THE PROCESS OF APOPTOSIS IN PATIENTS WITH PATHOLOGY OF THE CERVIX UTERI AND ENDOMETRIAL HYPERPLASIA

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Abstract. Patients with simple endometrial hyperplasia, not accompanied by cervical pathology, as well as at the combination of endometrial hyperplasia and cervical pathology, the level indicators of apoptosis increase which are quite much stated in the latter case. Therefore, in the examination of patients with cervical pathology and/or in the combination with endometrial hyperplasia it is necessary to determine the induction of apoptosis markers – the concentration of p53 and Bcl-2 in blood serum. The definition of these indicators can be used to predict the outcomes of hyperplastic states. Timely diagnosis and adequate monitoring of patients will prevent the development of cervical cancer and hyperplastic processes of endometria.

Keywords: endometrial hyperplasia, pathology of cervix uteri, apoptosis.

Introduction

According to recent data, the basis of endometrial hyperplastic processes is not only a hormonal imbalance, but also an abnormality of the apoptosis process, which represents a programmed death of cells and is the result of a balance of pro- and anti-apoptotic factors (Baryshnikov and Shishkin, 2002; Savill, Fadok, Henson and Haslett, 1993).

The study of apoptosis processes, regulated by set of biochemical, molecular and genetic factors, most of which are not fully understood, is necessary in patients with endometrial hyperplasia and concomitant diseases of the cervix uteri.

The most important regulators of apoptosis include cell death receptors, caspases, mitochondria, proto-oncogenes of Bcl-2 family, individual tumor-suppressing genes (Baryshnikov and Shishkin, 2002; Savill, Fadok, Henson and Haslett, 1993). The study of the molecular mechanisms of programmed cell death in recent years has become one of the pressing problems of Internal Medicine Clinic (Baryshnikov and Shishkin, 2002). One of the central links in the regulation of cell cycle and apoptosis is p53 gene and its product – the protein p53 (Zheltukhin and Chumakov, 2010; Kopnin, Kopnin, Khromova, et al., 2008; Chumakov, 2007).

The process of cell proliferation and survival of cells are supported by a number of proto-oncogenes, the most important of which relate to the Bcl-2 family. They isolate compounds that promote cell survival (Bcl-2, Bcl-xl, Bag-1, Bik) or predisposing to cell death (Bax, Bak, Bad). Bcl-2 as a structural and functional analog of the CED-9 encodes the synthesis of a membrane-associated protein, located in mitochondrial and perinuclear membranes (Nagata and Golstein, 1995). The role of this compound is the maintenance of cell survival and proliferation.

Purpose of the study


Subjects and methods

A total of 70 women at the age of 25 to 54 years (average age 38.6 ± 0.4 years) went to the Center for Women's Health (Women Wellness Centre) 2nd Clinic of Tashkent Medical Academy. All patients underwent clinical and gynecological examination with cytological examination of the cervix uteri and biopsy of the abnormal portion thereof, as well as the scraping of the uterine cavity for histological examination. According to the survey, patients started sex life in 16-25 years.

Depending on the detected pathology patients were divided into 3 groups. 1st group consisted of 34 women diagnosed with pathology of cervix uteri. In group 2, we included 12 patients with endometrial
hyperplasia without pathology of cervix uteri, who came to the clinic because of dysfunctional uterine bleeding. In the third group, we included 10 examinees with abnormal pathology of cervix uteri and endometrial hyperplasia. All women of the 3rd group reflected the episodes of meno and metrorrhagia and confirmed endometrial hyperplasia (ultrasound and histological analysis). The control group consisted of 14 healthy women.

Indicators of apoptosis in blood serum indicated in content its induction - p53 protein and Bcl-2 were measured by enzyme-linked immunosorbent assay (ELISA) for enzyme immunoassay analyzer firm «Stat-Fax» (USA) using a set of test systems manufactured by LLC "Cytokin" (St.-Petersburg).

The study results are processed with software programs Statistica 6, Biostat. Data are presented as arithmetic means (M) and standard deviation (m). For comparison, samples were used Student's t-test or paired Wilcoxon test. Results were considered as significant P <0.05.

In conducting clinical examination before taking tests visually cervix without pathology was diagnosed in 8 (23.5%) patients, cervical ectropion diagnosed in 20 (5.9%), post diathermocoagulation – in 5 (14.7%), deformation of cervix uteri – 12 (35.2%). Inflammation process – effects of exogenous and endocervicitis – were observed in 7 (20.5%) women.

According to the results of histological examination, conducted after cytological studies of cervix uteri, among patients in Group 1, mild dysplasia of multilayered squamous epithelium (MSE) of the cervix uteri was diagnosed in 10 (29.4%), moderate dysplasia of MSE – in 13 (38.2%), severe dysplasia MSE – in 2 (5.9%), the combination of warts with low-grade dysplasia MSE – in 5 (14.7%), with moderate dysplasia warts MBE - in 4 (11.7%). Consequently, the histological examination reveals the MSE damage degree of cervix. Thus, in the group of women with cervical pathology, we frequently observed moderate dysplasia of cervix MSE.

22 patients complained of bleeding from the genital tract with an established diagnosis of dysfunctional uterine bleeding (2nd and 3rd group), a uterine cavity curettage followed by histological examination was carried out. In all cases we revealed a simple hyperplasia (glandular and glandular-cystic) endometrium. It was decided to examine these patients targeted for detection or exclusion of cervical pathology. One month after treatment it was performed cytological examination of the cervix uteri. Simple endometrial hyperplasia, not accompanied by cervical pathology was diagnosed in 12 patients, the combination of endometrial hyperplasia and cervical pathology – at 10. Women with endometrial hyperplasia were divided into two groups to examine the relationship of cytogenetic and molecular responses to the concentration in the blood serum marker inducing apoptosis – the p53 protein.

**Results and discussion**

Study results of the apoptosis parameters in blood serum of women surveyed are given in the table below.

<table>
<thead>
<tr>
<th>Group</th>
<th>p53</th>
<th>Bcl-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, n=14</td>
<td>0.74±0.031</td>
<td>4.37±0.643</td>
</tr>
<tr>
<td>1st, n=34</td>
<td>0.77±0.033</td>
<td>4.82±0.52*</td>
</tr>
<tr>
<td>2nd, n=12</td>
<td>0.82±0.041*</td>
<td>5.11±0.59*</td>
</tr>
<tr>
<td>3rd, n=10</td>
<td>0.89±0.043*</td>
<td>5.96±0.63*</td>
</tr>
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</table>

Note. * P <0.05 in comparison with the control group.
When combined with endometrial hyperplasia with cervical pathology (group 3) one-way, more changes were also determined by the Bcl-2. This figure compared with the control group increased by 36.4%, and compared with patients with abnormal cervical and endometrial hyperplasia – by 23.7 to 16.6%.

Undoubtedly, researches on apoptosis pathophysiology offer great opportunities for prevention, prognosis and treatment of many still-difficult-to-manage, and sometimes hopeless states. Despite the key role of apoptosis in the implementation of physiological processes, connected with maintaining cellular homeostasis, without doubt, it is shown that apoptosis is not a mandatory component of the most typical pathological processes. This can be seen by the example of the inflammatory reaction (Yarilin, 2001; Nitsch, Ghilardi, Muhl et al., 1997). Although inflammation is characterized by tissue damage, cell death, in this case mainly on the mechanism of necrosis and accompanied by the release of cell contents into the extracellular space occurs, which can cause the death of neighboring cells and tissues melt. However, in the final stages of inflammation apoptosis plays an important role; as in this period the elimination of activated, operating cells of the immune system happens. The same is applied to allergic inflammation, wherein mentioned elimination of the effect or cells is difficult due to their ability to self-renewal and due to generation of autocrine cytokines (Yarilin, 2001).

Conclusion

In patients with simple endometrial hyperplasia, not accompanied by cervical pathology, as well as a combination of endometrial hyperplasia and cervical pathology, the level indicators of apoptosis increase. In this case, a more significant increase is observed in conjunction with cervical pathology of endometrial hyperplasia. Therefore, the concentration of p53 and Bcl-2 in the blood serum of patients with cervical pathology and/or in combination with endometrial hyperplasia may be used to predict the outcome of hyperplastic conditions. Timely diagnosis and adequate monitoring of patients will prevent the development of cervical cancer and endometrial hyperplasia. In patients with dysfunctional uterine bleeding, cervical pathology, as well as comorbid conditions determining the concentration of p53 and Bcl-2 in blood serum, it is advisable as indicators of apoptosis induction, which will develop modern methods of treatment in terms of the pathogenesis of such combined pathology.

References