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THE ROLE OF GENETIC DETERMINANTS IN THE OCCURRENCE OF HYPERPLASTIC PROCESSES OF THE REPRODUCTIVE SYSTEM OF WOMEN'S MENOPAUSAL AGE

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Abstract. When analyzing the allelic distribution of the GPITIa gene in women with endometrial hyperplastic processes compared with the population, the following was revealed: when using the method of observed and expected frequencies in patients with endometrial hyperplastic processes, the distribution of alleles of the GPIIIa gene statistically differs from the population ($p<0.05$), due to an increase in frequency occurrence of the PLA1A2 genotype; - when analyzing the allelic distribution of the GPIIIa gene in patients with endometrial polyps, there were no statistically significant changes in the allelic distribution of the GPIIIa gene compared to the population frequencies. However, the PLA1A2 genotype of the GPIIIa gene is statistically significantly more common in patients: with recurrent endometrial polyps ($p<0.05$).

Keywords: Endometrial hyperplasia, postmenopause, genotype, GPIIIa gene alleles, polyp.

RELEVANCE

Hyperplastic processes of the endometrium are a common gynecological pathology, the main clinical manifestations of which are abnormal uterine bleeding. The incidence of GPE increases during the period of peri- and postmenopause [3,7]. GPE occurs in 15-40% of gynecological patients of different age groups [8]. The problem of GPE deserves close attention due to the

possibility of their malignant transformation [11,14,15,20]. In premenopausal women, the frequency of malignant transformation of hyperplastic processes of the uterus reaches 10-12.4% [2,3].

Endometrial hyperplasia occurs in approximately 5 - 42% of gynecological patients [3,19]. In 1% of cases, simple endometrial hyperplasia without atypia turns into endometrial cancer, complex endometrial hyperplasia without atypia — in 3%, simple atypical endometrial hyperplasia turns into endometrial cancer in 8% of patients, complex atypical hyperplasia - in 29% of patients [15]. Endometrial polyps, according to various authors, occur in 5.3%- 39.2% of gynecological patients, while their malignancy occurs in 2-3% of women [4,7].

Cancer of the uterine body in women occupies the 4th place in the structure of oncological morbidity [11,14]. In the USA, more than 6,000 women die from uterine body cancer every year [15]. In Russia, as A.I. Maksimova points out, the incidence of endometrial cancer has increased by 2 times over the past 20 years [34]. According to the summary data of 69 clinics in the world, the five-year survival rate for uterine body cancer is 66.6% [5].

Hyperplastic processes of the endometrium are characterized by a high frequency of recurrence. Particularly noteworthy are often recurrent HPE, which turn into invasive uterine cancer in 20-30% of cases [16]. Endometrial hyperplasia recurs in 39.3% of women despite hormone therapy and in 9.5% of patients after endometrial ablation [17]. In untreated patients, HPE recurs in 71.78% [15]. In the pathogenesis of endometrial hyperplastic processes, hyperestrogenism and various pathological conditions leading to it play a leading role [1,2,18].

Recently, in connection with the introduction of high technologies in various branches of medicine, research in the field of molecular biology, genetics and immunology has become possible. There are studies devoted to the involvement in the pathogenesis of endometrial hyperplastic processes of genes that regulate the cell cycle, proto-oncogenes and hep-tumor suppressors, various growth factors, cytokines, steroid hormone receptors and genes encoding them.

One of the research areas is the study of cell adhesion molecules that provide intercellular and cell-matrix interaction. To date, more than 50 cell adhesion molecules have been isolated. Depending on their protein structure, they are divided into 4 families: cadherins, integrins, immunoglobulins and selectins. Integrins are transmembrane cell surface glycoproteins that perform a receptor function. These molecules also carry out the function of conducting intracellular signals that mediate the influence of the matrix on gene expression, movement, proliferation, differentiation, apoptosis, and other cell functions.

In recent years, at the Department of Obstetrics and Gynecology of the Bukhara Medical University named after Abu Ali Ibn Sino, a number of studies focusing on the involvement of the allelic distribution of a gene GPIIIa in the pathogenesis of various gynecological diseases such as fibroids uterus, endometriosis [1,13,16].

However, in these studies, little attention is paid to recurrent forms of endometrial hyperplastic processes, in addition, there is absolutely no data on the effect of the allelic distribution of the GPIIIa gene on the need for electrosurgical interventions in endometrial hyperplastic processes.

THE PURPOSE OF OUR RESEARCH

To determine the clinical significance of the allelic distribution of the GPIIIa gene in endometrial hyperplastic processes in the pre- and postmenopausal period.

MATERIALS AND METHODS

The work was performed on the basis of the gynecological departments of the perinatal center of the Bukhara region of the Republic of Uzbekistan in 2019-2022. We prospectively examined 117 patients of peri- and postmenopausal age who were hospitalized in the gynecological departments of the perinatal center of the Bukhara region with suspected endometrial hyperplastic process. All patients underwent hysteroscopy with separate diagnostic curettage followed by histological examination of the scrapings. In our work, we used the classification of endometrial hyperplasia proposed by the International Society for Gynecological Pathomorphology in 1994, according to

which there are simple and complex endometrial hyperplasia without atypia and simple and complex atypical endometrial hyperplasia. Endometrial polyps are considered separately.

In groups of patients with endometrial polyps and endometrial hyperplasia without atypia, depending on the recurrence factor of these hyperplastic processes, patients with newly diagnosed PE and HE and patients with relapse of this pathology were identified.

In the group of patients with endometrial polyps, the patients were also divided depending on the histological characteristics of PE. Among the patients examined by us with endometrial polyps, 30 (60%) patients had glandular fibrous polyps, 18 (40%) had glandular polyps. Fibrous polyps were not found in the examined patients.

In addition, in the group of patients with endometrial polyps, we identified 31 patients (26.5%), in whom polyps were completely removed during hysteroscopy with separate diagnostic curettage and 42 patients (35.9%), in whom a large or a smaller part of the polyp, which subsequently required a second hospitalization for electrosurgical resection of the remaining part of the polyp.

We have developed a statistical map in which we displayed passport data, complaints, gynecological anamnesis data, the presence of concomitant extragenital pathology, gynecological examination data, and the results of clinical and instrumental examination methods.

All patients underwent an ultrasound examination of the pelvic organs using HITACHI devices (Japan) using transabdominal and transvaginal sensors with a frequency of 3.5 and 6.5 MHz. Performed ultrasound of the pelvic organs in the longitudinal and transverse projections.

The criteria for the diagnosis of endometrial hyperplastic process were: 1) M-ECHO thickness > 4-5 mm in postmenopausal women; 2) thickening of the endometrium and an increase in its echogenicity in the proliferative phase in perimenopausal women; 3) heterogeneity, heteroechogenicity of the median structure of the uterine cavity; 4) the presence of various sizes of hyperechoic or anechoic inclusions in the uterine cavity.

In our work, we determined the distribution of alleles of the GPIIIa gene by polymerase chain reaction using the original oligonucleotide primers 5'gctccaatgtacggggta and 5'ctcctcagacctccaccttg, which make it possible to synthesize a specific DNA product 384 bp long. 80 bp in the case of the PLA1 allele and fragments of 170, 120 and 80 bp in the case of the PLA2 allele Analysis of the reaction products is carried out by standard polyacrylamide or agarose gel electrophoresis.

A dry blood drop on a paper carrier, which is Whatman ZMM paper (Whatman, England), was used as a DNA template.

Research results

In our study, the genotype of the GPIIIa gene was determined in 117 women. Analysis of the observed and expected frequencies (method x 2) showed that among patients in the control group, the frequency of occurrence of alleles of the GPIIIa gene did not statistically differ from that in the population ($p = 0.98$). Therefore, in the future, a statistical analysis of patients with HPE was carried out in comparison with population frequencies, as statistically more powerful.

In 53 patients with HPE, which was 58.9%, 96% CI (%), 29-79%, the PLA1A1 genotype was detected; PLA1A2 genotype in 32 patients, 39.5%, 95% CI 20-57(%) and PLA2A2 genotype in 3 patients, 2.1%, 94% CI 0-16(%). When analyzing the observed and expected frequencies (%2 method), the allelic distribution of the GPIIIa gene in patients with HPE was statistically significantly different from that in the population ($p < 0.005$). In the group of patients with endometrial polyps (n=51), 13 carriers of PLA1A2 alleles were identified, which was 28.9%, 95% CI 14-44%, 33 carriers of PLA1A1 alleles, 66.7%, 95% CI 55-82(%) and 2 carriers of PLA2A2 allele, 4.1%, 95% CI 1-29%. The frequency of the PLA1A1 genotype in this group was significantly higher than the frequency of the PLA1A2 genotype ($p=0.01$). At the same time, the distribution of GPIIIa genotypes did not differ statistically from the population ($p=0.32$). The calculation of the relative risk (A) of developing endometrial polyps in PLA1A2 heterozygotes compared with the average population frequency showed that patients carrying the PLA1A2 genotype were approximately 1.5 times more likely to develop endometrial polyps than those carrying the PL A1A1 genotype.

The values of the frequencies of the PLA1A1 and PLA1A2 genotypes in the population fall into the confidence intervals of the frequencies of the same genotypes in PE, thus, the PLA1A2 genotype is not significantly more common in PE than in the population, and the PLA1A1 genotype is less common than in the population (p=0.32).

For a more detailed study of the effect of the GPIIIa genotype PLA on PE, we The allelic distribution of the GPIIIa gene was analyzed depending on the recurrence of this pathology. We compared the PLA genotypes of the GPIII a gene in patients with newly identified endometrial polyps (n=31) with the PLA genotypes of patients with recurrent PE (n=21). In 33 patients with newly diagnosed PE (n=23), which was 28.2%, the PLA1A1 genotype was detected; the PLA1A2 genotype in 9 patients (7.7%) and the PLA2A2 genotype in 5 patients (3.4%). Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not statistically differ from the frequency in the population (p=0.92). The frequency of the PLA1A1 genotype was significantly higher than the frequency of the PL A1A2 genotype (p<0.05). Among patients with recurrent PE (p=21) in 11 patients, which was 52.3%, the PLA1A1 genotype was detected, The PLA1A2 genotype was detected in 10 (47.7%). The PLA2A2 genotype of 5 patients with recurrent PE was not detected. Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not differ statistically from each other (p=0.46). The frequency of occurrence of the PLA1A2 genotype in patients with recurrent PE was statistically significantly higher than in the population, and the P1A1A1 genotype was less frequent than in the population (p<0.05).

The calculation of the relative risk (A) showed that PLA1A2 heterozygotes, compared with the average population frequency, have about 2.2 times higher risk of recurrence of PE than individuals carrying the PLA1A1 genotype.

We also analyzed the distribution of the PLA polymorphism of the GPIIIa gene depending on the histological classification of endometrial polyps. In the examined patients with endometrial polyps (n=51), in 29 patients, which was 43.5%, PE was glandular-fibrous, in 22 patients (18.8%) glandular. No fibrotic endometrial polyp was found in any of the patients we examined. In 15 patients with glandular PE (n=22), which was 68.2%, the PLA1A1 genotype was detected; the PLA1A2 genotype in 3 patients (13.2%). The PLA2A2 genotype was not detected in patients with glandular PE. Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not statistically differ from the frequency in the population (p=0.91). The frequency of the PLA1A1 genotype was significantly higher than the frequency of the PLA1A2 genotype (p<0.05).

Among patients with glandular fibrotic PE (p=30) in 17 patients, which was 56.7%, the PLA1A1 genotype was detected, the PLA1A2 genotype was detected in 11 (36.7%), the PLA2A2 genotype was detected in 2 patients (6.6%). Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not differ statistically from each other (p=0.34). The frequency of occurrence of the PLA1A2 genotype in patients with glandular fibrous polyps of PE was statistically significantly higher than in the population (p<0.05), and the P1A1A1 genotype was less frequent than in the population.

The calculation of the relative risk (A) showed that in PLA1A2 heterozygotes, compared with the average population frequency, approximatelyIn 23 patients whose polyps were completely removed (n=33), which was 69.7%, the PLA1A1 genotype was detected; the PLA1A2 genotype in 5 patients (15.1%) and the PLA2A2 genotype in 1 patient (3.0%). Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not differ statistically from the frequency in the population (p=0.1). The frequency of the PLA1A1 genotype was significantly higher than the frequency of the PLA1A2 genotype (p<0.001).

Among the patients with PE who later required resection of the remaining part of the polyp (n=21), 9 patients, which was 42.9%, had the PLA1A1 genotype, 11 (50.0%) had the PLA1A2 genotype, and 1 patient (4.5%) had the PLA2A2 genotype. Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not differ statistically from each other (p=0.5). The incidence of the PLA1A2 genotype in patients with PE who required resection of the remaining part of the polyp was statistically significantly higher than in the population (p<0.001),

and the P1A1A1 genotype was less frequent than in the population.The calculation of the relative risk (A) showed that PLA1A2 heterozygotes, compared with the average population frequency, have about 4.2 times higher risk of PE, for the removal of which the use of a hysteroresectoscope will be necessary, than those of carriers of the PLA1A1 genotype.

In the group of patients with hyperplasia without atypia (n=42), 21 carriers of PLA1A2 alleles were identified, which was 50%, 95% CI 32-68%) and 19 carriers of PLA1A1 alleles, 50%, 95% CI 32-69(%). There were no carriers of the PLA2A2 allele in the group of patients with endometrial hyperplasia. The frequency of the PLA1A1 genotype in this group was the same as the frequency of the PLA1A2 genotype (p=1.0). The PLA1A2 genotype was statistically significantly more common in the group of patients with GE, and the PLA1A1 genotype was less common than in the population (p<0.001).

The calculation of the relative risk (A) of developing endometrial hyperplasia without atypia in PLA1A2 heterozygotes compared with the average population frequency showed that patients carrying the PLA1A2 genotype had about 3.4 times more probability of developing endometrial hyperplasia without atypia than those carrying the PLA1A1 genotype.

For a more detailed study of the effect of the GPIIIa genotype on the occurrence of GE, we analyzed the allelic distribution of the GPIIIa gene depending on the recurrence of this pathology. We compared the distribution of PLA genotypes of the GPIIIa gene in patients with newly diagnosed simple endometrial hyperplasia (n=19) and in patients with recurrent GE (n=21). In 13 patients with newly diagnosed GE (n=19), which was 68.4%, the PLA1A1 genotype was detected; the PLA1A2 genotype was detected in 5 patients (26.3%). Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not statistically differ from the frequency in the population (p=0.26). The frequency of the PLA1A1 genotype was significantly higher than the frequency of the PLA1A2 genotype (p<0.05). Among patients with recurrent HE (n=21) in 9 patients, which was 42.9 %, the PLA1A1 genotype was detected, 11 (57.9%) revealed the PLA1A2 genotype. Within the group, the frequency of occurrence of the PLA1A1 and PLA1A2 genotypes did not differ statistically from each other (p=0.22). The frequency of occurrence of the PLA1A2 genotype in patients with recurrent HE was statistically significantly higher than in the population (p<0.001), and the P1A1A1 genotype was less frequent than in the population.

The calculation of the relative risk (A) showed that PLA1A2 heterozygotes, compared with the average population frequency, have about a 5.8-fold higher risk of recurrence of GE than carriers of the P1A1A1 genotype.

CONCLUSIONS

1. The allelic distribution of the GPIIIa gene in patients with endometrial hyperplastic processes differs statistically from the population distribution (p<0.005), namely due to a significant increase in the frequency of occurrence of the PLA1A2 genotype.
2. In patients with endometrial polyps, the allelic distribution of the GPIIIa gene does not statistically differ from the population distribution. However, the PLA1A2 genotype of the GPIIIa gene is statistically significantly more common in patients with glandular fibrotic endometrial polyps (p<0.05) compared with patients with glandular endometrial polyps and the population.

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