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Assessment of Cytokine Status with Endometrial Hyperplastic Processes in the Reproductive Period

Miraliev F. K.

Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health, Tashkent, Uzbekistan

Abstract The purpose of the study was to study the assessment of cytokine status with endometrial hyperplastic processes in the reproductive period. The data obtained indicate that immune changes during abnormal uterine bleeding in combination with non-atypical endometrial hyperplastic processes occur at the systemic level and indicate an ongoing inflammatory process at the time of examination. In this regard, determining the concentration of cytokines in peripheral blood is prognostically significant for diagnosis and monitoring the effectiveness of therapy in this cohort of patients.

Keywords Endometrial hyperplasia, Cytokine status, IL-1β, TNFα, IL-2, IL-4, IL-6, IL-8

1. Introduction

Hyperplastic processes of the endometrium in the structure of gynecological pathology occupy from 15.0% to 50.0% in women of reproductive age. Women's health and gender pathology remain priority areas of prognostic, preventive and personalized medicine [1,2,6,9]. The relevance of the study of endometrial hyperplasia (EH) is primarily due to the high risk of malignant transformation and problems associated with menstrual irregularities, dysfunctional uterine bleeding, and anemia in women. Endometrial hyperplasia occupies a significant place in the structure of gynecological morbidity in women of reproductive age and is one of the most common reasons for hospitalization in a gynecological hospital (from 10% to 18%) [5,7,10].

With a high recurrence rate of endometrial hyperplasia, the risks of malignancy require further improvement and the search for new approaches to the diagnosis and treatment of this disease [3,4,8]. More studies on histological features and immunological profiles are needed to find an association between endometrioid and high-grade endometrial carcinoma and endometrial pathology.

Most scientific research in recent years has been devoted to the study of both systemic immunity and local immunity of the endometrium in endometriosis, uterine fibroids, chronic endometritis and recurrent miscarriage. At the same time, data on the state of immunity during endometrial hyperplastic processes (EHP) in patients with abnormal uterine bleeding (AUB) are extremely contradictory [3].

Purpose of the study is to study the assessment of cytokine status with endometrial hyperplastic processes in the reproductive period.

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2. Materials and Methods of the Research

The work was an open, prospective, comparative study in parallel groups. The criteria for inclusion of patients in the study were: 1) the age of the patients from 18 to 35 years; 2) the presence of AUB in combination with non-atypical forms of endometrial hyperplasia (simple endometrial hyperplasia (SHE) without atypia; 3) the presence of AUB in combination with non-atypical forms of endometrial hyperplasia (complex endometrial hyperplasia (CHE) without atypia The exclusion criteria were: 1) endometrial polyps; 3) atypical hyperplasia and endometrial cancer; 4) large uterine fibroids; submucosal localization of myomatous nodes; 5) external genital and extragenital endometriosis, grade I–III adenomyosis; 6) acute inflammatory diseases of the pelvic organs; 7) the presence of allergic reactions. All patients upon admission to the hospital underwent hysteroscopy with separate diagnostic curettage and subsequent histological examination of scrapings of the mucous membrane of the uterine cavity and cervical canal.

Based on histological examination of endometrial tissue, all patients were divided into two groups: group I consisted of 63 women with AUB in combination with PGE without atypia; Group II - 63 patients with AUB in combination with CGE without atypia. The control group consisted of 25 apparently healthy women with endometrium in the proliferation phase.

To study the levels of proinflammatory cytokines - tumor necrosis factor-α (TNF-α), interleukins (IL) - IL-1β, -2, -6, and interferon-γ (IFN-γ) - in peripheral blood plasma, the enzyme-linked immunosorbent assay method was used. analysis using the sandwich method using reagent kits for enzyme immunoassay “Vector BEST” (Russia).

Immunological data were processed according to the

principle of normal distribution using the Student's t test, the arithmetic mean and its standard error were calculated.

3. Results and Discussions

Analysis of the data we obtained on the concentration of cytokines in peripheral blood serum indicates an ongoing inflammatory process at the time of examination and has signs of a systemic inflammatory reaction.

As shown by the results of the study of cytokine status, patients with abnormal uterine bleeding with PGE without atypia had changes in the content of proinflammatory cytokines (Table 1).

Table 1. Cytokine levels in women with abnormal uterine bleeding

Options	Group I Patients with AUB in combination with PGE (n= 63)	Group II Patients with AUB in combination with CGE (n=63)	Control group (n=25)
IFN-γ pg/ml	9,47±0.27*	11,62±0.91* **	2,11±0,06
TNF-α pg/ml	4,22±0,15*	3,97±0,19*	1,1±0,11
IL-2 pg/ml	29.89±1.00*	34,71±1.13* **	8,12±0.32
IL-6 pg/ml	7,09±0,42*	8,03±0,41*	1,69±0,14
IL-1β pg/ml	6,35±0,32*	7,06±0,34*	4,3±0,38

*- $p < 0,05$ difference in indicators compared to patients in the control group
**- $p < 0,05$ difference in indicators compared to patients of groups I and II

Analysis of the content of pro-inflammatory cytokines in the peripheral blood showed: in patients with abnormal uterine bleeding in combination with simple endometrial hyperplasia without atypia, there is a statistically significant increase in the levels of TNF-α, IL-2, IL-6, IFN-γ and IL-1β in the blood serum compared with data from the control group. Thus, in women with AUB with PGE without atypia, a statistically significant ($p < 0.05$) increase in the concentration of TNF-α in the blood serum was noted - 4.22 ± 0.15 pg/ml compared with that in the control group - 1.11 ± 0.11 pg/ml. The level of IFN-γ in women in this group was 9.47 ± 0.27 pg/ml versus 2.11 ± 0.06 pg/ml in the control group and $p < 0.05$. The blood serum level of IL-2 in women suffering from AUB with PGE was 29.89±1.00 pg/ml versus the data in the control group – 8.12±0.32 pg/ml.

The level of IL-6 in the control group was 1.69±0.14 pg/ml, and in the group of women with PGE without atypia – 7.09±0.42 pg/ml and $p < 0.05$. The content of IL-1β in the blood of women in the control group was 4.3±0.38 pg/ml versus 6.35±0.32 pg/ml in group I.

In patients of group II who were diagnosed with AUB with CGE without atypia, a similar picture of proinflammatory cytokines was observed. Thus, the level of IFN-γ was 11.62 ±0.91 pg/ml versus 2.11±0.06 pg/ml in the control group. The content of TNF-α in the peripheral blood of patients was 3.97±0.19 pg/ml versus 1.1±0.11 pg/ml of the control. The IL-2 level was 34.71±1.13 pg/ml versus 8.12±0.32 pg/ml in the group of healthy women. The concentration of IL-6 was 8.03±0.41 pg/ml versus 1.69±0.14 pg/ml of control and $p <0.05$. The level of IL-1β in the blood of women with this pathology was 7.06± 0.34 pg/ml compared to the control group level of 4.3±0.38 pg/ml. Analysis of the obtained data on the serum level of the studied cytokines indicates the maintenance of inflammation at the systemic level in women with abnormal uterine bleeding with PGE and CGE without atypia. It should be noted that the serum concentration of IL-2 and IFNγ in patients of group II was statistically significantly ($p <0.05$) higher than that of patients with AUB with PGE without atypia. In recent years, the role of cytokines in the regulation of vascular-platelet hemostasis and the blood coagulation process has been proven [4]. Their effect on hemostasis is realized mainly through the vascular wall. Endothelial cells are both producers and effectors of IL-1β, TNFα, IL-2, IL-4, IL-6, IL-8 [6]. Works devoted to disorders of the blood coagulation system in endometrial diseases reflect mainly the oncological aspects of the problem, while studies of hemostasis in endometrial diseases that precede cancer remain extremely few.

4. Conclusions

Thus, the data obtained indicate that immune changes during abnormal uterine bleeding in combination with non-atypical endometrial hyperplastic processes occur at the systemic level and indicate an ongoing inflammatory process at the time of examination. Thus, the data is obtained to indicate that immune changes during abnormal uterine bleeding in combination with non-atypical endometrial hyperplastic processes occur at the systemic level and indicate an ongoing inflammatory process at the time of examination. The identified disorders may also indicate a local inflammatory process in the uterine mucosa if there are hyperplastic changes in it.

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