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# PATHOGENETIC GROUNDING OF THE NON-CANCEROUS UTERINE PATHOLOGY PHASE THERAPY AMONG REPRODUCTIVE AGE WOMEN

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**ПАТОГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ ЭТАПНОЙ ТЕРАПИИ ДОБРОКАЧЕСТВЕННОЙ ПАТОЛОГИИ МАТКИ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА**
*Национальный медицинский университет имени А. А. Богомольца, Киев, Украина,*
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Изучено влияние гормональной терапии а-ГнРГ и ЛНГ-ВМС на клиническое течение, показатели гомеостаза и функциональное состояние матки у женщин с аденомиозом, гиперплазией эндометрия и сочетанной патологией эндо- и миометрия в динамике. Выявлены новые звенья патогенеза в развитии доброкачественной патологии матки за счет нарушения функции рецептивности эндометрия. Разработана комплексная поэтапная гормональная терапия для женщин репродуктивного возраста с сочетанной доброкачественной патологией матки, проведена оценка ее влияния на рецептивность эндометрия.
**Ключевые слова:** комплексная гормонотерапия, доброкачественная патология матки, рецепторы к прогестерону, рецепторы к эстрогену, ЛНГ-ВМС, α-ГнРГ.

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The influence caused by the GnRH and intra-uterine gestational sac “Mirena” hormone therapy on the clinical progression and homeostasis indexes as well as the uterine functional state among women with adenomyosis, endometrium hyperplasia accompanied by the endo- and myometrium pathology in dynamics was studied. New components of the non-cancerous uterus pathology development caused by the endometrium receptive function disorder were established. Complex phase hormone therapy for the reproductive age women with the non-cancerous uterus pathology was developed; its effect on the endometrium receptive function was evaluated .
**Key words:** complex hormone therapy, non-cancerous uterus pathology, progesterone receptors, estrogen receptors, intra-uterine gestational sac “Mirena”, GnRH.

The topicality of the endometrial hyperplasia and adenomyosis process researches is determined by a high risk of malignancy and problems associated with menstrual irregularities, dysfunctional uterine bleeding, anemia. Endometrial hyperplasia occupies a significant place in the structure of gynecological diseases of women of reproductive age and is one of the most frequent causes of hospitalization in gynecology (10 to 18%) [1; 3; 5; 8].

Recent years, the new approaches to conservative and surgical treatments for benign uterine pathology have been introduced, but there is no single algorithm that determines the management of such patients’ treatment. In the early stages of the disease a differentiated approach to the treatment of women with adenomyosis and endometrial hyperplasia who have not realized their reproductive function is possible [2; 4; 6; 9]. Development of modern drugs has expanded the possibilities of conservative treatment of the non-cancerous uterine pathology. The most practical value of the entire set of drugs currently represents hormone [3; 7], but the issue of rational evidence-based treatment of combined pathogenesis of non-cancerous uterine pathology remains urgent and is the subject for discussion.

## Materials and Methods

The aim of our study was to improve the efficiency of conservative treatment of adeno-

myosis with endometrial hyperplasia in women of reproductive age by means of introducing pathogenic phased hormone therapy.

The study involved 135 women with combined non-cancerous uterine pathology (adenomyosis with endometrial hyperplasia) treated at the Center for Women's Health of "Feofania" Hospital and the City Maternity Hospital N 3, Kyiv.

Age of women who joined the control group ranged from 24 to 43 years. All patients underwent general examination according to the MOH of Ukraine order N 676 of 31.12.2004. In the study group diagnosis verification was performed by means of ultrasound investigation with further implementation of Hysteroresectoscopy or individual endometrium and cervical canal curettage.

The material obtained was subjected histological study, depending on results the proper management was chosen. The curettage, endometrium and cervical canal resectate that were fixed in 10% neutral formalin solution as well as 4.5 microns thick sections (they were processed by means of hematoxylin-eosin staining) served the subject for the morphological research.

The universal peroxidase set Ultra Vision LP Detection System: HRP Polymer (RTU) was used for the immune histological chemical reaction's visualization. The background tissue staining was provided by means of hematoxylin. The rabbit monoclonal antibodies were used for the immune histological chemical reaction. The glass plates were heated on a steam bath for a "tell-tale" technique. The estrogen receptors (ER) and progesterone receptors (PR) state was defined on the paraffine sections with the generally accepted methods involved. The scale developed by the manufacturer (HISTOScore) was used to evaluate the reaction results. The statistic processing of the results obtained was performed with the generally accepted methods with the Student Criterion being involved.

In order to achieve the aim of the research, the assessment of the hormone therapy effect applied towards 135 women with the non-cancerous uterine pathology (adenomyosis with endometrial hyperplasia) was performed on Phase 1: group 1 was composed of 69 women who used intra-uterine gestational sac (IUGS) "Mirena", group 2 was composed of 66 women who used GnRH. Phase II witnessed the assessment of the combined non-cancerous uterine pathology complex treatment effectiveness among 35 women of reproductive age (group 3) on the basis of the scheme developed by us, which included "Diferelin" 3.75 mg 1 every 28 days for 6 months with the following IUGS "Mirena" introduction. Assessment of health indicators conducted at 3, 6 and 12 months of therapy, the study of the effect of hormone therapy on endometrial status was performed after 6 months of treatment through paypel-biopsy or individual mucous uterine curettage.

## Results and their Discussion

Menstrual disorders by type hyperpolymenorrhoea prior hormonetherapy was detected in 92.6% of women examined. The volume of the menstrual blood loss was determined by means of menstrual blood loss maps, and the following results were obtained: I and II groups women — 183 points, 206 points for women of the group III which was twice as high as for groups I and II (see fig. 1). (group 1, group 2, group 3, initial phase, 3 months, 6 months, 12 months).

As fig. 1 shows, group I women indicated the gradual decrease of the menstrual blood loss on the background of IUGS "Mirena": 30 % on the 3rd month, 50% on the 6th and 78% on the 12th one. The group II women who used GnRH «Diferelin» showed the following indexes: 74% decrease of the menstrual blood loss on the 3rd month, absence of menstruation on the 6th month and the tendency towards the blood loss increase on the 12th month.

Decrease of menstrual blood loss to 74.8% on the background of the complex hormone was observed within the first 3 months

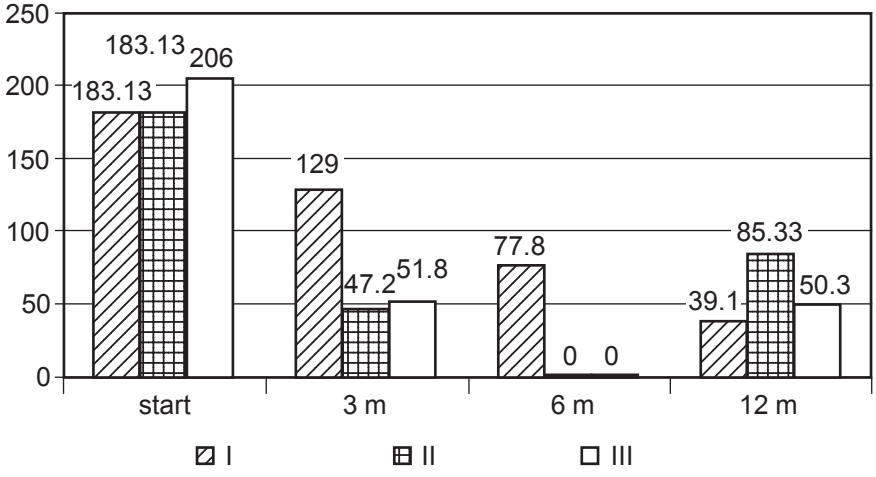


*Fig. 1.* Blood loss dynamics on the hormone therapy background

of observation; absence of menstruation for all the women on the 6th month, and (50.3±10.5) points of the menstrual blood loss on the 12th month which corresponds the norm.

We assessed pain syndrome on the background of hormonal therapy in women with the non-cancerous uterine pathology. In all the surveyed groups 3 and 6 months the intensive decrease of pain index (PI) was observed. After 12 months of IUGS "Mirena" therapy, PI decreased by 64.3% from baseline, while the second group had an increase of this indicator. The complex therapy showed the two times decrease of PI (57.84%) on the 3rd month, 85.29% decrease compared to the initial index on the 6th month, and the absence of the pain syndrome on the 12th month.

The hemoglobin index dynamic monitoring of women with the non-cancerous uterine pathology showed the given index increase on the 3rd and 6th months of observation: 20.5% for group 1 on the 6th month, 24.4% in group II on the 6th month, 20.2% in group III on the 6th month. Groups I and III showed the tendency towards the hemoglobin growth after 12 months, while group III indicated sharp decrease of hemoglobin level.

All the women with the combined non-cancerous uterine pathology who took part in the research underwent hysteroscopy with the endometrium biopsy and its following investigation.

The results of the hysteroscopy with the endometrium biopsy conducted in group II in 6 month showed the endometrium atrophy; pipal-biopsy conducted in 12 months showed the following results: 79.7% of women of group I indicated the lack of functional activity of glandular epithelium, endometrium with the atrophy signs and separate glands, stroma — with the endometrium infiltration, 20.3% — endometrium sectoral transformation. Group II showed 68.2% of the endometrium sectoral transformation (initial stage), 31.8% — endometrium in the proliferation stage.

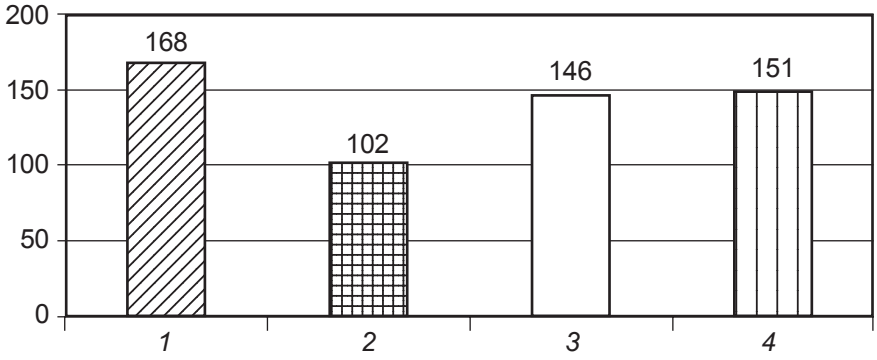


*Fig. 2.* IUGS "Mirena" effect on endometrium receptiveness: *1* — PR prior to treatment; *2* — PR after treatment; *3* — ER prior to tratment; *4* — ER after treatment

Women of group III underwent the hysteroscopy with the endometrium biopsy in 6 months. All the women indicated the endometrium atrophy with separate glands. The endometrium pipal-biopsy was performed after 12 months of complex therapy: 91.42% of women showed the lack of functional activity of glandular epithelium endometrium was atrophied, and 8.57% showed the endometrium sectoral transformation.

The analysis of the medicine therapy effect on the endometrium receptive function stated that the GnRH-"Diferelin" application for 6 months led to the receptors level normalization to progesterone and estrogen (Fig. 2), which emphasizes the application of the given medicine on Phase 1 and IUGS "Mirena" on the second one.

It is defined that the longtime application of levonorgestrel with the IUGS "Mirena" applied as the means of monotherapy led to the decrease of receptors levels towards progesterone and receptors level normalization towards estrogen. (Fig. 3).

Thus, the gradual application of GnRH with the sensitivity restoration to the progesterone hormone therapy with the following IUGS "Mirena" introduction determines the longtime medicinal effect of the combined non-cancerous uterine pathology (adenomyosis with endometrial hyperplasia).

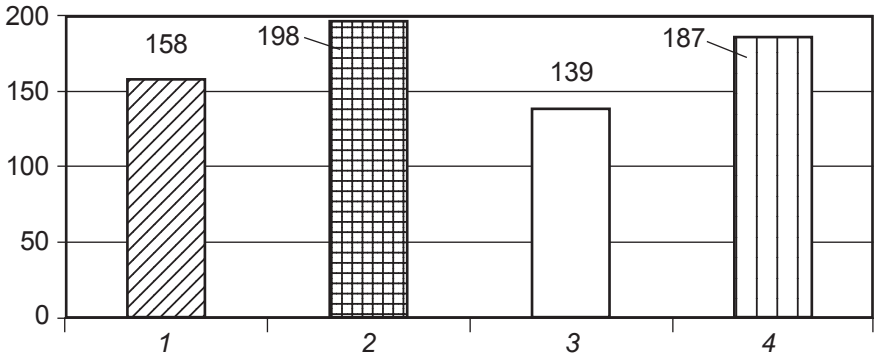


*Fig. 3.* GnRH effect on endometrium receptiveness: *1* — PR prior to treatment; *2* — PR after treatment; *3* — ER prior to tratment; *4* — ER after treatment

The study of the quality of life of women with the non-cancerous uterine pathology on the background of IUGS “Mirena”, GnRH and complex hormone therapy was performed by means of a simultaneous survey of the patients state with the help of the SF-36 questioner on the 12th month of observation. The integral life quality index stood 648 points for IUGS “Mirena”, 441 point for a GnRH and 722 points for complex therapy.

## Conclusions

GnRH appointment for 6 months to cause suspension of menstruation leads to endometrium sensitivity restoration recovery towards progestins, establishment of receptors systems physiological correlation that provides with the possibility to perform the pathology genetically targeted rational therapy of the combined non-cancerous uterine pathology (adenomyosis with endometrial hyperplasia).

Gradual application of GnRH and IUGS “Mirena” among women examined significantly improves hematologic, ultrasound, endoscopic and morphological parameters in dynamic observation data compared with monotherapy medicines.

The use of the offered combined adjuvant therapy of the non-cancerous uterine pathology in women of reproductive age significantly improves parameters of physical functioning, general health and vitality, improves performance of physical and psychological components of health, thus, improves quality of life.

**Ключові слова:** комплексна гормонотерапія, доброякісна патологія матки, рецептори до прогестерону, рецептори до естрогену, ЛНГ-ВМС, α-ГнРГ.

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