.G., Tretyakova T.V., Arkhipova S.V., Renge L.V., Zorin N.A. Imbalance in cytokine network/regulatory transport protein system in various types of infertility during in vitro fertilization programs. Medical Immunology (Russia), 2018, Vol. 20, no. 2, pp. 203-214. (In Russ.)

doi: 10.15789/1563-0625-2018-2-203-214.

Authors:
Po O.B.J., Assistant Professor, Department of Obstetrics and Gynecology, Kursk State Medical University, Kursk, Russian Federation

Konoplya A.A., PhD, MD (Medicine), Associate Professor, Department of Obstetrics and Gynecology, Kursk State Medical University, Kursk, Russian Federation

Medvedeva I.N., PhD (Medicine), Associate Professor, Department of Obstetrics and Gynecology, Kursk State Medical University, Kursk, Russian Federation

Received 31.03.2020
Accepted 19.04.2020