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ANALYSIS OF THE OBJECTIVE AND PREVENTATIVE TREATMENT AND EFFICACY OF THERAPEUTIC APPROACHES IN WOMEN WITH NON-ATYPICAL ENDOMETRIAL HYPERPLASIA

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Abstract

Non-atypical endometrial hyperplasia (EH) is prone to recurrence and has an unspecified residual monitoring and treatment algorithm. The main factors that influence the possibility of recurrence and progression are not known yet.

The objective: examination of the frequency of hyperproliferative endometrial pathology (HPE) in premenopausal women, organization of treatment and prophylactic measures and their influence on the recurrence or progression of HPE.

Design of the study: a retrospective observational study.

Results of the study: The results of monitoring and treatment were analysed in 380 premenopausal women according to STRAW+10 criteria. The structure was dominated by non-atypical endometrial hyperplasia (EH)- in 356 (93.7%) cases, atypical hyperplasia (AH) - in 16 (4.2%), endometrial cancer (EC) - in 8 (2.6%). 60 women underwent hysterectomy (24 - AH and EC, 36 - concomitant pathology). Results from 320 women with EH excluding

hysterectomy, have been monitored over 3 years. Hormonal treatment with gestagens was given to 138 of 320 women (43.1%), 78 (24.3%) received oral progestins without an interruption for 3 months, 34 (10.6%) for 6 months and 26 (8.1%) received LNG-IUDs 52 mg, in 182 (56.8%) no treatment was provided. The effectiveness of EH therapy in women with LNG-IUDs was achieved in 92.3% of cases, with gestagen treatment at 6 months in 70.6%, and at 3 months in 39.7%. With no therapy, regression of the disease was 28.8%. The incidence of EH at the 3rd year of follow-up in women without treatment was 2.4 times higher than at the 6-month course of oral gestagen therapy (71.4 vs 29.4%) and was not significantly different from the 3-month course (71.4 vs 60.3%).

There is a lack of clarity in the treatment and monitoring system for women with EH in the study centres; short timing of gestagen prescriptions are insufficiently effective and contribute to a high rate of recurrence; the LNG IUD showed the best efficacy results (93.7%) and absence of recurrence over the course of the study.

Key words: endometrial hyperplasia; premenopause; progestogens; recurrence; results of treatment; observation

Резюме

Неатипова гіперплазія ендометрія (ГЕ) схильна до рецидивів та має невизначений остаточно алгоритм спостереження та лікування. Основні чинники, що впливають на можливість рецидивів та прогресії, остаточно не з'ясовані. **Мета дослідження:** аналіз частоти випадків гіперпроліферативної патології ендометрія (ГПЕ) у жінок в пременопаузі, організації лікувальних і профілактичних заходів і їх вплив на рецидив або прогресію ГПЕ. **Дизайн дослідження:** ретроспективне обсерваційне дослідження. **Результати дослідження.** Результати спостереження та лікування проаналізовані у 380 жінок в пременопаузі за критеріями STRAW+10. В структурі домінувала ГЕ – в 356 (93.7%) випадках, АГ - 16 (4.2%), РЕ – 8 (2.6%). 60 жінкам виконано гістеректомію (24 - АГ та РЕ, 36 – супутня патологія). Данні 320 жінок з ГЕ без гістеректомії, проаналізовані за 3 роки. Протирецидивне лікування гестагенами проведено у 138 з 320 жінок (43,1%), оральні гестагени безперервно 3 місяці отримали 78 (24,3%), 6 місяців - 34 (10,6%), ЛНГ-ВМС 52 мг - 26 (8,1%). У 182 (56,8%) протирецидивне лікування не проводилось. Успішність терапії ГЕ у жінок з ЛНГ-ВМС досягнута в 92,3% випадках, при лікуванні гестагенами 6 місяців - в 70,6%, 3 місяці - 39,7%. При відсутності терапії регрес захворювання склав 28,8%. Частота ГЕ на 3-му році спостереження у жінок без лікування була в 2,4 рази більше, ніж при 6-ти

місячному курсі терапії оральними гестагенами (71,4 проти 29,4%), та мало відрізнялася від 3-х місячного курсу (71,4 проти 60,3%). **Висновки:** відсутня чітка система лікування та спостереження за жінками з ГЕ в досліджуваних центрах; короткотривалі курси призначення гестагенів недостатньо ефективні та сприяють високій частоті рецидивів; найкращі результати по ефективності (93,7%) та відсутності рецидивів протягом використання показала ЛНГ-ВМС.

Ключові слова: гіперплазія ендометрію; пре менопауза; прогестагени; рецидив; результати лікування; спостереження.

Non-atypical endometrial hyperplasia (EH) is a benign hyperproliferative disease in which conservative therapy is used in the majority of cases. The frequency of hyperplastic processes increases significantly during premenopause and the rate of atypical forms of endometrial hyperplasia increases in comparison with reproductive age. Progestins are regarded as the first-line therapy, due to a favourable ratio of efficacy and side effects of this group of medicines as well as cost-effective aspects [12, 14]. Despite the viability of the process, EH is prone to relapses with symptoms such as abnormal uterine bleeding. The incidence of EH recurrence depending on the reverse progestin and the time since the end of therapy has not been defined so far [5, 11]. Furthermore, the optimal treatment duration and follow-up regime for patients after completion of treatment has not been confirmed yet [1, 7, 15, 16]. The rate of progression of EH to atypicality either with monitoring or with treatment by various types of progestins and varying durations of use has also not been measured; the data range from 5% over 20 years to 1.5-2% per year, which is already quite significant [2, 4, 8, 10, 17]. An ever-increasing number of reports of individual unsuccessful hormone therapy for non-atypical endometrial hyperplasia or progression of the disease even in the course of treatment [3] has prompted clinicians and researchers to look for new approaches to the management of this disease. The current differences in approaches to both surveillance and treatment of women with EH were the background to our study.

Objective of the study: To analyse the incidence of different morphotypes of hyperproliferative endometrial pathology (HPE) in premenopausal women, organization of treatment and preventive measures after diagnosis and identification of the main factors that influence the recurrence or progression of the disease.

Study design: retrospective observational study, debriefing. We have analysed all the cases of pathomorphologic diagnostics of HPE found during two years in three medical institutions of different levels in Ukraine, including 698 cases at the communal hospital

"Municipal Clinical Hospital No. 9 of the Dnipropetrovsk City Council" (Dnipropetrovsk city), 50 cases in the Mirhorod Central District Hospital (Mirhorod) and 144 cases in the Clinical Hospital of the Poltava Municipal Council (Poltava). Overall, a total of 892 primary patients between 20 and 60 years old were enrolled in the analysis of registry patterns and pathomorphological examination of endometrial samples at the time of diagnosis of HPE. The research design and all methods which were used in the study were approved by the Bioethics Committee of the Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine and followed the requirements of the Declaration of Helsinki. Statistical evaluation of the results was carried out using the licensed statistical software Statistica (version 6.1; Statsoft, USA)

Results of the study: Having analysed the incidence of HPE in 892 women of different age groups (Fig. 3.1), we ascertained that 23 (2.6%) women with the pathology were in the early reproductive period (aged 20 to 25 years), 118 (13.2%) women were in the active reproductive age. A total of 277 (31.1%) women were in their late reproductive years, 113 (12.7%) were 36-40 year olds and 164 (18.4%) were 41-45 year olds. The highest incidence of HPE was among women 46 to 55 years old – 419 (46.9%). Females with HPE were 40 (4.5%) between 56 and 60 years old, 9 (1.0%) between 61 and 65 years old, and 6 (0.7%) between 66 and 70 years old.

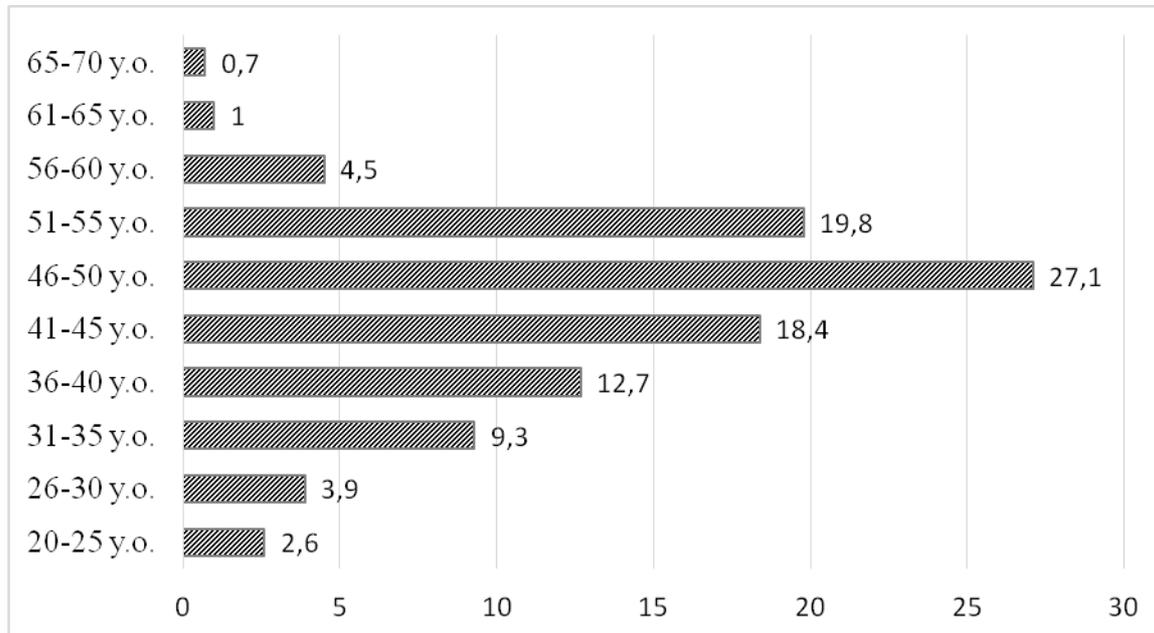


Fig. 1. Distribution of women with hyperproliferative endometrial pathology by age, %

A retrospective study was conducted to more precisely determine the incidence of HPE in premenopausal women as well as at different reproductive phases, and all patients

were further classified into STRAW+10 groups based on their medical history [6]. According to these criteria, we included 23 (2.6%) women in the early reproductive age group, 118 (13.2%) women in the active reproductive age group, 277 (31.1%) women between the ages of 36 and 45 with a regular menstrual cycle in the late reproductive age group, the premenopausal group - 380 (42.6%) women aged 46-55 years with menstrual cycle variability in duration, the occurrence of menstrual interruptions with amenorrhea duration of at least 60 days, as well as symptoms of a vasomotor nature (Fig. 2).

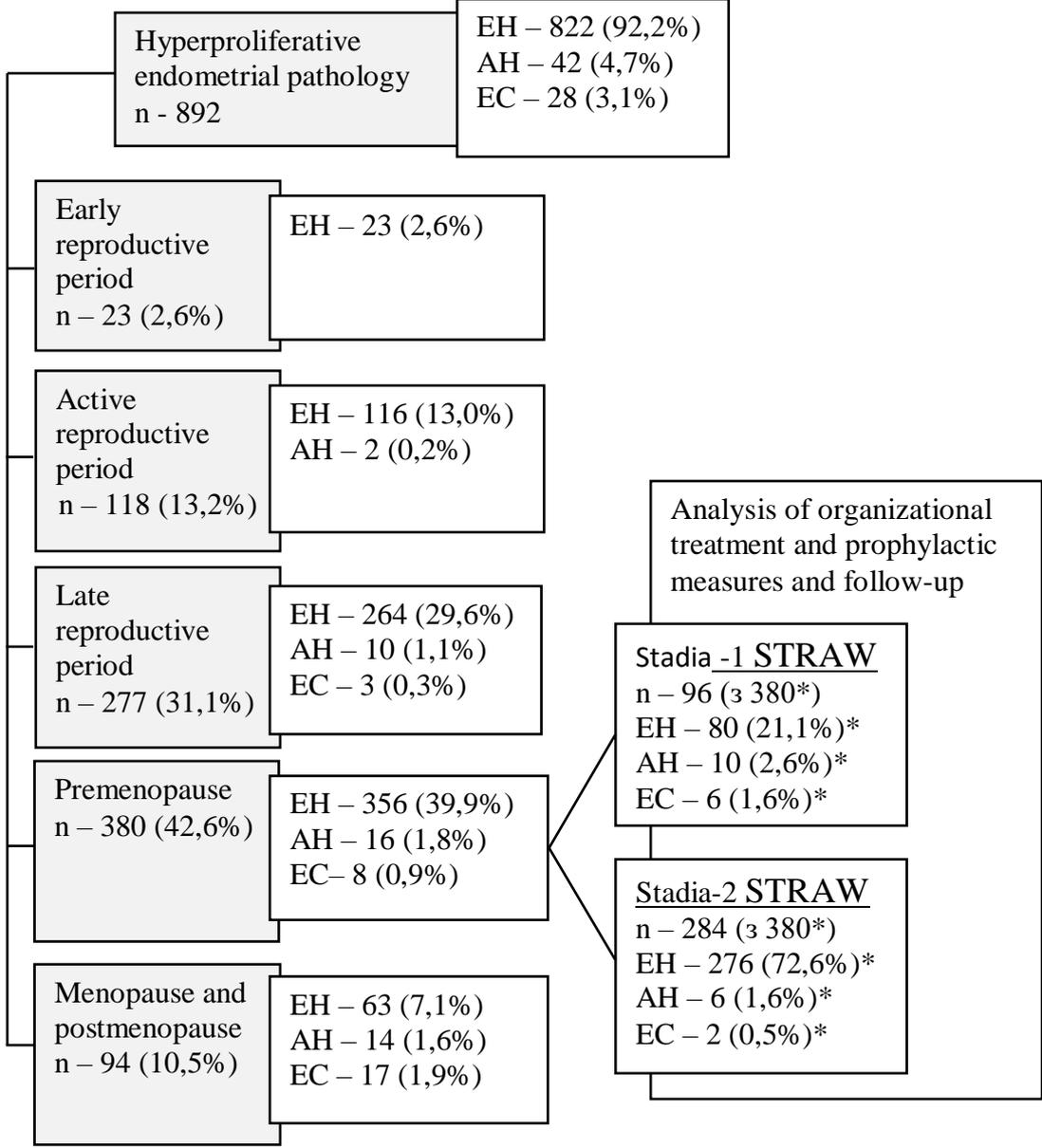


Fig. 2. Design of the retrospective study

There were 39 (4.4%) women with HPE in menopause, which occurred in 12 cases at 46-50 years and in 27 cases at 51-55 years old; 55 (6.1%) women were in postmenopause. Thus, the menopausal/postmenopausal group included 94 women with HPE.

This study followed the 2014 WHO classification of endometrial hyperplasia [9], which defines non-atypical hyperplasia (EH) and atypical endometrial hyperplasia (AH). The incidence of EH among women with HPE was 822 (92.2%), with AH - 42 (4.7%), and endometrial cancer (EC) - 28 (3.1%). Thus, HE was the most common pathology (Fig. 3).

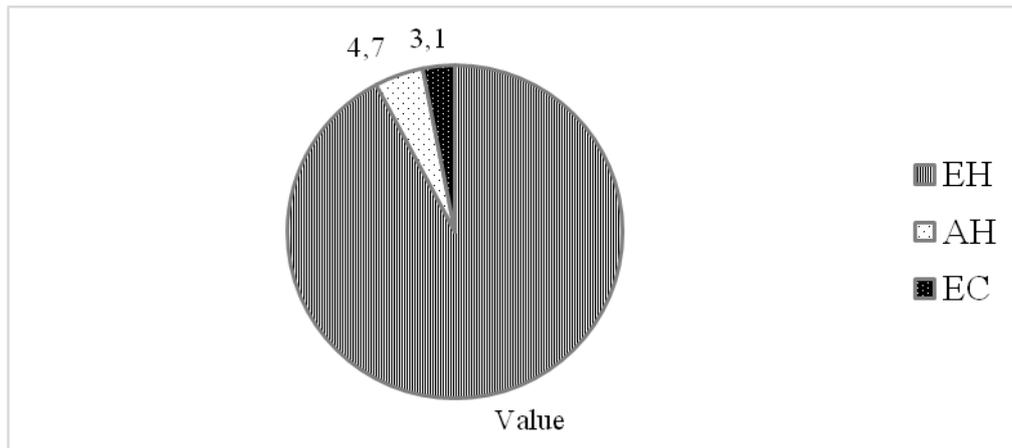


Fig. 3. Structure of different morphological pathological conditions of the endometrium among the examined women, %

According to Figure 4, the highest incidence of EH was in the late reproductive period - 264 (29.6%) women (average age of the women was 44.3±0.18 years), and in the transitional period up to menopause - 356 (39.9%) women (average age of the women was 49.9±0.15 years). It is during this period most women undergo involutional changes in their reproductive system organs with impaired function of numerous intracellular signals, this period is also associated with a total hypoprogesteroneemia due to the extinction of hormonal function of the ovaries.

This complex of age-related changes enables pathological transformation of the endometrium to become manifest. The number of women with EH occurring in the early and active reproductive years was significantly lower - 23 (2.6%) and 116 (13.0%) cases respectively, as well as 63 (7.1%) cases in menopause and postmenopause (Figure 4).

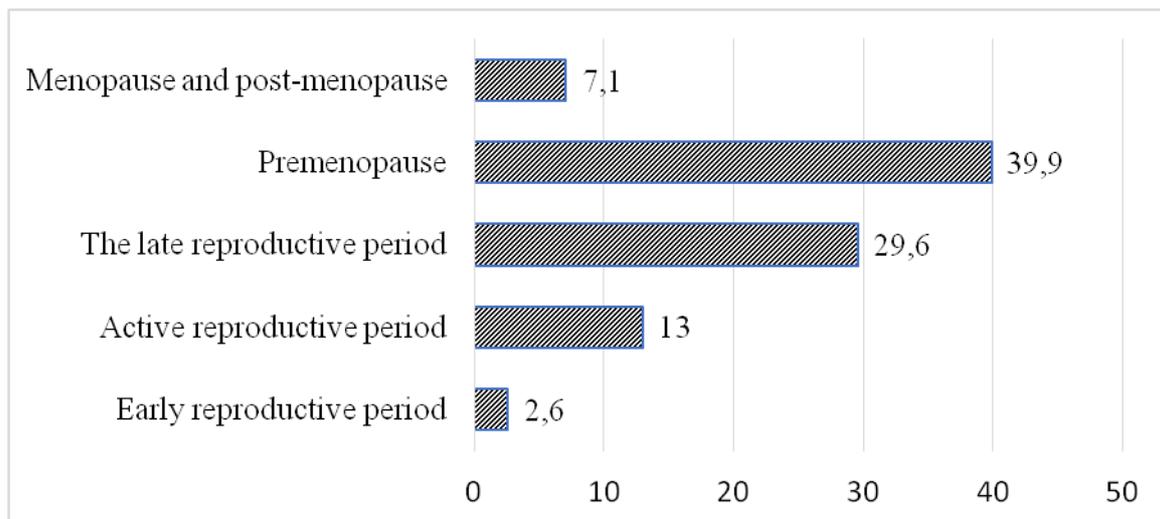


Fig. 4. Frequency of GE among women in different periods of life, %.

It should also be mentioned that, in the structure of age groups, AH occurred more or less frequently in the biopsy samples, both in premenopausal women - 16 (1.8%) cases, and in menopausal/postmenopausal women - 14 (1.6%) cases in total (Fig. 5). However, there were also enough cases of AH in the late reproductive period - 10 (1.1%).

AH is known to increase the risk of endometrial malignancy, which occurs more frequently among older women, as evidenced by the results of our analysis (Fig. 5). Thus, EC was detected in 17 (1.9%) women in menopause and postmenopause, whereas there were 8 (0.9%) such cases in premenopause and 3 (0.3%) in the late reproductive age. Thus, in premenopause AH was 2 times more frequent than EC (2.1:1 ratio), while in menopause and postmenopause AH and EC rates in the study sample were almost the same.

The aim of the study was to determine the incidence of different morphotypes of hyperproliferative and neoplastic endometrial pathology in premenopausal women, and the history of diseases in 380 women of this age category was analysed according to STRAW+10 criteria, the results being presented in Table 1.

Table 1 shows that 284 (74.7%) of 380 premenopausal women were diagnosed with HPE in the early transitional period (stage -2 according to STRAW+10 criteria), the other 96 (25.3%) women were detected 1-3 years before menopause, or in the late transitional period (stage -1 according to STRAW+10 criteria).

The structure of endometrial pathology among women of the above age category was dominated by EH in 356 (93.7%) cases, AH was detected in 16 (4.2%) cases, EC in 8 (2.6%) ones. There were some differences in the structure of HPE. Thus, the STRAW+10 criteria for females in the "Stage -2" age category accounted for 72.6% of EH, 1.6% for AH, and 0.5%

for EC. Women classified as STRAW+10 age group -1 had 21.1% of HE, 2.6% of AH and 1.6% of EC.

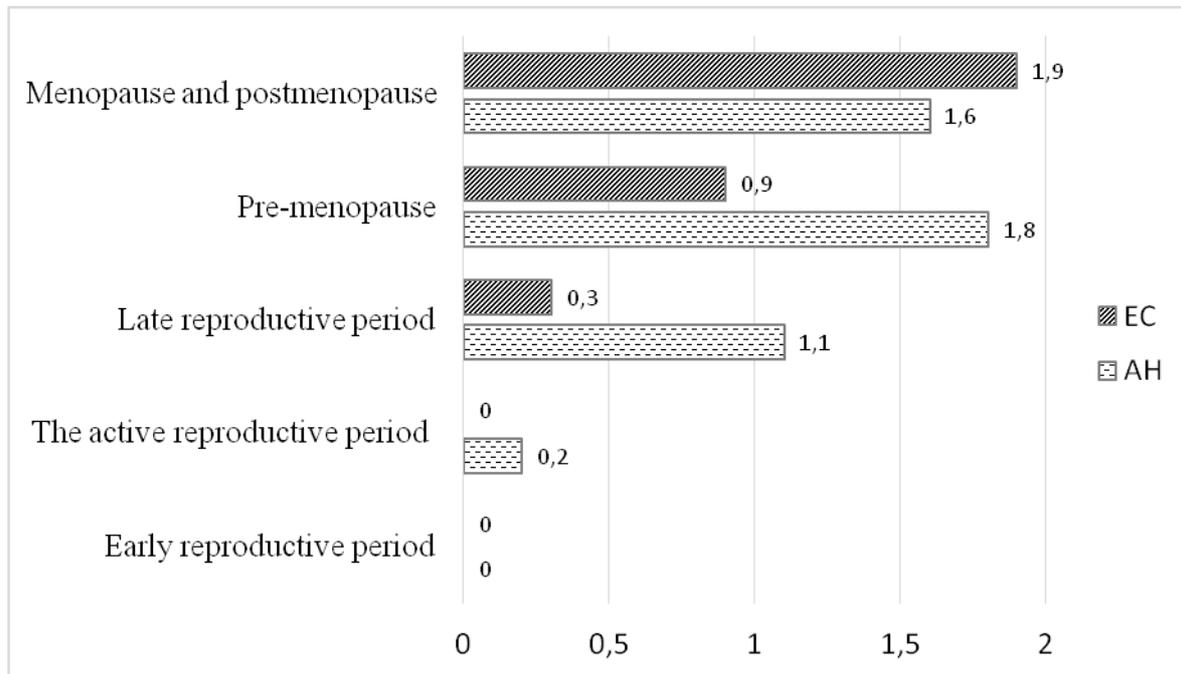


Fig. 5. Frequency of AH and EC in women in different periods of life, %.

Table 1

Distribution of different morphological conditions of the endometrium in premenopausal women according to STRAW+10 criteria (n, %)

Groups behind the morphotype	Creteria- STRAW		
	Pre-menopause	Stadia- 1	Stadia - 2
	1	2	3
EH	356 (93.7%)	80 (21.1%)	276 (72.6%)
AH	16 (4.2%)	10 (2.6%)	6 (1.6%)
EC	8 (2.1%)	6 (1.6%)	2 (0.5%)
In total	380 (100%)	96 (25.3%)	284 (74.7%)

The incidence of benign hyperplastic endometrial pathology in premenopausal women decreased 3.4-fold at the time close to menopause, due to a gradual reduction in menstrual function and the effect of sex-steroid hormones on cell proliferation in the endometrium. At

the same time, the rate of detection of precancerous pathology and EC increased shortly before menopause, probably due to the accumulation of genomic alterations that affect the way cells differentiate and the mechanisms of elimination of transformed cells [2]. The data we obtained do not contradict the data of the National Cancer Registry of Ukraine over the last ten years that indicate that EC ranks 3 in the age structure of the disease among women aged 30-54 years and 2 in those aged 55-74 years [13]. All women with AH and EC were referred to oncological clinics after diagnosis and underwent surgery for total hysterectomy. An analysis of initial medical documents and questionnaire results of premenopausal women with endometrial pathology revealed that the main reason for endometrial biopsy in 279 (73.4%) cases, the main reason for endometrial biopsy was abnormal uterine bleeding (AUB) at a menses interruption up to 2-3 months; in 65 (17.1%) cases, pathological thickness and structure abnormalities of the endometrium by ultrasound examination of women with asymptomatic disease. Additionally, HPE was detected in 36 (9.5%) women during a diagnostic endometrial biopsy at a stage of examination before the scheduled surgical treatment: before hysterectomy for myoma - 23 (6.1%) cases, in total pelvic prolapse - 6 (1.6%) and adnexal mass - 7 (1.8%). Therefore, out of 60 patients who underwent hysterectomy for the mentioned reasons, 320 women diagnosed with EH in premenopause were monitored further. The next step of the retrospective study was an analysis of organisational measures to prevent relapse or progression of EH and to identify the main determinants of its risk in this group of women.

Thus, according to the medical documentation and the results of the questionnaire, 45 (14.0%) women underwent surgical treatment due to the impossibility of hormonal treatment because of the presence of concomitant extragenital pathology, including hysteroscopic resection of the endometrium in 33 (10.3%) and hysterectomy in 12 (3.8%) cases.

Conservative antirecurrence treatment after instrumental removal of the endometrium was performed in 138 (43.1%) of the 320 premenopausal women with EH who did not receive a hysterectomy, this includes 112 (35.0%) women using oral gestagens, 78 (24.3%) women receiving gestagens without interruption for 3 months and 34 (10.6%) women for 6 months, 26 (8.1%) women were treated with a 52 mg levonorgestrel IUD (LNG IUD) as a long-term treatment.

The main criteria for the effectiveness of conservative treatment were the results of the control morphological examination of the endometrial biopsy samples obtained during the observation period of the mentioned group of women, which lasted three years after the initial diagnosis was made. It is noteworthy that the recommendation of systematic morphological

examination of the endometrium every 6 months before two consecutive negative biopsy results are obtained has not been implemented in most cases in practice. We examined the medical records of 138 women who received antireciprocal gestagen treatment for the next 3 years. An analysis of follow-up data showed that in the group of women who were treated with oral gestagens (n = 112), endometrial biopsy was carried out in 71 (63.4%), including 42 (37.5%) in the first year of treatment, 21 (18.8%) in the second year, and 8 (7.1%) in the third year. Women with EH who were treated with LNG IUDs and had their endometrial pipel-biopsy samplings were morphologically examined over a 3-year period in 19 (73.1%) of 26 such women. In 17 (65.4%) of 26 LNG IUDs group regression of EH was detected, but 2 (7.7%) showed evidence of AH one and three years after the LNG-IUD was inserted into the uterine cavity. However, this can be explained by a possible error in the sampling of endometrial samples at the stage of initial diagnosis of the endometrial state, as well as progression of the disease due to the insensitivity of the endometrium to gestagens.

It should be noted that in the majority of cases, endometrial biopsy was conducted when the patients were seeking AUB renewal, therefore, the true extent of pathological transformation of the endometrium in women with EH was difficult to judge, especially in regard to the possible asymptomatic progression of the disease. In the vast majority of cases, the efficacy of treatment in women with EH was monitored by ultrasound examination of the endometrium, and we found that in 24 (12.2%) of the 169 cases monitored the ultrasound findings were inconsistent with the morphological diagnosis.

The results of an analysis of the findings of the pathomorphological examination of control specimens of the endometrium obtained during different periods of follow-up women with EH after treatment are shown in Figure 6.

Stratification of endometrial pathology by the timing of its detection in the biopsy control material showed (Fig. 6), a recurrence of EH was possible within the first 12 months after initial diagnosis in 19 (24.4%) of 78 women who received 3 months of gestagen treatment and in 4 (11.8%) of 6 months. By the end of the year, there were more women with recurrent EH and they accounted for 32 (41.1%) and 5 (14.7%) cases respectively. Following histological examination of the endometrial biopsy samples at 24 months there were a total of 43 (55.2%) and 9 (26.5%) women, and at 36 months there were 47 (60.3%) and 10 (29.4%). Therefore, prolonged therapy with gestagens, at least for 6 months, resulted in a 2-fold decrease in the recurrence rate compared to a 3-month course of therapy. A total of 112 patients treated with gestagens were found to have a recurrence of HE in 57 (50.9%), i.e. in

every second woman. Therefore, short-term therapy with gestagens did not eliminate the risk of recurrence.

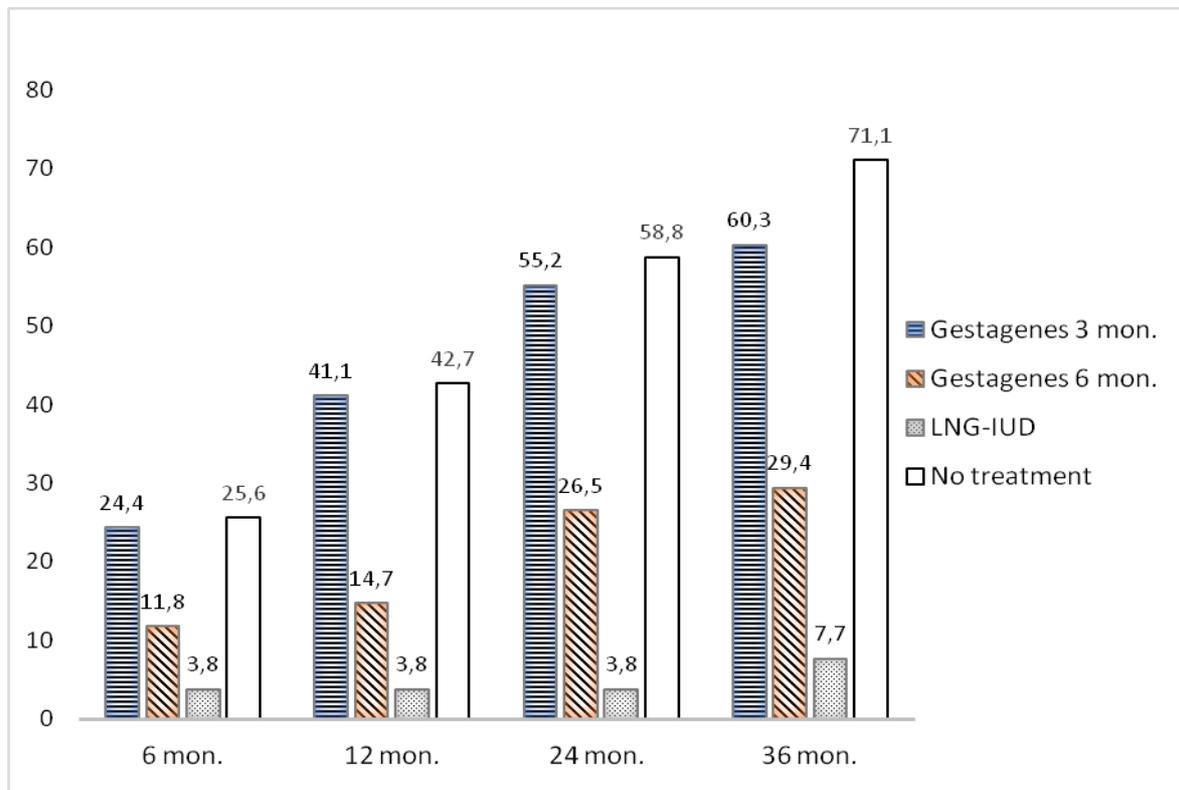


Fig. 6. Cumulative incidence of recurrence and progression HE cases in the women under examination (%).

In this regard, the reliably low rate of EH recurrence in women using the LNG IUD (Fig. 6) is noteworthy, possibly due to a more prolonged suppression of the endometrium as a result of continuous dosage injection of the levonorgestrel directly into the uterus.

To summarise this part of the study, it can be concluded that the success of EH therapy by the end of the third year of follow-up among women, LNG IUDs were achieved in 92.3% of cases, in 70.6% of cases treated with gestagens at 6 months and in 39.7% of cases treated at 3 months.

For women diagnosed with a recurrence of EH during the three-year follow-up after treatment with gestagens, GnRH agonists were prescribed as the second line of conservative therapy for a period of at least 6 months. A total of 31 (54.4%) of the 57 women with relapsed EH, representing 22.5% of the number of women who received conservative EH therapy. It should be emphasized that all of these women were in the age category "stage -1" according to STRAW criteria + 10. And 24 (77.4%) of them went into menopause after completing their treatment with GnRH agonists, which was expected when this group of drugs was prescribed.

The regression of EH after GnRH agonist therapy was observed in 27 (87.1%) cases and was presumably associated with the expected menopause, absence of effect was observed in 4 (12.9%) cases.

Surgical treatment was performed in 29 (21.0%) of 138 women who underwent conservative treatment, including total hysterectomy in 20 (14.5%) patients and hysteroscopic resection of the endometrium in 9 (6.5%) women. Total hysterectomy was indicated in endometrial biopsy specimens of AH in 5 (3.6%) women, EC in 2 (1.5%) cases, recurrent EH after treatment with GnRH agonists and ablation of the endometrium in 5 (3.6%) and 1 (0.7%) women, respectively. In 7 (5.1%) women, hysterectomy was caused by the occurrence of severe IUB, which could not be treated conservatively.

The absence of treatment for EH in 182 (56.8%) of the 320 women who underwent follow-up after diagnosis is controversial. The 182 women who did not participate in the treatment were questioned and 74 women (40.6%) refused the treatment, 36 (19.7%) were not treated because of hadn't prescriptions, other 72 women (39.5%) stopped taking gestagens after 1-2 months after having little side effects (most often breakthrough bleeding) and were classified by us as those who did not take treatment. However, all of these women were monitored for at least a year after diagnosis and had a transvaginal ultrasound examination once every 6 months on average and an endometrial biopsy once a year.

An analysis of the follow-up and the results of recurrent endometrial biopsies in the 36-month follow-up period after the diagnosis of EH showed that in the absence of therapy, the rate of recurrence of endometrial pathology at the end of the follow-up (36 months) was 2.4 times higher (130 cases out of 182 or 71%) than in women who underwent a 6-month course of gestagen therapy, but this rate was not significantly different in women with a 3-month course of similar therapy (Fig. 8). This once again demonstrates, on the one hand, the ineffectiveness of short courses of gestagen therapy in preventing recurrence of EH and, on the other hand, the possibility of spontaneous EH regression without any therapy in 28.8% of patients (Fig. 7).

According to an analysis of morphological examination of repeated endometrial biopsy samples, EC was diagnosed in 6 (3.3%) of 182 women who did not take EH treatment and in 1 (1.3%) of 78 women with EH who were treated with gestagens for only 3 months. No EC was found once in women who had received gestagens for 6 months and in LNG- IUD patients. AH was found in 11 (6.0%) women with HE who didn't have treatment, in 2 (2.6%) of 78 women and in 1 (2.9%) of 34 women who took gestagens consistently for three and six months (Fig. 8).

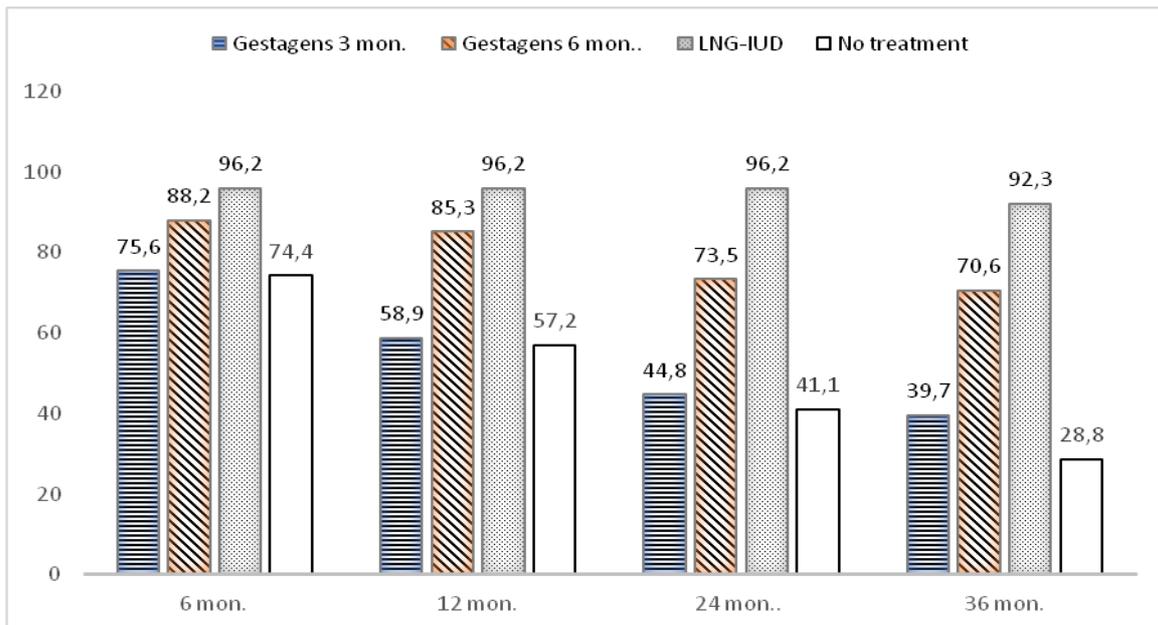


Fig. 7. Frequency of positive treatment outcomes for EH in the women surveyed, depending on the form and duration of gestagen treatment (%).

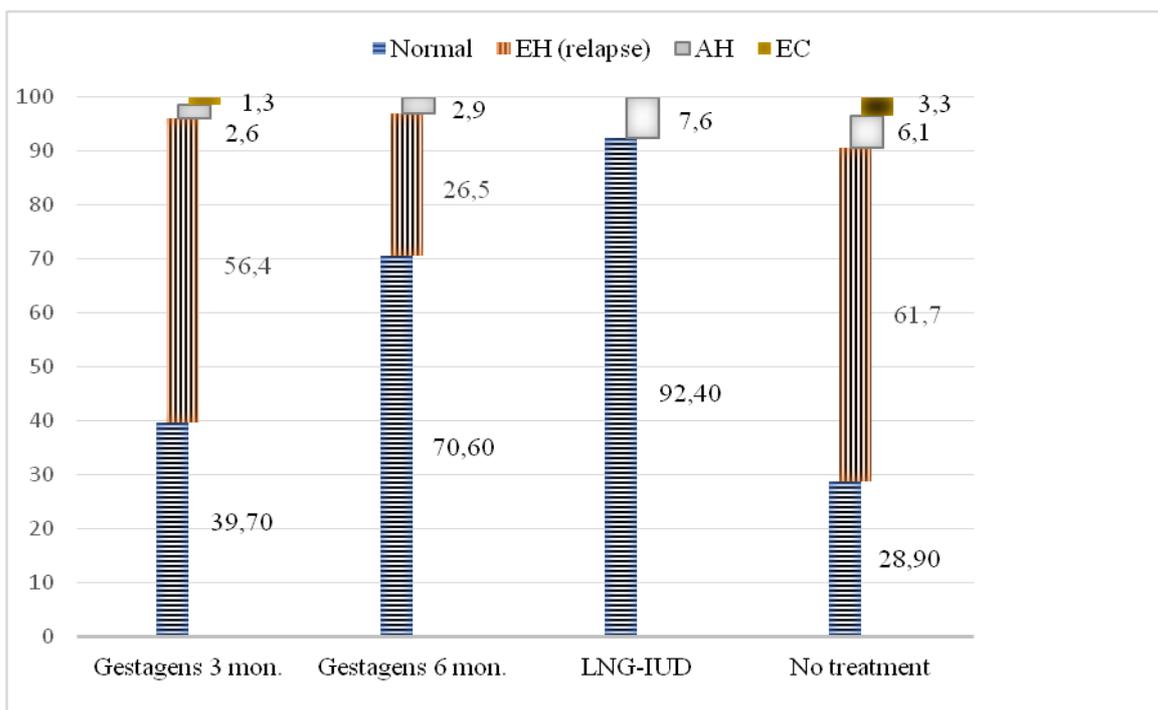


Fig. 8. Frequency of recurrence of EH, AH and EC in control endometrial biopsy samples of women with EH (%).

During a 36-month follow-up of women with EH who retreated from hormonal treatment, 100 (54.9%) cases of HE persistence resulted in the prescription of gestagen therapy and 8 (4.3%) cases were treated with GnRH agonists. Three (1.6%) women

underwent endometrial ablation and 19 (10.4%) patients underwent total hysterectomy for the progression to AH and EC.

As a result, only 52 (28.8%) of the 180 women with EH regressed spontaneously, while 130 (71.4%) women underwent various preventive treatments and all women were healthy at the time of the control endometrial biopsy in 36 months.

Summary of the results of the research

The results of the retrospective study suggest that the premenopausal period is the most risky with regard to the risks of various pathological conditions of the endometrium, especially EH, AH and EC. According to morphological examination of endometrial biopsy samples taken for diagnostic purposes at three regional medical centres in the cities of Dnipro, Poltava and Mirgorod over two years, In premenopausal women, AH and EC were found in 4.7% and 3.1% cases, respectively, but the dominant form of endometrial pathology was HE, which was diagnosed in 39.9% of endometrial biopsy specimens.

Approaches to therapy for EH in premenopausal women vary among research centres, but they all have one thing in common: the lack of systematization of treatment and a clear strategy for further monitoring of disease progression. In 21.9% of patients, treatment with gestagens, the first-line therapy according to international standards, was short-term with 39.7% efficacy in the regression of EH. Long-term use of gestagens in the treatment of EH in 10.6% of patients increased the regression rate of the altered endometrium to 76.6% as well. The best results were achieved with the use of the LNG IUD (92.3% efficacy), but it was indicated in only 8.1% of women, while a hysterectomy was performed in 22.5% of women due to recurrence or progression of the disease in the absence of efficacy of conservative treatment.

More than half of the HE patients (56.8%) were only monitored due to refusal of treatment or lack of its prescription, but their endometrial biopsies were performed irregularly, mostly due to women's complaints about the recurrence of AUB episodes, which were caused in 6.1% by AH, 3.3% by EC, and 61.7% by EH persistence or recurrence. But the spontaneous regression of EH in 28.8% of women who did not receive treatment is noteworthy from both a scientific and practical points of view.

Thus, the controversial results of the observational study, as well as the lack of counter-cycling effect of gestagens in the treatment of HE, undoubtedly provide the basis for further studies on improving the monitoring strategy for women with EH and clarifying the molecular and genetic features of the mechanisms of its occurrence as well as the cancer-causing transformation of endometrial cells.

Conclusions

1. There is no clear system for the treatment and follow-up of women with EH in the monitoring centres.
2. Short-term gestagen therapy (less than 3 months) is ineffective and contributes to a high rate of relapse (56.4%) after one year of therapy, which is practically the same as the rate of persistence of EH without therapy (61.7%).
3. The LNG IUD is the most effective (93.7%) and has no recurrence during the course of use, but the use of this method is insufficient

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