

NEW APPROACHES TO PROPHYLAXIS OF ENDOMETRIUM HYPERPLASIA RELAPS IN PREMENOPAUSAL WOMEN

INTRODUCTION

The problem of hyperproliferative diseases and tumors of the female reproductive system continues to be one of the leading problems in modern gynecological practice and has no tendency to decrease [1, 2, 6]. Endometrial hyperplasia (EH) deserves a special place in the hyperproliferative diseases structure. Its frequency reaches 14–63% in the gynecological diseases structure despite the improvement of existing and modern methods of diagnosis and treatment. According to native and foreign authors, the EH relapse rate ranges from 25.9% to 78% [5, 9, 14, 20].

Nowadays, EH is a significant medical and social problem, because the main manifestation of this condition is abnormal uterine bleeding (AUB) which leads to hospitalizations in a gynecological hospital, to inability to perform professional duties and generates to isolation and self-doubt development [3, 15, 22].

Especially relevant, from a medical point of view, the problem of EH is considered in women of premenopausal and menopausal age. Clinical course of EH during this period is characterized by a high relapse rate. Thus, according to modern studies, despite hormone therapy application for 6 months or more, the relapse rate in premenopausal women is 24.5%, and in postmenopausal women is 17.0% [7, 9, 11, 12]. In cases when hormone therapy was not conducted relapse rate within 6 months is increased up to 95.6%. In 2.1% of cases the progression of glandular hyperplasia to atypical is observed and in 50% of cases leads to malignant transformations [6, 12, 16]. At the same time, EH is characterized by limited opportunities for conservative treatment in premenopausal women group due to concomitant extragenital diseases and a high risk of malignancy [8, 13, 21, 23].

Physiologically, premenopausal period is characterized by variability in menstrual cycles, which begin at the age of 40–45 years and end with the onset of menopause. Against the background of menstrual disorders, vasomotor and psychoemotional symptoms of estrogen deficiency may appear, variable levels of follicle-stimulating hormone, estradiol (E_2), decreased of progesterone (PG), inhibin B and anti-Mullerian hormone levels are noted [7, 9].

Due to a gradual E_2 and PG levels decrease, an imbalance between intake and expenditure energy, and the beginning of a metabolism slowdown, the vast majority of premenopausal wom-

en increase their body weight. An important marker of adverse metabolic changes in women is a sharp increase in weight and redistribution of adipose tissue with the formation of abdominal and/or visceral type of obesity. That leads to metabolic syndrome development which increases heart diseases and stroke possibilities in 3 times [8, 10, 13, 23]. From another side increase in adipose tissue accumulation leads to the metabolic form of hyperestrogenemia due peripheral androstenediol aromatization which increase the “estrogen pool” in the body and initiates the EH development [21, 25].

An important role in the EH genesis is assigned to the pathology of the hepatobiliary complex, which can cause chronic hyperestrogenism due to delayed utilization of estrogen in the liver. That mechanism is realized through sex hormone binding globulin content decrease that leads an increase in biologically active estrogens levels due to decreased androgens inhibition [21, 25].

For an intime diagnosis and an adequate treatment tactics a comprehensive diagnostic algorithm have to be applied which includes an assessment of complaints, anamnesis, objective and instrumental examination data. The main method for complete EH diagnosis verification is pathohistological examination of the material obtained during hysteroscopy or fractional curettage of the uterine cavity and cervical canal. Indications for this intrauterine intervention are determined taking into account clinical manifestations, anamnesis data and additional methods of examination [1, 3, 5, 6, 16].

After the EH diagnosis is established, the physician faces the question of determining the optimal medical therapy, which should first of all be effective, with low toxicity and adverse reactions, and suitable for long-term period. The appointment of hormone therapy for EH in reproductive and premenopausal age involves the elimination of anovulation, the achievement of cyclic secretory transformation of the endometrium. Currently, progesterone drugs, both hydroxyprogesterone derivatives (mainly medroxyprogesterone and oxyprogesterone) and 19-nortestosterone, are widely used for the EH treatment [19, 20, 22].

In order to improve the effectiveness of hormone therapy the group of authors' advice to add phytochemicals based on indole compounds which are isolated from the cruciferous family plants (Cruciferous) – all types of cabbage, brussels sprouts, cauliflower and broccoli. Taking

V.O. BENIUK

MD, professor, head of the Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0002-5984-3307

V.H. GINZBURG

MD, associate professor, professor, Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0001-6667-1913

D.O. GOVSIIEV

MD, professor, Department of Obstetrics and Gynecology, Institute of Postgraduate Education, Bogomolets National Medical University, Kyiv
ORCID: 0000-0001-9669-0218

V.F. OLESHKO

PhD, assistant, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0003-2493-2892

T.V. KOVALIUK

PhD, assistant professor, Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0001-9339-881X

Y.V. KRAVCHENKO

graduate student, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0001-6263-3514

A.S. LUCHKO

graduate student, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv
ORCID: 0000-0002-6625-3460

Contacts:

Tetiana V. Kovaliuk
Kyiv City Maternity Hospital No. 3, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University
7 V. Kuchera str.
03148 Kyiv, Ukraine
Tel.: +38 (066) 422 47 21
email: tatyana7@meta.ua

into account anti-oncogenic and anti-estrogenic properties of the drug can be widely used in the treatment of dishormonal diseases of the female reproductive system: EH, endometriosis, uterine fibroids, functional ovarian cysts and benign breast pathology. Indole-3-carbinol blocks the development of hyperplastic processes in hormone-dependent tissues due to the cytochrome P450-CYP1A1 isoform expression, which hydroxylates E_2 in the second position with the formation of 2-hydroxyestron, which has a pronounced antiproliferative activity [4, 17, 18, 24].

Research aim: to evaluate the effectiveness of therapy aimed on EH relapse prevention in premenopausal women.

MATERIALS AND METHODS

A prospective, clinical and paraclinical examination of 76 premenopausal age women who were hospitalized with an established diagnosis of EH was conducted. In addition to the general clinical examination, all women underwent transvaginal ultrasound examination (TVUSE), determination of E_2 , PG, homocysteine (HC), folic acid (FA) and HOMA index in blood serum. Special attention was paid to the body mass index (BMI) and blood pressure (BP) determination. In order to verify the diagnosis and as the first stage of treatment, all women underwent hysteroresectoscopy, followed by pathohistological examination (PHE) of the endometrium. Later, after receiving the results of PHE, women were divided into two groups:

- Main group included 40 women who received twice a day oral progestins (dydrogesterone 10 mg) in combination with Depapilin® 395 mg (Ozymuk Pharm, Kyiv, Ukraine) which includes indole-3-carbinol, *Vitex agnus-castus*, *Brassica*, *Camellia sinensis*, as well as dietary recommendations for conservative therapy aimed at preventing EH recurrence.
- Comparison group included 36 women who received only oral progestins (dydrogesterone 10 mg) twice a day for conservative therapy aimed at preventing EH recurrence.

Depapilin® addition to conservative therapy was justified by the pronounced antiproliferative effect of indole-3-carbinol on the endometrium. It is known that *Brassica* and *Camellia sinensis* extracts are natural source of FA, which is necessary to normalize the level of HC and has a positive effect on the gastrointestinal tract.

Comparison of results and evaluation of the effectiveness of proposed conservative therapy was carried out after 6 and 9 months from the treatment beginning.

Results were processed using variation statistics methods using Statistica for Windows and Microsoft Excel 13.0 programs. Discrepancies were defined as possible at $p < 0.05$.

RESULTS OF THE RESEARCH

The average age of the examined women was 47 ± 3.5 years. In the vast majority of examined women – 58 (76.3%) the main characteristic symptom and reason for medical help encounter was chronic AUB, while the remaining 18 women (23.7%) applied urgently in due to the acute AUB.

The average duration of menstrual bleeding was 8.6 ± 0.3 days, which was 7% higher than the maximum allowable norm. The average duration of the menstrual cycle in most of the examined women was within the normal range – 32.7 ± 2.6 days.

The structure of gynecological morbidity in patients with EH was dominated by recurrent AUB, which was characteristic for 38 (50.0%) of the examined women. 32 (84.2%) of them have already performed surgical interventions in the uterine cavity: separate diagnostic curettage – 12 (37.5%) and hysteroresectoscopy – 20 (62.5%). Among the pathohistological responses, simple non-atypical EH was detected in 8 (25.0%) cases, complex non-atypical EH in 19 (59.4%) cases, endometrial polyps in 5 (15.6%) cases. Conservative therapy was performed in 4 (10.5%) cases. Also, attention was paid to the high percentage of inflammatory diseases of the female genital organs – 40 (52.6%), as well as background and precancerous diseases of the cervix – 24 (31.6%).

The structure of extragenital morbidity in the examined women was dominated by cardiovascular diseases – 28 (36.8%), gastrointestinal tract diseases – 38 (50.0%), obesity – 22 (28.7%) and chronic urinary tract diseases – 14 (18.4%).

Almost in half of the patients – 32 (42.1%) the primary signs of metabolic syndrome which were characterized by BP increase and abdominal type of obesity were revealed. Thus, the average BP values ranged from $136 \pm 8.6 / 94 \pm 6.2$ mm Hg, which we regarded as the initial manifestations of arterial hypertension. The average BMI of the examined women was 28.6 ± 2.6 , which we considered as overweight and, in combination with BP indicators, was an indication for further examination for the metabolic syndrome presence. The average waist circumference in the examined women was 89 ± 6.4 cm, which exceeded the maximum allowable norm by 10%.

The average E_2 value in the examined women was 167 ± 6.2 pg/mL, the average PG value was 10.6 ± 0.4 nmol/L, which was considered as hyperestrogenemia manifestations.

Taking into account the anamnestic data, the structure of extragenital pathology and the results of a physical examination that established the presence of metabolic syndrome manifestations, the determination of HOMA index, HC and FA indicators were added to the comprehensive examination of women with EH.

The average HOMA index value was 27.6 ± 2.1 , which exceeded the maximum value by 22.7% and was regarded as insulin resistance manifestation. Attention was paid to the high HC level in the blood serum of the examined women, which average value was 18.4 ± 0.6 mmol/L, which was 67.3% higher than the maximum permissible norm. At the same time, moderate FA deficiency was determinate in the blood serum of women, the average value of which was at the lower limit of the permissible physiological norm and was 3.42 ± 0.31 ng/mL.

The next stage of diagnostics involved TVUSE performance in order to determine the condition of the endometrium in the examined women. The average endometrial thickness was 22 ± 3.1 mm, which was considered as a hyperplastic endometrial process. In the vast majority of women – 44 (57.9%), the endometrium was defined as heterogeneous due to hypoechoic areas with indistinct contours without pronounced blood flow in the color Doppler mapping mode.

All women who applied with an established diagnosis of EH underwent hysteroresectoscopy, followed by PHE of the received material. In 100% of cases, according to the PHE results non-atypical EH was obtained which structure was distribut-

ed as follows: simple non-atypical EH 24 (31.6%), complex non-atypical EH – 52 (68.4%), which was the basis for conservative therapy prescription in order to prevent EH recurrence.

Evaluation of the proposed conservative therapy effectiveness in 6 months after the treatment beginning in women of the main group revealed the normalization of endometrial thickness which average value was 8.3 ± 0.46 mm. The average endometrial thickness in 9 months after the treatment beginning was stable – 9.7 ± 0.31 mm (Fig. 1). The average duration of menstrual bleeding in women of the main group decreased to 5.4 ± 0.2 days, the average duration of the menstrual cycle decreased to 26.3 ± 3.4 days.

The positive effect of the proposed therapy with dydrogesterone 10 mg twice a day and Depapilin® 395 mg twice a day led to a stable normalization of E_2 and PG levels in women of the main group (Fig. 2). In the follow-up dynamics after 6 and 9 months from the beginning of treatment, the average E_2 value was 68.4 ± 5.7 pg/mL and 62.7 ± 6.0 pg/mL, respectively, which is significantly lower than the average E_2 value before treatment ($p < 0.05$). The average PG value in women of the main group significantly increased after 6 months and amounted to 54.1 ± 4.0 nmol/L. After 9 months from the treatment beginning, PG had a stable concentration – 56.3 ± 5.2 nmol/L ($p > 0.05$).

Six months after the beginning of conservative therapy the average endometrial thickness approached the maximum allowable physiological norm and amounted to 14.1 ± 0.34 mm ($p < 0.05$) in comparison group. The average value of endometrial thickness 9 months after the beginning of treatment exceeded the maximum indicator of the physiological norm by 14.6% and amounted to 17.2 ± 0.29 mm ($p < 0.05$). The average duration of menstrual bleeding in women of the comparison group decreased to 5.6 ± 0.2 days ($p > 0.05$), but 9 months after the beginning of treatment it approached the maximum permissible physiological norm – 7.6 ± 0.3 days. The average duration of the menstrual cycle decreased to 27.2 ± 3.1 days 6 months after the beginning of treatment, but increased to an average of 31.6 ± 0.2 days 9 months after the beginning of treatment.

In comparison group on the background of therapy with dydrogesterone 10 mg twice a day 6 months after the beginning of treatment E_2 and PG levels normalization was noted. The average E_2 value was 61.7 ± 4.8 pg/mL and PG – 50.3 ± 4.2 nmol/L (Fig. 2). After 9 months from the beginning of therapy, the average E_2 value was 96.7 ± 7.1 pg/ml ($p > 0.05$), and the average PG value had a steady downward trend – 41.5 ± 3.9 nmol/L ($p < 0.05$), which was regarded as the initial stage of EH development.

Depapilin® use in women of the main group resulted in a persistent decrease in the HC levels which average value became 7.1 ± 0.4 mmol/L 6 months after beginning of treatment and 6.8 ± 0.3 mmol/L 9 months after beginning of treatment ($p < 0.05$) (Fig. 3). The restoration of HC's levels to the physiological norm resulted in a synergistic increase in FA levels which average value became 5.91 ± 0.22 ng/mL 6 months after begin-

ning of treatment and 6.51 ± 0.24 ng/mL 9 month after beginning of treatment.

Normalization of HC and FA average levels due to Depapilin® addition the basic therapy contributed to the BP normalization in women of the main group. The average BP values under the background of the proposed treatment decreased to the levels of $125 \pm 4.1 / 87 \pm 5.1$ mm Hg 6 months after beginning of treatment. After 9 months from the beginning of treatment BP level were stable at the numbers of $119 \pm 5.8 / 82 \pm 6.1$ mm Hg.

There was a tendency to BMI average value decrease in women of the main group – 24.1 ± 2.1 after 9 months against the background of diet correction. The average waist circumference in women of the main group almost approached the upper limit of the permissible norm and amounted to 82 ± 5.1 cm, exceeding it by 3.1%. The average HOMA index value was within the physiological norm – 20.1 ± 2.4 .

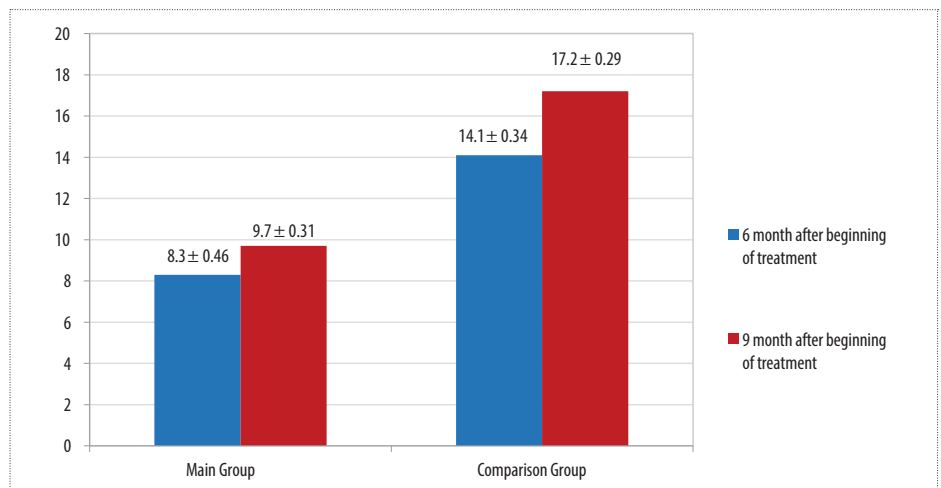


Figure 1. The average value of endometrium in the dynamics of treatment, mm

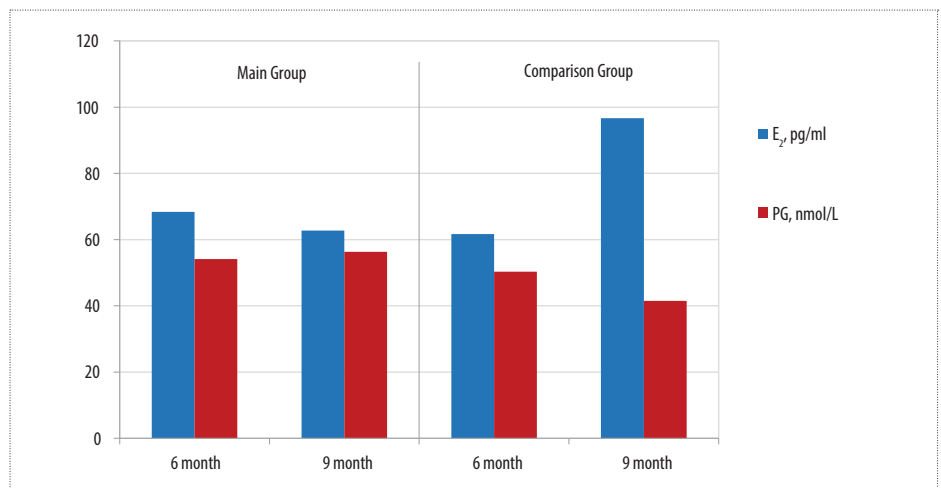


Figure 2. The average E_2 and PG levels after 6 and 9 months in dynamics of treatment

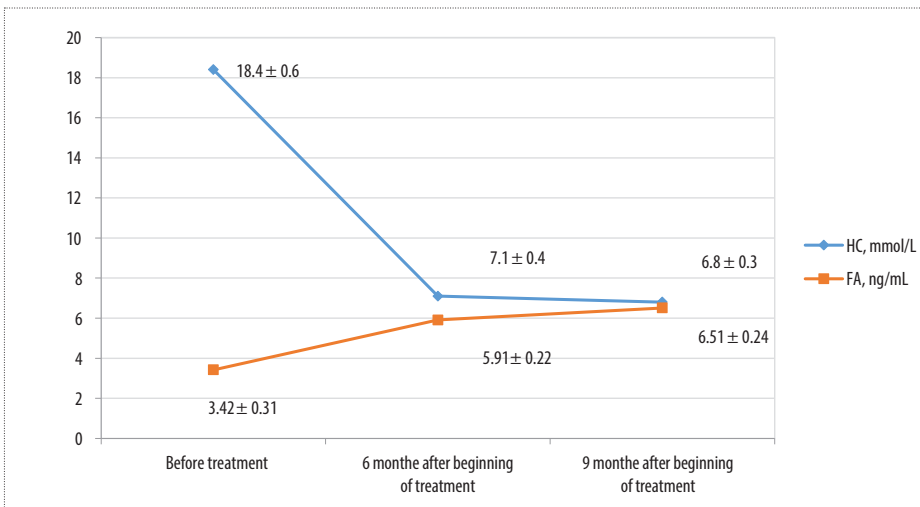


Figure 3. HC and FA average levels in women of the main group in dynamics of treatment

In the dynamics of observation 3 (7.5%) women in 6 months after treatment beginning and 4 (10.0%) women in 9 months after treatment beginning EH relapses were revealed which required repeatable examination with further hysteroresectoscopy. Thus, the total amount of EH relapse in the main group amounted 7 (17.5%) cases.

In the dynamics of observation 9 (25.0%) women in 6 months after treatment beginning and 7 (19.4%) women in 9 months after treatment beginning EH relapses were revealed which required more detailed examination and change in the treatment tactics. The total amount of EH relapse in the compar-

ison group amounted 16 (44.4%) cases ($p < 0.05$).

CONCLUSIONS

The premenopausal aged women with endometrium hyperplasia are characterized by high percentage of chronic (76.3% cases) and acute AUB (23.7% cases). The gynecological anamnesis data revealed high rate of inflammatory diseases of the female genital organs – 52.6% women together with background and precancerous diseases of the cervix – 31.6% women. In 42.1% patients the primary signs of metabolic syndrome with BP increase and abdominal type of obesity were found.

Against the background of dydrogesterone twice a day together with Depapilin® (Ozymuk Pharm) 395 mg twice a day (indole-3-carbinol in combination with *Vitex agnus-castus*, *Brassica*, *Camellia sinensis* extracts) in premenopausal women for 9 months led to a stable indicator of endometrial thickness, which was within the physiological norm in women of the main group during follow-up (before treatment – 22 ± 3.1 mm, 6 month after beginning of treatment – 8.3 ± 0.46 mm, 9 month after beginning of treatment – 9.7 ± 0.31 mm, $p < 0.05$).

Depapilin® including to basic EH treatment in premenopausal women is pathogenetically justified due to its complex effect on extragonadal estrogens synthesis which is realized in folic acid levels correction, which leads to homocysteine synthesis regulator. These effects helps to compensate the manifestations of metabolic syndrome, which is demonstrated by a decrease in the average BMI in women of the main group to 24.1 ± 2.1 and waist circumference to 82 ± 5.1 cm together this average values of HOMA index and blood pressure normalization.

The positive effect of the proposed therapy is represented by a significant decrease in the EH relapse rate which amounted 7 (17.5%) in the main group and 16 (44.4%) in the comparison group respectively ($p < 0.05$).

9. Серов, В.Н.

Практическое руководство по гинекологической эндокринологии / В.Н. Серов, В.Н. Прилепская, Т.Я. Пшеничникова. – М.: Русфармамед, 2015. – 427 с.

Serov, V.N., Prilepskaja, V.N., Pshenichnikova, T.Y.

Practical guide to gynecological endocrinology. Moscow.

Rusfarmamed (2015): 427 p.

10. Татарчук, Т.Ф.

Метаболічний синдром та гіперпроліферативні процеси ендометрію / Т.Ф. Татарчук, Н.Ю. Педаченко, З.Б. Хомінська // Репродуктивна ендокринологія. – 2014. – №2 (16): 61–72.

Tatarchuk, T.F., Pedachenko, N.Y., Hominska, Z.B.

“Metabolic syndrome and endometrial hyperproliferative processes.” Reproductive endocrinology 2.16 (2014): 61–72.

11. Ткаченко, Л.В.

Гіперпластичні процеси ендометрія в менопаузі: сучасні можливості гормональної корекції та профілактики / Л.В. Ткаченко, Н.И. Свиридова // Гінекологія. – 2013. – №2 (15). – С. 8–12.

Tkachenko, L.V., Sviridova, N.I.

“Hyperplastic processes of endometrium in premenopause: modern possibilities of hormonal correction and prevention.” Gynecology 15.2 (2013): 8–12.

12. де Вільєрс, Т.

Національний консенсус щодо ведення пацієнток у клімактерії / Т. де Вільєрс, Т.Ф. Татарчук // Репродуктивна ендокринологія. – 2016. – №1 (27). – С. 8–25.

de Villiers, T., Tatarchuk, T.F.

“National consensus on the management of menopausal patients.” Reproductive endocrinology 1.27 (2016): 8–25.

13. Afshin, A., Forouzanfar, M.H., et al.

“Health effects of overweight and obesity in 195 countries over 25 years. GBD 2015 Obesity Collaborators.” N Engl J Med 377.1 (2017): 13–27.

14. Armstrong, A.J., Hurd, W.W., Elguero, S., et al.

“Diagnosis and Management of Endometrial Hyperplasia.” J Minim Invasive Gynecol 19.5 (2012): 562–71.

15. Clark, T.J., Stevenson, H.

“Endometrial Polyps and Abnormal Uterine Bleeding (AUB-P): What is the relationship, how are they diagnosed and how are they treated?” Best Pract Res Clin Obstet Gynaecol 40 (2016): 89–104.

16. Inoue, M.

“Current molecular aspects of the carcinogenesis of the uterine endometrium.” Int J Gynecol Cancer 11 (2017): 339–48.

17. Jae Kwang Kim, Sang Un Park.

“Current results on the biological and pharmacological activities of indole-3-carbinol.” EXCLI Journal 17 (2018): 181–5.

18. Kim, E.K., Kim, Y.S., Milner, J.A., Wang, T.T.

“Indole-3-carbinol and 3,3'-diindolylmethane modulate androgen's effect on C-C chemokine ligand 2 and monocyte attraction to prostate cancer cells.” Cancer Prev Res (Phila) 6.6 (2013): 519–29.

19. Podzolkova, N.M., Tatarchuk, T.F., Doshchanova A.M., et al.

“Menstrual cycle normalization with dydrogesterone.” Akusherstvo i Ginekologiya (Russian Federation) 6 (2018): 70–5.

20. Royal College of Obstetrician and Gynecologists.

Management of Endometrial Hyperplasia. GreenTop Guideline No. 67 (2016).

21. Scheuer, S.H., Færch, K., Philipsen, A.

“Abdominal fat distribution and cardiovascular risk in men and women

with different levels of glucose tolerance.” J Clin Endocrinol Metab 100.9 (2015): 3340–7. DOI: 10.1210/JC.2014-4479

22. Sobczuk, K., Sobczuk, A.

“New classification system of endometrial hyperplasia WHO 2014 and its clinical implications.” Prz Menopauzalny 16.3 (2017): 107–11.

23. Wise, M.R., Jordan, V., Lagas, A., et al.

“Obesity and endometrial hyperplasia and cancer in premenopausal women: A systematic review.” Am J Obstet Gynecol 214.6 (2016): 689–97.

24. Yati, M., Susilowati, A.

“Changes in folate characteristics and its identification in broccoli (*Brassica oleracea Italica*) extract fermented by Lactic Acid Bacteria Mixed Culture (LAB).” MATEC Web of Conferences 154.2 (2018): 04001. DOI: 10.1051/mateconf/201815404001

25. Zhang, H., Sairam, M.R.

“Sex hormone imbalances and adipose tissue dysfunction impacting on metabolic syndrome; a paradigm for the discovery of novel adipokines.” Horm Mol Biol Clin Invest 17.2 (2014): 89–97. □

НОВІ ПІДХОДИ ДО ПРОФІЛАКТИКИ РЕЦИДИВІВ ГІПЕРПЛАЗІЇ ЕНДОМЕТРІЯ В ЖІНОК У ПРЕМЕНОПАУЗІ

В.О. Бенюк, д. мед. н., професор, зав. кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ
В.Г. Гінзбург, д. мед. н., доцент, професор кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ
Д.О. Говсєєв, д. мед. н., професор кафедри акушерства і гінекології Інституту післядипломної освіти НМУ імені О.О. Богомольця, м. Київ
В.Ф. Олешко, к. мед. н., асистент кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ
Т.В. Ковалюк, к. мед. н., доцент кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ
Ю.В. Кравченко, аспірант кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ
А.С. Лучко, аспірант кафедри акушерства і гінекології №3 НМУ імені О.О. Богомольця, м. Київ

Мета дослідження: оцінити ефективність терапії, спрямованої на попередження рецидиву гіперплазії ендометрія в жінок у пременопаузі.

Матеріали і методи. Проведено клініко-параклінічне обстеження 76 жінок пременопаузального віку. Виконане трансвагінальне УЗД, визначення рівнів естрадіолу, прогестерону, гомоцистеїну, фолієвої кислоти, індексу НОМА в сироватці крові, індексу маси тіла й артеріального тиску. Після отримання гістологічних результатів жінки були розділені на дві групи: в основну групу увійшли 40 жінок, які двічі на добу отримували пероральні прогестини (дидрогестерон 10 мг) в поєднанні з препаратом Депапілін® 395 мг, в групу порівняння – 36 жінок, які отримували тільки пероральні прогестини (дидрогестерон 10 мг) двічі на добу. Порівняння результатів та оцінку ефективності терапії проводили через 6 та 9 місяців від початку лікування.

Результати. У жінок основної групи протягом 9 місяців відбувалась стабілізація товщини ендометрія, яка знаходилась в межах фізіологічної норми (до лікування – $22 \pm 3,1$ мм, через 6 місяців після початку лікування – $8,3 \pm 0,46$ мм, через 9 місяців – $9,7 \pm 0,31$ мм, $p < 0,05$). Позитивний ефект запропонованої терапії полягав у достовірному зниженні частоти рецидивів гіперплазії ендометрія, яка склала 17 (17,5%) випадків у основній групі та 16 (44,4%) випадків у групі порівняння ($p < 0,05$). В основній групі також мали місце стійка нормалізація рівня естрогену й прогестерону, стійке зниження рівня гомоцистеїну та синергічне підвищення рівня фолієвої кислоти, нормалізація артеріального тиску та зниження індексу маси тіла.

Висновки. Включення препарату Депапілін® до базисної терапії гіперплазії ендометрія в жінок пременопаузального віку є патогенетично обґрунтованим у зв'язку з комплексним впливом компонентів препарату на екстрагональний синтез естрогенів та антипроліферативним впливом на ендометрій.

Ключові слова: гіперплазія ендометрія, метаболічний синдром, пременопаузальний період, Депапілін.

NEW APPROACHES TO PROPHYLAXIS OF ENDOMETRIUM HYPERPLASIA RELAPS IN PREMENOPAUSAL WOMEN

V.O. Beniuk, MD, professor, head of the Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
V.H. Ginzburg, MD, associate professor, professor, Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
D.O. Govsiev, MD, professor, Department of Obstetrics and Gynecology, Institute of Postgraduate Education, Bogomolets National Medical University, Kyiv
V.F. Oleshko, PhD, assistant, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv
T.V. Kovaliuk, PhD, assistant professor, Obstetrics and Gynaecology Department No. 3, Bogomolets National Medical University, Kyiv
Y.V. Kravchenko, graduate student, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv
A.S. Luchko, graduate student, Obstetrics and Gynecology Department No. 3, Bogomolets National Medical University, Kyiv

Research aim: to evaluate the effectiveness of therapy aimed at preventing endometrial hyperplasia recurrence in premenopausal women.

Materials and methods. Clinical and paraclinical examinations of 76 premenopausal women were carried out. Transvaginal ultrasound was performed, levels of estradiol, progesterone, homocysteine, folic acid, serum HOMA index evaluated, body mass index and blood pressure assessed. Women were divided into two groups after histological results obtained: the main group included 40 women who received oral progestins (dydrogesterone 10 mg) twice a day in combination with Depapilin® 395 mg twice a day; the comparison group included 36 women who received only oral progestins (dydrogesterone 10 mg) twice a day. Comparison of the therapy effectiveness was performed 6 and 9 months after the start of treatment.

Results. Endometrial thickness stabilized within 9 months in women of the main group, and was within the physiological norm (before treatment – 22 ± 3.1 mm, 6 months after the start of treatment – $8,3 \pm 0.46$ mm, after 9 months – $9,7 \pm 0.31$ mm, $p < 0.05$). The positive treatment effect consisted in a significant decrease in the frequency of endometrial hyperplasia recurrence, which was 17 (17.5%) cases in the main group and 16 (44.4%) cases in the comparison group ($p < 0.05$). Women of the main group also showed stable normalization of the level of estrogen and progesterone, a steady decrease in the level of homocysteine and a synergistic increase in the level of folic acid, normalization of blood pressure and reduction of body mass index.

Conclusions. Depapilin® inclusion in the basic therapy of endometrial hyperplasia in premenopausal aged women is pathogenetically justified due to the complex effect of the drug components on the extragonadal estrogens synthesis and the antiproliferative effect on the endometrium.

Keywords: endometrial hyperplasia, metabolic syndrome, premenopausal period, Depapilin.

НОВЫЕ ПОДХОДЫ К ПРОФИЛАКТИКЕ РЕЦИДИВА ГИПЕРПЛАЗИИ ЭНДОМЕТРИЯ У ЖЕНЩИН ПРЕМЕНОПАУЗАЛЬНОГО ВОЗРАСТА

В.А. Бенюк, д. мед. н., професор, зав. кафедрой акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев
В.Г. Гинзбург, д. мед. н., доцент, профессор кафедры акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев
Д.А. Говсєєв, д. мед. н., профессор кафедры акушерства и гинекологии Института последипломного образования НМУ имени А.А. Богомольца, г. Киев
В.Ф. Олешко, к. мед. н., ассистент кафедры акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев
Т.В. Ковалюк, к. мед. н., доцент кафедры акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев
Ю.В. Кравченко, аспирант кафедры акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев
А.С. Лучко, аспирант кафедры акушерства и гинекологии №3 НМУ имени А.А. Богомольца, г. Киев

Цель исследования: оценить эффективность терапии, направленной на предупреждение рецидива гиперплазии эндометрия у женщин в пременопаузе.

Материалы и методы. Проведены клинико-параклинические обследования 76 женщин пременопаузального возраста. Выполнено трансвагинальное УЗИ, определение уровней эстрадиола, прогестерона, гомоцистеина, фолиевой кислоты, индекса НОМА в сыворотке крови, индекса массы тела и артериального давления. После получения гистологических результатов женщины были разделены на две группы: в основную группу вошли 40 женщин, получавших пероральные прогестини (дидрогестерон 10 мг) дважды в сутки в сочетании с препаратом Депапилин® 395 мг дважды в сутки, в группу сравнения вошли 36 женщин, которые получали только пероральные прогестини (дидрогестерон 10 мг) дважды в сутки. Сравнение результатов и оценку эффективности терапии проводили через 6 и 9 месяцев от начала лечения.

Результаты. У женщин основной группы в течение 9 месяцев происходила стабилизация толщины эндометрия, которая находилась в пределах физиологической нормы (до лечения – $22 \pm 3,1$ мм, через 6 месяцев после начала лечения – $8,3 \pm 0,46$ мм, через 9 месяцев – $9,7 \pm 0,31$ мм, $p < 0,05$). Положительный эффект предложенной терапии заключался в достоверном снижении частоты рецидивов гиперплазии эндометрия, которая составила 17 (17,5%) случаев в основной группе и 16 (44,4%) случаев в группе сравнения ($p < 0,05$). У женщин основной группы также наблюдалась устойчивая нормализация уровней эстрогена и прогестерона, устойчивое снижение уровня гомоцистеина и синергическое повышение уровня фолієвої кислоти, нормалізація артеріального тиску та зниження індексу маси тіла.

Выводы. Включение препарата Депапилин® в базисную терапию гиперплазии эндометрия у женщин пременопаузального возраста является патогенетически обоснованным в связи с комплексным воздействием компонентов препарата на экстрагональный синтез эстрогенов и антипролиферативным влиянием на эндометрий.

Ключевые слова: гиперплазия эндометрия, метаболіческий синдром, пременопаузальний період, Депапилін.