THE FEATURES OF ENDOMETRIUM STRUCTURE IN ALCOHOL-ABUSED HIV-INFECTED INDIVIDUALS

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Abstract
Background. Patients with comorbid pathology occupy leading positions in the practice of a doctor of any specialty especially in patients with HIV. The reproductive system is known to be the gateway for viruses. This fact could explain severity of changes developing in the female reproductive system infected with HIV, in particular in the endometrium. The purpose of this study was to assess the morphological changes of the endometrium caused by the combined effects of HIV infection and chronic alcoholism. **Materials and Methods:** The study involved autopsy material taken from 60 women of reproductive age (20–40 years). They were all divided into two groups. Group 1 (30 persons) consisted of HIV-positive individuals in whom, according to the relatives and according to the autopsy findings (the main symptom was the presence of alcoholic cirrhosis of the liver), alcohol abuse was confirmed. The following parameters were determined: the average diameter of the endometrial glands (proliferative type), the minimum diameter of the endometrial glands (proliferative type), the maximum diameter of the endometrial glands (proliferative type), wall thickness (proliferative type), the relative volume of the epithelium (proliferative type), the average diameter of the glands (secretory type), the minimum diameter of the glands (secretory type), the maximum diameter of the glands (secretory type), the relative volume of the epithelium (secretory type), the thickness of the epithelium. **Results.** The average diameter of the endometrial glands (proliferative type) decreased from $51.71 \pm 2.90 \times 10^{-6}$ m compared to $39.42 \pm 2.35 \times 10^{-6}$ m in the HIV-infected group, which was 23.77%. The minimum diameter of the endometrial glands (proliferative type) reduced from $32.47 \pm 1.83 \times 10^{-6}$ m to $27.13 \pm 1.73 \times 10^{-6}$ m (16.45%), the maximum diameter from $72.14 \pm 2.21 \times 10^{-6}$ m to $63.84 \pm 3.29 \times 10^{-6}$ m (11.5%). the relative volume of the epithelium (proliferative type) decreased by 5.41% (from $54.43 \pm 1.79\%$ in the study group to $49.02 \pm 2.65\%$ in the control group). The thickness of the uterine wall was also significantly reduced from $15.18 \pm 1.60 \times 10^{-6}$ m to $14.52 \pm 1.19 \times 10^{-6}$ m, which was 4.35%. The maximum volume of glands (secretory type) changed from $127.98 \pm 2.10 \times 10^{-6}$ m to $97.18 \pm 3.12 \times 10^{-6}$ m (24%). Changes by 3.6% were also observed when examining the wall thickness (from $13.02 \pm 1.36 \times 10^{-6}$ m to $12.55 \pm 1.68 \times 10^{-6}$ m). **Conclusion.** We can conclude about significant severity of pathological changes in the endometrium in HIV-infected women who were addicted to alcohol. This fact makes it possible to assume that the presence of alcohol addiction increases the changes caused by HIV infection in the endometrium. The described changes are mainly expressed in the maximum and average diameter of the endometrial glands in both the proliferative and secretory phases of the menstrual cycle.
Keywords: endometrium, HIV, alcohol, histology, morphometry.

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Introduction

In Ukraine, the number of HIV-infected people is growing every year with the overwhelming majority the young persons (77.6% of reproductive and working age (15–49 years)), the number of HIV-infected pregnant women is also increasing [1], which is explained by the high proportion of women of reproductive age among the patients with HIV infection [2].

The patients with comorbid pathology occupy leading positions in the practice of a doctor of any specialty especially deaing with HIV patients [3]. Working with such a group of people, the physician needs to assess the risks of the combined influence of several abnormal processes, which often reinforce each other, leading to an even more pronounced reaction to the development of the pathological process in various organs and tissues [4]. Such patients always require an individual approach in sense of diagnostic procedures, diagnosis confirmation and selection of therapy [5].

HIV infection is the leader in the frequency and severity of comorbid pathology among all diseases. In almost one hundred percent of cases [3], HIV infection is combined with a variety of diseases that drastically aggravate its course, and often cause the death of patients. Meanwhile, it is known that alcohol abuse is the cause of cancer deveopment in women [6, 7]. Considering the behavior of people who abuse alcohol, their low social responsibility, concomitant diseases of chronic alcoholism are often infectious diseases, including HIV infection (AIDS) [9, 10].

The reproductive system is known to be the gateway for viruses. This fact could explain severity of the changes developing in the female reproductive system infected with HIV, in particular in the endometrium. It can be assumed that these changes may increase in the presence of any of the diseases associated with HIV infection, especially alcohol abuse [10].

Today there are many studies covering the influence of chronic alcoholism on the state of the reproductive organs in women, as well as the impact of HIV infection. However, there are practically no data on the combined effect of these factors.

2. Purpose, subjects and methods:

2.1. The purpose

Considering all of the above, the purpose of this study was to assess the morphological changes in the endometrium caused by the combined effects of HIV infection and chronic alcoholism.

2.2. Subjects & Methods

The study included autopsy material taken from 60 women of reproductive age (20–40 years). They were all divided into two groups. Group 1 (30 persons) consisted of HIV-positive individuals in whom, according to their relatives and according to the autopsy findings (the main symptom is the presence of alcoholic cirrhosis of the liver), alcohol abuse was confirmed. HIV infection was determined by a serum enzyme-linked immunosorbent assay (ELISA) with confirmation by Western blot. CD4 lymphocyte count <100 cells/µL was considered "low" [2]. The control group (30) consisted of women without any concomitant diseases, with a negative HIV status, who had no confirmed alcohol abuse, who died as a result of accidents.

The material was fixed in 10% neutral buffered formalin, then the selected samples were embedded in paraffin. At the next stage, sections with a thickness of 5×10^{-6} m were made from the prepared paraffin blocks. Subsequently, staining with hematoxylin and eosin was performed. Microscopic examination was carried out on an Olympus BX41 microscope, followed by morphometric examination using the Olympus DP-soft 3.12 software [11].

The following parameters were determined: the average diameter of the endometrial glands (proliferative type), the minimum diameter of the endometrial glands (proliferative type), the maximum diameter of the endometrial glands (proliferative type), wall thickness (proliferative type), the relative volume of the epithelium (proliferative type), the average diameter of the glands (secretory type), the minimum diameter of the glands (secretory type), the maximum diameter of the glands (secretory type), the relative volume of the epithelium (secretory type), the thickness of the epithelium.

Statistical processing was performed using the methods of variation statistics. Correspondence of the distribution to the norm was determined by the Shapiro-Wilk test, which showed that the samples were close to the normal distribution. Statistical indicators are presented in $M \pm \sigma$ format, where M is the arithmetic mean, σ is the standard deviation, Student's t-test. Correlation analysis was carried out using Spearman's rank correlation coefficient. The statistical difference between the studied parameters was considered significant at p less than 0.05.

The procedure was done strictly in compliance with Helsinki Declaration after approval from the Re-gional Ethical Review

Board at Odessa National Medical University, records No. 3 dated 17 October 2011.

3. Results & Discussion

The results of the study carried out in a group of HIV-infected women suffering from chronic alcoholism and in the control group are presented in *Table*.

meter of the glands (secretory type) was reduced by 9% and in the comparison group it was $33.86 \pm 1.17 \times 10^{-6}$ m; $30.81 \pm 1.79 \times 10^{-6}$ m in the group of HIV-infected women with alcoholism.

The maximum volume of glands (secretory type) changed from $127.98 \pm 2.10 \times 10^{-6}$ m to $97.18 \pm 3.12 \times 10^{-6}$ m (24%). The changes by

Indicators of the endometrium structure

The investigated indicator	Comparison group	HIV infection and alcoholism
Average diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	51.71±2.90	39.42±2.35*
Minimum diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	32.47±1.83	27.13±1.73*
Maximum diameter of the endometrial glands (proliferative type), $\times 10^{-6}$ m	72.14 ±2.21	63.84±3.29*
Wall thickness (proliferative type), $\times 10^{-6}$ m	15.18±1.60	14.52±1.19
Relative volume of the epithelium (proliferative type), %	54.43±1.79	49.02±2.65*
Average diameter of the glands (secretory type), $\times 10^{-6}$ m	101.55±3.12	82.44±3.59
Minimum diameter of the glands (secretory type, $\times 10^{-6}$ m	33.86±1.17	30.81±1.79*
Maximum diameter of the glands (secretory type), $\times 10^{-6}$ m	127.98±2.10	97.18±3.12*
Wall thickness (secretory type), $\times 10^{-6}$ m	13.02±1.36	12.55±1.68
Relative volume of the epithelium (secretory type), %	61.24±1.11	47.18±1.62*
Thickness of the epithelium, $\times 10^{-6}$ m	49.14±1.44	53.04±1.13*

* $p < 0.05$ significant between groups.

As it can be seen from *Table*, the presence of HIV infection in patients with chronic alcoholism caused significant morphological changes in the structure of the endometrium. In the group of HIV-infected women who abused alcohol, practically all studied parameters significantly decreased in comparison with the control group.

Namely, the average diameter of the endometrial glands (proliferative type) decreased from $51.71 \pm 2.90 \times 10^{-6}$ m in the comparison group to $39.42 \pm 2.35 \times 10^{-6}$ m in the HIV-infected group, which was 23.77%. The minimum diameter of the endometrial glands (proliferative type) reduced from $32.47 \pm 1.83 \times 10^{-6}$ m to $27.13 \pm 1.73 \times 10^{-6}$ m (16.45%), the maximum diameter from $72.14 \pm 2.21 \times 10^{-6}$ m to $63.84 \pm 3.29 \times 10^{-6}$ m (11.5%) according to the above order.

Obviously, the changes affected not only the glands, but also the epithelium itself. Meanwhile, the relative volume of the epithelium (proliferative type) decreased by 5.41% (from 54.43 ± 1.79% in the study group to 49.02 ± 2.65% in the control group). The thickness of the uterine wall was also significantly reduced from $15.18 \pm 1.60 \times 10^{-6}$ m to $14.52 \pm 1.19 \times 10^{-6}$ m, which made 4.35%.

As can be seen from the table, the changes affected the endometrium, both in the proliferative and secretory phases.

The average diameter of the glands (secretory type) in the comparison group was $101.55 \pm 3.12 \times 10^{-6}$ m, which was 18.82% more than in the study group ($82.44 \pm 3.59 \times 10^{-6}$ m). The minimum dia-

3.6% were also observed when examining the wall thickness (from $13.02 \pm 1.36 \times 10^{-6}$ m to $12.55 \pm 1.68 \times 10^{-6}$ m).

The relative volume of the epithelium in the study group compared with the comparison group decreased from 61.24 ± 1.11% to 47.18 ± 1.62%.

The thickness of the epithelium increases by 7.35% (from 49.14 ± 1.44 in the control group to 53.04 ± 1.13 in the study group).

As can be seen from the table, the parameters that maximally reacted to the combined effect of HIV infection and chronic alcoholism on the endometrium were the maximum and average diameter of the glands both in the proliferative and secretory phases of the menstrual cycle that could be coordinated with the earlier findings [12].

Thus, it can be assumed that the effect of HIV infection on the endometrium may be enhanced by the presence of chronic alcoholism. HIV is known to cause a violation of the immune status of a person, which affects the state of all organs and tissues, including the endometrium [13, 14]. Many authors have shown a violation of the supervisory functions of the immune system, which regulate the processes of cell proliferation. These changes can be both hereditary and developed during the expression or mutations of the corresponding genes during life. The results of other studies allow suggestion that there is a genetic predisposition to the development of endometrial hyperplastic processes, and the main risk factor and trigger of the pathogenic

mechanisms of proliferative processes in the uterus are genetic determinants (PL-AI allele of the GP-IIIa gene), xenobiotics, PTEN [15, 16].

There are reports of the "inflammatory" origin of endometrial hyperplastic processes [17, 18]. It is known that in the presence of long-term, often exacerbated inflammatory processes of the genital organs, the risk of endometrial cancer increases 20 times, and 15 times against a background of hyperplastic processes of the endometrium. Long-term persistent infection of the genitals leads to a change in estradiol and progesterone receptors in the tissue of the endo- and myometrium [19, 20].

Nevertheless, it is probably fair to consider the fact that in the development of hyperplastic processes, the main role is traditionally assigned to an increase in the concentration of estrogens [21].

It should be considered the most frequent problem of the state of the endometrium and as a consequence of the pressing issue in the female population and oncological alertness due to its high prevalence [22]. Today, it is officially recognized that endometrial hyperplastic processes are one of the important and potentially health-damaging medical problems that challenge doctors around the world [23, 24]. A steady increase in the number of patients suffering from endometrial hyperplastic processes, unclear etiology, variable clinical manifestations and a high recurrence rate and risk of malignancy, as well as low treatment efficacy have led to the fact that in recent years, the scientific interest in this problem has increased significantly [25].

Currently, interesting and at the same time contradictory statistical data are cited in relation to the combined pathological processes of the endo- and myometrium, which to some extent can be explained by a fairly frequent asymptomatic course [24]. Hyperplastic processes of the endometrium constitute 15–40% in the structure of all gynecological diseases, and up to 80% when combined with adenomyosis. Contradictory data can be found as to the combination of endometrial hyperplastic processes and uterine leiomyoma, the frequency of which ranges from 13% to 80%. In the asymptomatic course of uterine leiomyoma in postmenopausal women, every sixth patient has endometrial hyperplasia, at the same time, when uterine bleeding appears, the parallel development of hyperplasia is diagnosed in every other woman [26, 27]. Endometrial hyperplasia in our study manifested by thickening of the epithelium. Thus, it can be assumed that additional ultrasound

diagnosis of the state of the endometrium is required in this group of women as a way to determine the endometrium thickness. Such persons should be especially wary in connection with the increased risks of developing cancer and bleeding. The risk of malignant neoplasms can also be enhanced by the direct toxic effect of ethanol, the main component of alcoholic beverages [7]. Ethanol is known to exert a carcinogenic effect at prolonged and excessive use.

In addition, one should not forget that HIV infection, similar to chronic alcoholism, leads to the changes in the structure of the endometrium also due to the development of hormonal imbalance. Under the influence of both diseases, dystrophic-sclerotic changes occur in the ovaries. Thus, there is a decrease in the size of all types of follicles in the ovaries, a decrease in the number of primordial follicles. The described changes lead to a violation of the ovarian-menstrual cycle, a change in the production of estrogen and progesterone [19].

Thus, the women with concomitant pathology in the form of HIV infection and alcoholism should be especially alert in terms of infertility development. Follicle-stimulating hormone hypoproduction entails a decrease in the production of estrogen by the ovaries. These effects can also be enhanced by the occurrence of dystrophic-sclerotic changes in the ovaries themselves. These pathological processes are known to be manifested by the proliferation of the connective tissue, a violation of the relationship between the cortex and medulla, a decrease in the size of all types of follicles (primary, secondary and tertiary), and even a decrease in the number of primordial follicles. The described changes inevitably lead to a decrease in the production of estrogen. The endometrium is regarded as a target organ for estrogen. Proliferative changes occur under their influence. Thus, hypoproduction or complete absence of estrogen by the ovaries, which is also due to dystrophic processes in them, can cause oligomenorrhea or even cause early menopause. This fact could explain the changes obtained in the course of the study, namely: a decrease in the average diameter of the endometrial glands, the minimum diameter of the endometrial glands, the maximum diameter of the endometrial glands, wall thickness, the relative volume of the epithelium, which were calculated in the proliferation phase of the menstrual cycle [28]. Based on the study and literature data, it can be assumed that gynecologists sometimes need to look for concomitant factors that influence

the female body for the correct selection of therapy for women with oligomenorrhea and early menopause [29, 30].

In addition, an imbalance in the concentration of FSH and LH can lead to the development of follicular and corpus luteum cysts, which, although functional, are sometimes associated with the development of complications and require urgent surgical treatment.

In the course of the study, data were obtained that could help in the diagnosis, selection of adequate therapy for gynecological diseases. In addition, this study can be used for the timely diagnosis of conditions that threaten the life of women (bleeding, rupture of cysts) and even malignant neoplasms [31–35], which is intended to reduce the percentage of mortality or disability among this group of patients.

Conclusions

Our findings indicate a significant severity of pathological changes in the endometrium in HIV-infected women who were addicted to alcohol. This fact makes it possible to assume that the presence of alcohol addiction increases the changes caused by HIV infection in the endometrium. The described changes are mainly expressed in the maximum and average diameter of the endometrial glands in both the proliferative and secretory phases of the menstrual cycle.

Conflict of interests

The authors of the article declare no conflict of interests.

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