

# Norcolut with immune modulators in the complex treatment for hyperplastic uterine processes

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*Summary:* The results are presented of the treatment of 55 patients for hyperplastic endometrial processes with the preparation norcolut combined with the immune modulators thymalinum and myelopidum. It was found that the application of the suggested schemes of the introduction of the medicines mentioned increase the treatment effectiveness and enlarges its possibilities.

## INTRODUCTION

At present, the tendency towards enlarging the possibilities of conservative treatment for benign uterine diseases has formed, this fact being conditioned by the achievements of modern pharmacotherapy first of all. Among highly active hormonal combinations introduced into practice, the preparations of the norsteroid series, in particular, norcolut should be noted. This latter possesses local antiestrogenic, anti-fibromatous and anabolic effects, is why it can be applied for either hyperplastic

endometrial processes or for uterine myomas<sup>(3)</sup>. According to our data, endometrial hyperplasia relapses still occur in from 25.6% to 51% of cases depending upon the duration of observation; patients experience depression of the liver absorption function, and also develop immune suppression<sup>(1, 4, 9)</sup>. The correction of the after-effects detected and, above all, of the immune system state, can be accomplished by means of the preparations of the thymus gland (thymalinum) and of the bone marrow (myelopidum), which belong to a new class of biological regulators - cytomedines. The preparations perform the transfer of specific information which is necessary for normal dynamic, development and interaction of cellular populations. Thymalinum is a preparation representing the complex of polypeptide fractions singled out of the thymus gland of cattle. It is able to stimulate immunological reactivity, i.e. it regulates the number of T- and B-lymphocytes, stimulates the reaction of the cellular immunity, intensifies phagocytosis and promotes regenerative processes<sup>(6)</sup>. Myelo-

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pidum is a preparation developed at the Institute of Immunology of Ministry of Health Protection, the USSR. It is a preparation of polypeptide nature, as it contains peptides of the molecular mass of 1000-3000 Daltons which were obtained from the cells of the bone marrow of mammals. It influences the functioning of the B-system of the immunity. The preparation intensifies the production of antibodies at the peak of the immune response, involving "silent" cells in the population of mature antibody producers into the synthesis. The analgetic effect of myelopidum was discovered recently which fact enables us to apply this preparation to patients with the expressed algic syndrome.

## MATERIALS AND METHODS

Fifty five patients at the age of  $37.8 \pm 1.5$  were under our observation. They received one of the above preparations in the complex treatment. Thus, 25 women received norcolut combined with myelopidum, while 20 received norcolut combined with thymalinum. Myelopidum was administrated at the first phase of the menstrual cycle simultaneously with taking norcolut, in intramuscular injections of 3 mg every other day for 3 months. During the following 3 months the patients received norcolut only. Thymalinum was administrated in 10 mg, in intramuscular injections on the 5th, 7th, 9th, 11th and 13th days of the menstrual cycle during the 6 months of taking norcolut. Follow-up examination of the patients was performed at 3 and 6 months after the beginning of the treatment.

Patients' complaints, case histories, heredity, states of the genital, menstrual and generative functions were studied. General and special examinations were also performed before and during the treatment. All the patients underwent gynaecological examination, colposcopy, ultrasonic scanning of the small pelvic organs ("Toshiba", Japan). The state of the uterine body mucosa was evaluated by means of histological examination of endometrial scrapings obtained before the observation and in the 7th month of it, during the second phase of the cycle after hysteroscopy (hysteroscope by "Storz", Germany). The immune and endocrine system indices were also defined.

The state of the endocrine system was defined by the data of the rectal temperature and the

levels of gonadotrophic (luteinizing - LH, follicle stimulating - FSH) and steroid (estradiol - E<sub>2</sub>, progesterone - P) hormones in the blood serum by means of radioimmunologic methods with the use of standard kits of reagent "Sea-Sorin" (France).

The state of T- and B-systems of lymphocytes was defined by such indices as the total number of cell (T<sub>total</sub>). T-lymphocytes carrying receptors to Fc-fragments of immunoglobulin M (T<sub>m</sub> - helpers chiefly) and G (T<sub>g</sub> - suppressors chiefly); the total number of B-lymphocytes (B<sub>total</sub>) (7) and carrying receptors to erythrocytes of a mouse - B<sub>m</sub> (?); lymphocytes forming rosettes with their own erythrocytes (A-RFC); concentration of immunoglobulins, A, M, G (Ig A, Ig M, Ig G). The received data were treated by the Student-Fisher method of the variation statistics, t-criterion and the reliability of the differences were evaluated according to the Student-Fisher's tables.

In apparently healthy women and also in the patients with the preserved menstrual cycle, taking the blood for the evaluation of the above mentioned indices was carried out on the 20-24th day of the cycle at the same morning hours, before the treatment and during the cycle of cancellation after the completion of the treatment. In the group of women having anovulation, taking the blood was carried out at the same terms, taking for the first day of the cycle the first day of the menstrual-like reaction.

## RESULTS

As a result of the examination performed, it was found that the patients' chief complaints involved acyclic bleeding, pains in the lower part of the abdomen, abundant menses, general weakness, giddiness and secondary infertility. Thirty five women who subsequently received the course of norcolut and myelopidum, complained of pains in the lower part of the abdomen associated with menses. Women who received norcolut combined with thymalinum suffered chronic gastritis (5 patients) with the secretory activity preserved and with chronic colitis (7 patients). Besides the above complaints, the overwhelming majority of women of this group noted occasional pains in the area of the liver and in the epigastric and other parts.

Heredity was an aggravation in only 6 women. It was found that close relations—generally on the mother's side, of 32.7% of the patients examined had had tumours of the genital system. In the genealogy of every fourth patient, a myoma of the uterus was noted, and tumours of various localizations were also in every fifth patient.

Estimating the childhood sickness rate of our patients and during their adolescence, it is necessary to indicate that 45 (81.8%) women had had children's infections, 49 (89%) had had virus diseases, every second had had quinsies, every fourth had suffered from diseases of the bronchi and lungs. At mature age, there was an increased proportion of diseases of the gastro-intestinal-hepatic complex and of metabolism (every second patient), of allergic reactions (every fifth), of the vascular system (every fifth) and also of inflammatory diseases. Every third patient had undergone tonsillectomy, every fifth - appendectomy. So in the patients examined there was a markedly high degree of hereditary aggravation of the infectious toxic diseases, and also those of the peripheral organs of the immune genesis (quinsies, chronic tonsillitis, appendicitis) during the period of formation of the function of the female reproductive system, and also a high rate of extra-genital disease at mature age.

As a result of hysteroscopy and diagnostic curettage, it was found that, of 35 women who subsequently underwent the course of norcolut and myelopidum, endometrial hyperplasia was detected in 17, while endometrial polyps were detected in 18. In 9 of 18, polyps were present in the background of the secretorily changed endometrium, and in 9 more women they were associated with the hyperplastic endometrium. In 12 patients, uterine myomas were found with predominant subserous location of myomatous knots, in 33 women, internal endometriosis was found.

The preserved rhythm of menses with the two-phase rectal temperature in the initial cycle was found in 9 women; the two-phase temperature with insufficiency of the lutein phase was found in 19 patients. Acyclic bleedings developed in the background of the monophasic rectal temperature occurring in 7 women. Of the group of women (20 patients) who underwent the course of norcolut with thymalinum, hyperplasia was found in 16, while in 8 of them, it was focal; in the remaining 4 women, glandular fibrous endometrial polyps were found in the background of the unchanged mucosa of the uterine body (in 2, the proliferation phase, was observed, in 2 the secretion phase was observed). Endometrial polyps associated with hyperplasia were found in 9 patients. In these patients, the above changes of the endometrium were combined with uterine myomas. As has been mentioned, 12 patients of this group had suffered mild episodes of gastro-intestinal-hepatic diseases before.

As a result of follow-up examinations, it was found that in just 3 months after taking norcolut and myelopidum the overwhelming majority of patients noted reduction of pain intensity as well as reduction of the blood volume discharged during menses. In only 3 patients the applied therapy failed to have the required effect. In 6 months the above positive results were maintained. All the patients demonstrated the regular cycle during the whole period of observation, two patients, who were sterile before, became pregnant in the 6th month of treatment. In the evaluation of the menstrual cycle state it was found that in 3 months the cycle was two-phase in 13 patients, in 19 patients it was two-phase associated with the lutein-phase insufficiency, while it was monophasic in 3 women. After the treatment course completion, defective two-phase rectal temperature occurred in 26 pa-

tinets, while in 9 patients, it was of full value. At the same time it was found that the normalization of the endometrial structure and its secretory transformation occurred in 23 patients (65.7%), endometrial hyperplasia was found again in 9 patients (25.7%) and in 3 patients (8.6%), there was endometrial hyperplasia associated with glandular endometrial polyps. At the same time, we noted complete regression of the endometriosis foci in 34.3% of patients, and in 57.1% of patients, their reverse development was observed.

Examination of the immune and endocrine system states showed that their indices demonstrated expressed reaction to the medicine applied. In from 3 to 6 months of treatment, there occurred increase of LH and FSH concentrations. Simultaneously initially increased concentration of E<sub>2</sub> dropped and there occurred some increase of progesterone concentration (see Figure 1). The effect of the preparation results in increasing of the number of A-RFC (young undifferentiated thymocytes), was accompanied by the intensifying of the B-cell function that deve-

loped temporary increase of Ig M and Ig A concentration and Ig G normalization (see Figure 2).

By the time of the follow-up examination, all the women belonging to the 2nd group noted improvement in general well-being, regular menstrual rhythm and reduction of blood loss during menses after 6 months of treatment with norcolut and thymalinum. In none of the cases, were complaints of aggravation of the gastro-intestinal-hepatic complex state found. All the patients took the treatment well. One patient, who had suffered infertility before, became pregnant, though her pregnancy ended with partus maluris. In evaluating the state of the menstrual cycle, its normalization was observed. Thus, in just 2 women, the rectal temperature was two-phase before the treatment, in 8 women, the temperature was two-phase associated with insufficiency of the lutein phase, and in 6 women, the temperature was two-phase of full value. As a result of follow-up diagnostic curettage and hysteroscopy, histological examination of scrapings demonstrated the endometrium at the secretion phase in 13 patients of 20,

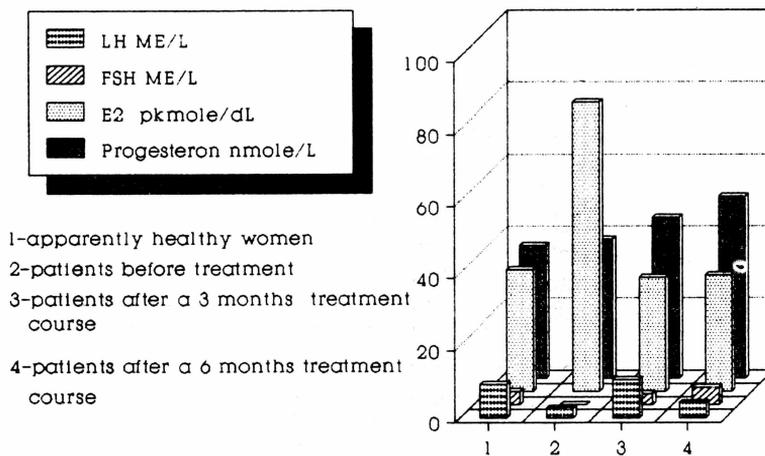


Fig. 1. — Endocrine system index changes in patients of reproductive age treated with norcolut and myelopidum.

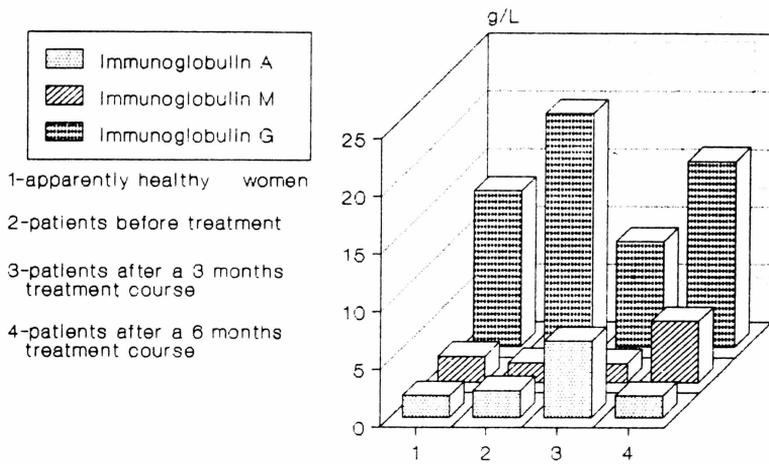


Fig. 2. — B-lymphocyte system index changes in patients of reproductive age treated with norcolut and myelopidum.

in 7 patients, there was focal endometrial hyperplasia, while in 3 of them glandular fibrous endometrial polyps were found.

The application of thymalinum and norcolut promoted normalization of FSH, E<sub>2</sub> and P content (see Figure 3). Among the immunity indices, the indices of T-lymphocyte system, i.e. T<sub>tot</sub> and the coeffi-

cient T<sub>m</sub>/T<sub>g</sub> were responsible for most changes. Normalization of the latter vividly shows the change of antitumoural immunity (see Figure 4).

It is worthwhile mentioning that all the patients who experienced disease relapse subsequently underwent either intrauterine cryointervention or surgery.

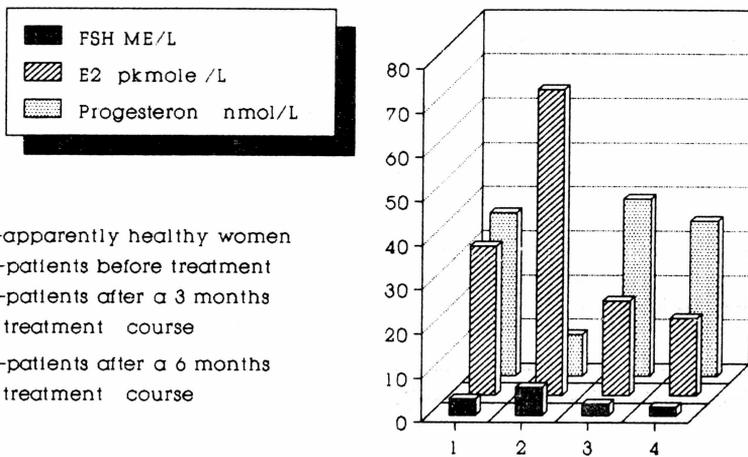


Fig. 3. — Endocrine system index changes in patients of reproductive age treated with norcolut and thymalinum.

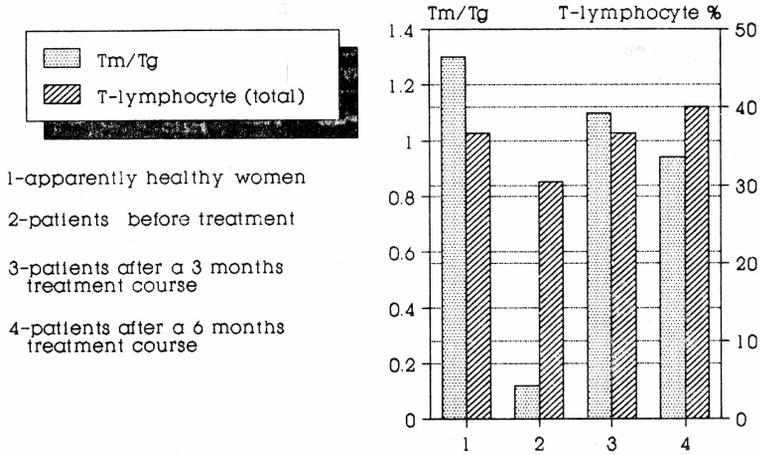


Fig. 4. — T-lymphocyte system index changes in patients of reproductive age treated with norcolut and thymalinum.

## DISCUSSION

Our study showed that the application of the immune modulators thymalinum and myelopidum combined with norcolut improves the clinical effect of the latter. Practically all the patients noted improvement of general well-being, sleep, appetite and being of good cheer. At the same time, the features of the preparation are worth noting. Thus, myelopidum, being an immune modulator, possessed analgesic characteristics as well and is advisable to a greater deal in the combined uterine pathology, including endometriosis, associated with expressed algescic syndrome. According to the data obtained by R. V. Petrov and co-authors<sup>(8)</sup>, the latter effect is realized through the opioid receptors, i.e. myelopidum completely displaces the marked opiates from the spots of their specific binding on the neural cells of the brain.

Thymalinum renders a more generally expressed therapeutic effect and its application is most effective in chronic genital or external genital pathologies. We suppose that this effect is conditioned by cytomedine effect in restoring specific

functions of organs and tissues in cases of their depression. Regulating effect on ribosome function is supposed to be one of the action mechanisms of cytomedines, which promote the synthesis of specific proteins in cells and also restore and preserve regular mechanisms of protein synthesis that results in homeostasis normalization<sup>(5)</sup>. Neurotrophic characteristics of cytomedines, including thymalinum, are also known. The above characteristics are notable for a wide spectrum central activity. These data are likely to account for the therapeutic effect of thymalinum, that is applied in combination with norcolut.

Our study enables us to draw the conclusion that the application of norcolut in combination with immune modulators proves to be highly effective, it promotes restoration of the dynamics of the reproductive system organs and can be a method of choice in the complex treatment of patients for hyperplastic uterine processes.

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