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COMPARATIVE ASPECTS OF TREATMENT OF ENDOMETRIAL HYPERPLASIA IN WOMEN OF REPRODUCTIVE AGE WITH OVERWEIGHT

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Abstract

The aim. Minimization of the frequency of recurrence of endometrial hyperplasia (EH) in women of reproductive age with overweight (OW) depending on the tactics of treatment.

Materials and methods. 90 women of reproductive age with endometrial hyperplasia and OW were selected. They, in turn, were divided into three groups: group 1 – 30 women who took a gonadotropin-releasing hormone agonist (GnRH agonist), namely at a dose of 3.75 mg intramuscularly once every 28 days; group 2 – 30 women who used progestin (norethisterone) at a dose of 10 mg per day from day 16 to 25 of the cycle, group 3 – 30 women who took combined oral contraception (COC) (30 mcg ethinyl estradiol and 150 mcg desogestrel) in a cyclic mode 21/7.

Evaluation of the effectiveness of therapy included a clinical picture of the disease 6 months after the start of treatment, assessment of the variability of the average values of endometrial thickness and uterine size on ultrasound (US) of the pelvis 6 months after treatment. Also analyzed the effectiveness of therapy based on the results of morphological examination of the endometrium in a biopsy of the uterine mucosa, performed 6 months after the start of treatment. In addition, a general analysis of the frequency of EH recurrence was performed 6–24 months after treatment.

Results. The results showed that in the group in which women were prescribed GnRH agonist, there was a significantly higher effectiveness of treatment, in particular the absence of uterine bleeding and menstrual disorders (MD). At the same time, in the other norethisterone group, 53.3 % (16) of women had intermenstrual uterine bleeding. In patients in the group in which women received COC, uterine bleeding was observed in 30.0 % (i.e. 9) of patients ($p < 0.05$).

Immediately after treatment, the average values of endometrial thickness in patients of group 1, according to ultrasound, was 3.59 ± 0.47 mm, which was significantly less than in women of groups 2 and 3 – 6.81 ± 0.59 mm ($p < 0.001$) and 7.58 ± 0.69 mm ($p < 0.001$).

In addition, patients in group 1 at 3, 6, 12, 24 months after the end of hormone therapy were registered significantly lower average values of endometrial thickness, compared with patients receiving norethisterone and estrogen-progestogen drugs.

Conclusions. In a comparative evaluation of the effectiveness of treatment of endometrial hyperplastic processes in overweight women, it was found that the recurrence rate after 6–24 months occurs in 6.7 % (i.e. 2) of patients after GnRH agonist therapy, in 33.3 % (i.e. in 10) patients receiving norethisterone ($p < 0.001$), and in 50 % (i.e. 15) of women treated with COC ($p < 0.001$).

Keywords: endometrial hyperplasia, overweight, reproductive age of women, hormone therapy.

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1. Introduction

Endometrial hyperplasia is considered to be the most common pathology of the uterine mucosa. The frequency of EH in young women, according to the literature, is from 6.5 to 37.0 %. A number of publications of the authors indicate the possibility of spontaneous regression of endometrial hyperplasia, which is from 15.0–28.0 % to 48.9–70.0 %. In addition, hyperplastic processes in the endometrium belong to the proliferative processes, which in the long run without treatment could serve as a background for the development of malignant lesions of the uterine mucosa [1, 2].

The development of EH is due to the dysfunction of the four main levels of the regulatory system: the central hypothalamic-pituitary axis, «signals» of direct and feedback between the hypothalamic-pituitary level and the ovaries, local «responses» and changes in the ovaries and endo. The leading theory of its development is hyperestrogenism: absolute – in polycystic ovary syndrome, obesity (increased peripheral conversion from androstenedione to estrone, and then to

estradiol) and relative – a decrease in the production of hormones that neutralize the effects of estrogen, especially anus, prone luteal phase, luft syndrome. The duration of estrogen action on the mucous membrane of the uterine cavity plays a significant role [3, 4].

Obesity and associated metabolic disorders are also a significant risk factor for the development of endometrial hyperplastic processes, which inevitably cause abnormalities in hormonal metabolism. The value of obesity as a risk factor for EH in reproductive age is significantly higher than in menopause. The main symptoms of obesity and metabolic syndrome are insulin resistance, impaired glucose tolerance and hyperinsulinemia. Hyperinsulinemia increases the number of cytosolic receptors for steroids in the endometrial tissue, which leads to its hyperplasia. These mechanisms support the proliferative activity of the endometrium, leading to frequent recurrences of endometrial hyperplasia, reduce the effectiveness of therapy. Significant difficulties in treatment are caused by the metabolic syndrome itself, as it is accompanied by somatic disorders (obesity, diabetes, hypertension, etc.), which limits the use of drugs, exacerbates side effects of therapy, complicates the choice of dose [5, 6].

The most accurate methods of diagnosing EH are ultrasound and pathomorphological examination. In about 90 % of cases, the ultrasound picture of endometrial hyperplasia coincides with the obtained morphological data. Ultrasound diagnosis of EH is based on the assessment of the thickness of the uterine echo (U-echo), increase in U-echo – the main prognostic marker of endometrial pathology [7, 8].

In addition, the recurrence of proliferative diseases of the endometrium due to cancer vigilance is often the basis for radical surgery, which leads to premature loss of reproductive function, reducing the quality of life of women [9, 10]. Therefore, reducing the incidence of endometrial hyperplasia in women of reproductive age with OW is relevant.

The aim is to minimize the frequency of recurrence of endometrial hyperplasia in women of reproductive age with overweight, depending on the tactics of treatment.

2. Materials and methods

The study was conducted from 2017 to 2020 on the basis of the Department of Obstetrics, Gynecology and Perinatology of the Shupyk National Healthcare University of Ukraine on the basis of the Kyiv Maternity Hospital No. 1 (gynecological department). To achieve this goal, 90 women of reproductive age with endometrial hyperplasia and with OW were selected. They, in turn, were divided into three groups: group 1 – 30 women who took a gonadotropin-releasing hormone agonist, namely buserelin at a dose of 3.75 mg intramuscularly once every 28 days; group 2 – 30 women who used progestin (norethisterone) at a dose of 10 mg per day from 16 to 25 days of the cycle, group 3 – 30 women who took COC (30 mcg ethinyl estradiol and 150 mcg desogestrel) in a cyclic mode 21/7. All studies of the patient received hormone therapy for 6 months. These women were also offered basic OW treatment, namely, adherence to a balanced diet, increased exercise, and behavioural therapy.

The effectiveness of the therapy was evaluated on the basis of the clinical picture of the disease 6 months after treatment, assessment of variability in mean endometrial thickness and uterine size on ultrasound of the pelvis 6 months after treatment, as well as on the analysis of morphological examination of the endometrium in biopsy of the uterine mucosa, performed 6 months after treatment. In addition, a general analysis of the frequency of EH recurrence was performed 6–24 months after treatment.

The study was conducted in accordance with the Declaration of Helsinki according to the conclusion of the Commission on Ethics of the Shupyk National Healthcare University of Ukraine (minutes No. 2 from 09.02.2017). Informed consent to participate in the study was obtained from all women.

The age of the studied women of all groups did not differ statistically significantly. The mean age of patients in group 1 was 35.4±3.5 years, group 2 – 36.7±3.6 years, group 3 – 33.6±3.1 years ($p>0.05$).

No significant differences in obstetric, gynecological and somatic anamnesis were found in all patients studied.

The study groups included women of reproductive age who had morphological examination revealed simple endometrial hyperplasia without atypia, as well as those who had OW, namely body mass index (BMI) greater than 25.0 and less than 40.0 kg/m^2.

In order to include women in the study groups and determine the effectiveness of hormone therapy, a gynecological study was conducted, which included the analysis of complaints, including the presence and features of uterine bleeding, as well as the nature of the menstrual cycle.

Determination of BMI was to estimate the ratio of body weight (kg) to his height (m) squared.

Ultrasound was performed on a color digital scanner «Aloka SSD 3500» (Japan), which provides three-dimensional image reconstruction and equipped with a transvaginal multifrequency transducer with an acoustic oscillation frequency of 4.7–5–7.5–10 MHz. Ultrasound of the uterus was performed in phase I MD – for 5–7 days. The thickness of the endometrium along the anterior and posterior walls, features of its shape, internal structure, contours, and echogenicity were taken as the ultrasound picture. The overall size of the uterus was also assessed.

For morphological studies of endometrial biopsies were recorded in 10.0 % formaldehyde solution according to standard methods. After appropriate treatment and pouring into paraffin (paraffin blocks) were obtained sections, which were subjected to staining with hematoxylin-eosin. Morphological study of the obtained drugs was performed using light microscopy.

Statistica and Microsoft Office Excel were used for statistical processing of the obtained results. Evaluation of the statistical significance of the obtained data was performed using the Newman-Kayles and χ^2 criteria. The differences were considered statistically significant at $p < 0.05$.

3. Results

The effectiveness of the therapy was evaluated on the basis of the clinical picture, namely the presence of intermenstrual uterine bleeding, the nature of menstrual cycles, based on the assessment of variability of uterine size and endometrial thickness in control ultrasound of the pelvis, and on the analysis of endometrial morphological changes mucous membrane of the uterus, which is carried out 6 months after treatment.

According to the obtained results, in 1 group receiving GnRH agonist, in 100.0 % (in 30 women) patients the clinical effectiveness of the therapy was registered, namely – the absence of uterine bleeding. With regard to group 2, on the background of norethisterone treatment, uterine bleeding was detected in 53.3 % (16 women) of patients. In women of group 3 who received a combined estrogen-progestogen drug, uterine bleeding was observed in 30.0 % of patients, i.e. in 9 women ($p < 0.05$).

In dynamic transvaginal ultrasound after treatment (i.e. 6 months after the start of therapy), the thickness of the endometrium at day 5–6 MD in patients of group 1, according to ultrasound, was 3.59 ± 0.47 mm, which was significantly less than in women 2 and 3 subgroups – 6.81 ± 0.59 mm ($p < 0.001$) and 7.58 ± 0.69 mm ($p < 0.001$). There was also a significant reduction in uterine size in women treated with GnRH agonist, compared with patients receiving norethisterone ($p < 0.001$) and COC ($p < 0.05$) (**Table 1**).

Table 1

Dynamic changes in endometrial thickness and biometric parameters of the uterus in women of reproductive age with endometrial hyperplasia and OW on the background of hormone therapy

Parameters	Group 1 ($n = 30$)		*P*	Group 2 ($n = 30$)		*P*	Group 3 ($n = 30$)		*P*	*P* after treatment		
	before treat.	after treat.		before treat.	after treat.		before treat.	after treat.		1:2	1:3	2:3
Endometrial thickness, mm	12.81 ± 1.79	3.59 ± 0.47	0.001	12.71 ± 1.29	6.81 ± 0.59	0.001	12.29 ± 1.33	7.58 ± 0.69	0.001	0.001	0.001	0.379
The size of the uterus, mm	63.93 ± 6.78	54.29 ± 5.43	< 0.001	67.78 ± 6.68	67.01 ± 6.23	0.708	64.98 ± 6.37	63.99 ± 5.88	0.708	0.001	0.001	0.066
	47.89 ± 4.12	40.97 ± 4.06	0.009	52.48 ± 5.21	51.19 ± 4.89	0.605	47.49 ± 4.09	47.48 ± 5.47	0.989	0.001	0.008	0.068
	53.96 ± 5.31	46.03 ± 4.57	0.006	58.96 ± 5.41	57.58 ± 5.61	0.718	51.97 ± 5.17	52.03 ± 4.96	0.928	0.001	0.011	0.071

The effectiveness of the treatment was evaluated not only 6 months after the start of treatment, but also 3, 6, 12, 24 months after the end of the course of hormone therapy, in particular the measurement of endometrial thickness (**Fig. 1**).

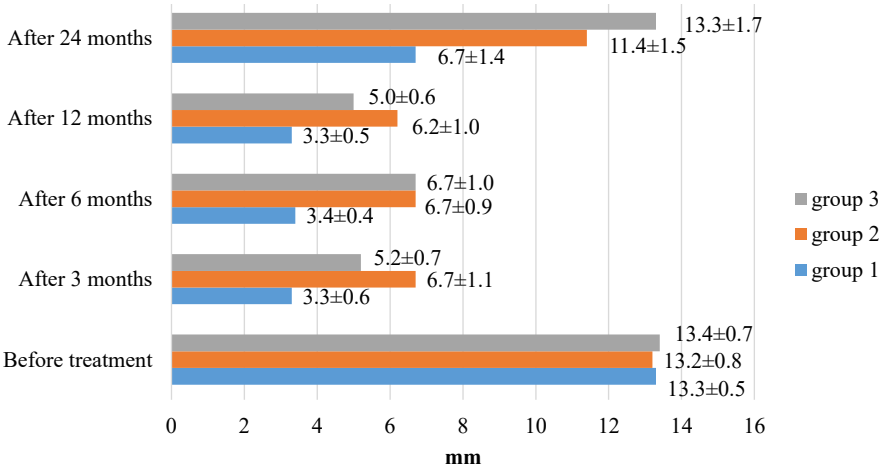

Fig. 1. Dynamic changes in endometrial thickness after hormone therapy

In the dynamic monitoring of endometrial thickness after treatment during ultrasound was registered after 3 months ($p < 0.05$), after 6 months ($p < 0.01$), after 12 months ($p < 0.05$) and after 24 months ($p < 0.001$) significantly lower mean values in patients who were prescribed GnRH agonist for the treatment of EH with OW, compared with patients receiving norethisterone and estrogen-progestogen drugs. The mean values of endometrial thickness in women receiving norethisterone did not differ significantly from patients treated with COC ($p > 0.05$).

Morphological examination of the endometrial biopsy taken after the course of hormone therapy revealed that 100.0 % of patients (i.e. 30 women) receiving GnRH agonist had no endometrial hyperplasia, i.e. the effectiveness of treatment was 100 %. At the same time, it was also found that 63.3 % of patients (19 women) who took norethisterone had endometrial hyperplasia. In group 3, in which women took COC, this pathology was detected in 50 % (i.e. 15) patients. Thus, when using GnRH agonist, the effectiveness of therapy is significantly higher than in patients treated with norethisterone ($p < 0.001$) and COC ($p < 0.001$).

In the analysis of cases of recurrence of endometrial hyperplasia, it was found that in group 1 6–24 months after treatment they were 6.7 % (in 2 women), in group 2 their frequency was 33.3 % (in 10 women) ($p < 0.001$), and in group 3 – 50 % (in 15 women) ($p < 0.001$).

It should also be noted that recurrence of the disease in patients after treatment with GnRH agonist was observed in patients who did not follow the recommendations for weight correction (diet, exercise).

Therefore, patients who received GnRH agonist for EH treatment had significantly lower mean endometrial thickness values 3, 6, 12, 24 months after the end of hormone therapy than patients who received norethisterone and estrogen-progestogen drugs. In group 1, 100 % of patients after treatment had no uterine bleeding. At the same time, women taking norethisterone and COC had a significantly higher incidence of intermenstrual uterine bleeding, more irregular MD, and recurrence of EH. At the same time, patients receiving estrogen-progestogen drug showed a significantly lower frequency of uterine bleeding compared to women who were prescribed norethisterone, while the other studied parameters in groups 2 and 3 did not differ significantly.

4. Discussion of research results

Endometrial hyperplasia is a benign pathological process in the inner layer of the uterus, which is characterized by the proliferation of endometrial glands with different size of the underlying stroma on the background of relative or absolute hyperestrogenism [11]. Hyperplastic processes of the endometrium could be considered as an imbalance in the direction of reducing

the suppression of apoptosis, on the one hand, and increasing the proliferative potential, on the other hand. The main causes of hyperestrogenism include overweight, liver disease, adrenal glands, on the background of hypereinsulinemia and others [12].

According to the literature, in metabolic disorders, excess fat leads to higher estrogenic saturation of the body. In stromal and vascular cells of adipose tissue there are aromatase enzyme systems capable of converting androstenedione to estrone, there is an uncontrolled gonadotropin synthesis of estrogen, which leads to an increase in the «estrogen pool». It should also be noted that the analysis of the literature showed the lack of consensus on treatment tactics that would be most effective in women of reproductive age with EH simultaneously with OW [13, 14].

It is known that the main clinical symptoms in women of reproductive age with EH with OW are MD disorders, the presence of intermenstrual uterine bleeding. Therefore, most often the effectiveness of treatment of such pathology is evaluated by these parameters [15, 16]. The results of the study showed that patients who received GnRH agonist during treatment had the highest efficacy of therapy. They had no uterine bleeding. Women taking norethisterone had the highest incidence of uterine bleeding in 53.3 % (16) of patients. At the same time, in the group where women received COC, this pathology occurred in 30 % of patients, i.e. in 9 women.

Also, the evaluation of the effectiveness of EH treatment in women of reproductive age with OW is based on dynamic changes in ultrasound, including endometrial thickness and biometric parameters of the uterus after 6 months from the start of therapy [17, 18]. The results showed that the thickness of the endometrium at day 5–6 MD in patients receiving GnRH agonist was significantly lower and was 3.59 ± 0.47 mm compared with patients receiving norethisterone and COC, namely 6.81 ± 0.59 mm ($p < 0.001$) and 7.58 ± 0.69 mm ($p < 0.001$), respectively. The same pattern was observed for uterine size, where their mean values were significantly lower in women taking a GnRH agonist.

In addition, to determine the most effective method of treatment, it is necessary to evaluate the effectiveness not only immediately after treatment, but also 3, 6, 12, 24 months after treatment [19]. Thus, during ultrasound of the pelvic organs in patients who were prescribed GnRH agonist for the treatment of EH, after 3 months ($p < 0.05$), after 6 months ($p < 0.01$), after 12 months ($p < 0.05$) and 24 months ($p < 0.001$) after the end of hormone therapy were also significantly lower average values of endometrial thickness compared with patients receiving norethisterone and COC.

According to the literature, the most informative methods of diagnosing EH include pathomorphological examination [20]. Data obtained from pathomorphological examination of endometrial biopsy, which was performed after completion of treatment with hormonal drugs, were presented as follows: endometrial hyperplasia was absent in 100.0 % (30) of patients receiving GnRH agonist, in 63.3 % (in 19) patients who received norethisterone and 50.0 % (15 women) who received COCs. These data reaffirmed that the administration of GnRH agonists for the treatment of EH in women of reproductive age with OW is significantly the most effective method compared with norethisterone ($p < 0.001$) and COC ($p < 0.001$).

Therefore, after analyzing the data, it was found that the lowest incidence of EH recurrence after 6–24 months was observed in the group where the treatment tactics were the use of GnRH agonist, namely in 6.7 % (i.e. 2) women.

Study limitations. The study did not include women with atypical hyperplasia, who has BMI was 40.0 or more kg/m^2, with severe genital and extragenital pathologies.

Prospects for further research. Study of the features of the pathogenesis of pathological processes of the endometrium, their diagnosis and treatment tactics to reduce the frequency of recurrence of such processes in postmenopausal women with overweight.

5. Conclusions

The results of the study showed that all women of reproductive age with OW, who were prescribed GnRH agonist for the treatment of EH, had no uterine bleeding compared with women who took norethisterone and COC, i.e. this pathology was observed in 53.3 % (in 16 patients) and 30 % (i.e. 9) of women, respectively ($p < 0.05$).

After 6 months of treatment, the mean endometrial thickness and uterine size in patients receiving GnRH agonist were significantly lower than in patients receiving norethisterone and COC. Thus, the obtained data on the thickness of the endometrium were represented by the following values: 3.59±0.47 mm, 6.81±0.59 mm ($p < 0.001$) and 7.58±0.69 mm ($p < 0.001$), respectively.

Dynamic monitoring of endometrial thickness by ultrasound after treatment found that patients in group 1 were significantly lower after 3 months ($p < 0.05$), after 6 months ($p < 0.01$), after 12 months ($p < 0.05$) and 24 months ($p < 0.001$) compared with women in groups 2 and 3.

Pathomorphological examination of the endometrial biopsy showed that significantly the lowest amount of EH after treatment was in the group where women received GnRH agonist, namely the absence of cases, i.e. the effectiveness of treatment is 100 %. In the same group, the lowest incidence of EH recurrence was observed 6–24 months after the end of treatment, namely in 6.7 % (i.e. 2) of women.

Conflict of interest

The authors declare that they have no conflicts of interest.

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