

CLINICAL AND LABORATORY MARKERS FORECASTING OF CERVICAL DISEASES AND ITS PREVENTION

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ABSTRACT

Goal: To study the complex pathogenetic approaches to the diagnosis and prevention of pathological conditions of the cervix.

Methods: For the period 2019-2020, at the Bukhara Regional Medical Diagnostic Center, we examined 51 women who consulted with various gynecological diseases at the age of 20 to 59 years. All patients underwent a comprehensive preventive examination with the inclusion of the method of classical and extended colposcopy on a portable device Digital electronic colposcope SW-3303, manufactured by Sanwe Science (China), Femoflor-16, homocysteine study and genetic research.

Results: In 51 (100%) women, certain diseases were identified, including: pseudo-erosion and erosion of the cervix 34 (67%), exocervicitis in 15 (26%), cervical polyp in 2 (4%), simple and partially occluded ectopia in 3 (6%), cervicitis caused by herpes and fungal infection in 9 (17.6%), leukoplakia in 2 (3.9%) women.

Conclusions: For all women with a burdened gynecological history, colposcopy is recommended for widespread introduction into the practice of obstetricians-gynecologists for the purpose of comprehensive diagnostic measures. Due to the use of digital video systems with software in modern colposcopes, the effectiveness of this diagnostic method increases significantly, which allows for adequate timely treatment

KEYWORDS: colposcopy, base-line and pre-cancer diseases of cervix of the the uterus, diagnostics of diseases of cervix of the uterus, Metafolin, femoflor-16.

INTRODUCTION

Diseases of the cervix are one of the most common pathological conditions of the female reproductive system and do not tend to decrease. Any gynecological diseases can be combined with pathology of the cervix [2, 5, 7]. That is why, despite modern advances in diagnostics, cervical pathology remains the most important problem in obstetrics and gynecology.

Pathology of the cervix is one of the most common diseases in the world and requires a lot of attention. This is due to the fact that they leave their mark on the reproductive activity of women. But the main problem is different: all background diseases at some point can lead to malignancy of the formations. Meanwhile, cervical cancer ranks third in terms of frequency of occurrence among diseases of the reproductive system [8,9].

There are various types of cervical pathologies, among which there are three main groups: background diseases, precancerous and cancerous. The former include cervical erosion, ectopia, polyps, and leukoplakia. The group of precancerous diseases is mainly represented by different types of cervical dysplasia [4,13].

Tumors and malignant neoplasms (MN) of the reproductive organs are important in clinical oncoepidemiology, despite the availability and visibility of localizations for diagnosis, morbidity and mortality rates tend to grow steadily[17,30].

On average, 2844 new cases of oncogynecological pathology are diagnosed in the Republic of Uzbekistan annually, which is 13.5% of the total number of malignancies. Among oncogynecological pathology in 2016, the largest number of patients was registered with cervical cancer (CC) - 1465. These indicators were the highest in Andijan - 10.2, Khorezm - 6.9, Namangan regions - 6.7, Tashkent city - 6.8 and Karakalpakstan - 5.9, morbidity / mortality 1.8. Their dynamic change is characterized by a stable increase in morbidity and the accumulation of a contingent of patients. The lowest rates were noted in Syrdarya - 2.5, Surkhandarya - 2.9 and Kashkadarya regions - 3.0. The age peak falls on 45-59 years, the percentage of patients in stages III and IV remains high, which requires a study of the oncoepidemiological situation depending on the territory of detection[1].

Dysplasia of the cervix (cervical interepithelial neoplasia) refers to precancerous diseases. Cervical dysplasia is characterized by the presence of atypical cells in the cervix. Often there are no symptoms of cervical dysplasia. Therefore, this condition is dangerous, as the disease progresses and can progress to cancer. Cervical cancer is diagnosed annually in 37,000 cases [3]. Cervical cancer plays an important role among cancer patients. 190,000 women die of cervical cancer every year. In Russia, 12,300 new cases are registered annually [6,8]. Since 1941, the Papanicalau method or PAP smear cytology has been used for diagnostic purposes. This method allows early detection and treatment of cervical dysplasia and cervical cancer. As a result, the level of cervical cancer and cancer mortality decreased to 11.6% of women [10,16]. Risk factors for the development of cervical dysplasia include female relatives who have a history of malignant oncological diseases, women with unhealthy habits (alcohol abuse, smoking), multiple abortions, chronic inflammation of the uterus and cervix.

Modern technology - Femoflor 16, based on the use of polymerase chain reaction (PCR) "in real time". This technology today allows to give the most complete quantitative and qualitative characteristics of the normal and conditionally pathogenic flora of the urogenital tract in women. The study is carried out to determine the presence, degree and nature of microflora imbalance. This, in turn, is extremely important for the clinician when choosing treatment tactics and for monitoring the effectiveness of the treatment. The data of modern domestic and foreign literature by the study of material obtained with the help of scraping is of great importance in the diagnosis of colpitis [24,25].

Since the discovery of folates in the 1940s and up to the present, there has been an accumulation of information about their role in shaping human health. The name "folic acid" (FA) is due to the fact that the active substance was first isolated from spinach leaves. Currently, this term unites a group of compounds based on pteroylglutamic acid. Compounds containing a pteric acid nucleus are collectively referred to as folates; compounds with an action similar to tetrahydropteroylglutamic acid - the term "folacin" [12,14].

In one of the foreign studies, the C677T polymorphism of the MTHFR gene was studied in a large group of European women with breast and ovarian cancer. These studies demonstrated that women with a heterozygous type had a double risk of cancer, and in patients with a homozygous type, the risk was three times higher than in the control group [15,23]. In the case of cervical cancer, epidemiological studies have also been controversial regarding the role of folate in the etiology of cervical dysplasia and the subsequent development of invasive cancer [9, 11, 22].

Homocysteine (HC) is a sulfur-containing amino acid with a free sulfhydryl group, which is an intermediate product of the exchange of amino acids methionine and cysteine. HC is contained in food in residual amounts, therefore the only source of its intake into the body is methionine, which is contained primarily in animal products. In the body, HC is formed from methionine by demethylation. Inside the cell, its content is low - less than 1 mmol / l, in blood plasma, it is normal from 5 to 15 mmol / l [17,19,26]. HC is diagnosed when the HC level exceeds 15 mmol / L. At a concentration of HC in blood plasma of 15-30 mmol / l, the degree of hyper HC is considered moderate, 30-100 mmol / l - intermediate, or medium, above 100 – severe. In children and adolescents of both sexes, its level is lower, with age there is an increase in the concentration of HC by about 3-5 mmol / l, and in men, the content of HC in the blood is about 2 mmol / l higher than in women, with average concentrations of about 11 and 9 mmol / l, respectively. An increase in the level of HC in the blood with age is associated with a decrease in renal function or with impaired absorption of vitamin B12 in the intestine. The reasons for sex differences are most likely a different hormonal background and a more correct lifestyle that women lead.

Most studies have found a significant association between homozygous or heterozygous C677T carriage and an increased chance of developing this disease. But this relationship was significant not for the entire group of examined patients, but only for a subgroup of premenopausal women [3,11,24]. Differences in the effect of the influence of this polymorphism are also shown for different population groups - it is observed in the population of women in East Asia, in the European population there is no data on the effect [18,23,31]. In the case of cervical cancer, epidemiological studies have also been controversial regarding the role of folate in the etiology of cervical dysplasia and the subsequent development of invasive cancer [21,27,28].

Folate has been widely studied as a possible mechanism for the development of cancer. (Liew S.C. 2016), however, its role in predicting the course of neoplastic processes has not yet been fully studied and is of great interest from a scientific and practical point of view. At present, numerous publications have proven the importance of the components of the folate cycle as an essential link in cellular metabolism due to their direct participation in the synthesis of nucleotides, on the one hand, and in the processes of DNA methylation, on the other. It was also shown that a change in the activity of key enzymes of the folate cycle, caused by polymorphism of their genes, increases the risk of developing cancer. One of the key mechanisms by which changes in folate metabolism can affect the integrity and stability of DNA and promote neoplastic transformation is the change in methylation processes. Thus, hypermethylation of the gene promoter regions suppresses the expression of tumor suppressor genes, and total hypomethylation leads to chromosomal instability and an increase in mutational events [20,29,].

MATERIALS AND METHODS

For the period 2019-2020, at the Bukhara Regional Medical Diagnostic Center, we examined 51 women who consulted with various gynecological diseases at the age of 20 to 59 years. All patients underwent a comprehensive preventive examination with the inclusion of the method of classical and extended colposcopy on a portable device Digital electronic colposcope SW-3303, manufactured by Sanwe Science (China), Femoflor-16, homocysteine study and genetic research.

Information about clinical and anamnesis data included: filling out a questionnaire developed by us, indicating the full name of the patient. of the patient, age, date of birth, the presence of bad habits, information about the somatic history and previous operations, age of sexual debut, methods of contraception, age of menarche and features of gynecological history.

A thorough history collection was carried out, which included the following data:

- Diseases transferred in childhood and as an adult
- Onset of menarche
- The nature and formation of menstrual function
- Lifestyle and bad habits
- Postponed gynecological diseases
- Outcome of pregnancies and childbirth

RESULTS

The average age is 35 ± 1.3 years. Most often, the pathology of the cervix was detected at the age of over 29 years, in 29 (39.2%) women, which indicates the rejuvenation of this pathology (Table 1).

Table 1. Distribution of patients by age

Age	n=51	%
Up to 29	20	39,2
30-39	15	29,4
40≤	16	31,4
Total	51	100%
Average M±m	35±1,3	

Infectious diseases transferred in childhood and adolescence take place in general in slightly larger numbers than in the population (Table 2).

Table 2. The incidence of diseases suffered by patients in childhood

Somatic diseases	n=51	%
Flu	44	86,3
ARVI 2 or more times a year	25	49
Hepatitis A	7	13,7
Rubella	33	64,7
Chickenpox	21	41,2
Parotitis	11	21,6
Scarlet fever	4	7,8
Whooping cough	2	3,9

When analyzing somatic diseases, it was found that the most frequently examined women suffered from gastrointestinal tract pathology (Table 3).

Table 3. The structure of the main extragenital diseases in the examined patients

Extragenital diseases	n=51	%
Hypertonic disease	5	9,8
Vegeto-vascular dystonia (VVD)	9	17,6

Coronary artery disease (CAD)	3	5,9
Varicose veins of the lower extremities	4	7,8
Respiratory diseases	3	5,9
Diseases of the urinary system	6	11,8
Type 1 diabetes mellitus	2	3,9
Type 2 diabetes mellitus	2	3,9
Diseases of the thyroid gland	15	29,4
Diseases of the thyroid gland	1	2
Diseases of the gastrointestinal tract	23	45,1

Data on previous infections in the examined patients indicate that 14 (27.5%) women have mixed infections (a combination of 3 or more infections) (Table 4).

Table 4.Previous infections in the examined patients

Symptoms	n=51	%
Recurrent bacterial vaginosis	21	41,2
Chlamydia	8	15,7
Trichomoniasis	4	7,8
Gonorrhea	1	2
Herpes simplex virus	11	21,6
Ureaplasmosis (mycoplasmosis)	9	17,6
Mixed infections (combination of 3 or more)	14	27,5

Data on the age of onset of menarche are presented in table. 5 and generally correspond to the average in the population.

Table 5.Age of onset of menarche

Age	n=51	%
11	1	2
12	9	17,6
13	17	33,3
14	16	31,4
15	4	7,8
16	3	5,9
17	1	2

Analysis of the reproductive history revealed that 33 (64.7%) women had childbirth. Noteworthy is the fact that 24 (47.1%) had induced abortions, and 19 (37.3%) had post-abortion and postpartum traumatic CD injuries (Table 6).

Table 6.Features of the reproductive history in the examined patients

Anamnesis	n=51	%
Miscarriage	9	17,6
Infertility	6	11,8

Infertility 1	1	2
Infertility 2	5	9,8
Childbirth	33	64,7
1 childbirth	14	27,5
2 childbirth	9	17,6
3 or more genera	10	19,6
Induced abortion	24	47,1
1-2 abortions	13	25,5
3 or more abortions	11	21,6
Traumatic CD injuries (postpartum, post-abortion, etc.)	19	37,3

When analyzing clinical manifestations, the most frequent complaints were meno- and metrorrhagia (25 (49%) patients (Table 7).

Table 7. Main clinical symptoms

Symptom	n=51	%
Meno-, metrorrhagia	25	49
Pathological discharge from the genital tract	14	27,5
Pain syndrome	7	13,7
Dyspareunia	8	15,7
Disruption of the menstrual cycle	16	31,4

In the process of a detailed analysis of the frequency and structure of gynecological diseases in the studied patients, the prevalence of chronic cervicitis was also revealed in 26 (51%) patients. In addition, attention is drawn to the presence of combined pathology of the uterus (adenomyosis, uterine myoma, endometrial hyperplasia) in 40 (21.6%) women (Table 8).

Table 8. The main concomitant gynecological diseases in patients

Gynecological diseases	n=51	%
Uterine fibroids (no combination)	8	15,7
Adenomyosis (no combination)	7	13,7
Endometrial hyperplastic process (no combination)	10	19,6
Combination of uterine fibroids with adenomyosis and / or endometrial hyperplastic process	13	25,5
Chronic cervicitis	26	51
Chronic salpingo-oophoritis	6	11,8
Ovarian cyst	5	9,8
Chronic endometritis	11	21,6
Polycystic ovary syndrome	3	5,9
External endometriosis	9	17,6
Fibrocystic disease	10	19,6

In 51 (100%) women, certain diseases were identified, including: pseudo-erosion and erosion of the cervix 34 (67%), exocervicitis in 15 (26%), cervical polyp in 2 (4%), simple and partially occluded ectopia in 3 (6%), cervicitis caused by herpes and fungal infection in 9 (17.6%), leukoplakia in 2 (3.9%) women.

Taking into account the clinical and echographic prognosis, women with significant discrepancies in the diagnosis were assigned to the group of active observation by a gynecological oncologist (Table 9).

Table 9. Pathology detected during colposcopy

№	Revealed pathology	A6c	%
1	Exocervicitis	15	26%
2	Endometriosis	7	13,7%
3	Pseudo-erosion and erosion of the cervix	34	67%
4	Cervical polyp	2	4%
5	Ectopia	3	6%
6	Herpetic and fungal infection	9	17,6%
7	Leukoplakia	2	3,9%

Extended colposcopy. The extended colposcopy method was used to visualize diseases of the cervix, the nature of the pathological process and determine the exact location. The mucous membrane of the vagina, vulva and cervical epithelium was examined with a microscope magnification of 7-30 times or more. This method makes it possible to identify and concretize changes in the epithelial lining of the cervix, vagina and vulva, the interpretation of which during routine observation is difficult or completely impossible.

For colposcopic examination, we used a Digital electronic colposcope SW-3303, manufactured by Sanwe Science (China), with 7-15-30x magnification. Extended colposcopy was performed in all patients according to the generally accepted technique when examining the skin and mucous membranes of the anogenital area to identify small papillomas and warts. The mucous membrane of the cervix was examined at first without samples and then Schiller's test was performed with 0.5% Lugol's solution. During the extended colposcopy, places were outlined for the targeted collection of scrapings and biopsies from pathological areas of the cervix for subsequent morphological examination.

Description of the localization of the lesion anatomically and by the clock, schematically, introduced to better transfer information about the lesion between specialists and to reduce errors in data transmission.

The dark brown, homogeneous staining of the cervix and a normal colposcopic picture allowed these women to be classified as healthy. Often, pathological changes in the mucous membrane of the cervical canal were found in the presence of hypertrophy, scars, deformities of the vaginal part of the cervix. It is important to note that in 12 (23.5%) women, pathological changes in the cervix were detected without any complaints and clinical signs, which proves the undoubted role of colposcopy in preclinical diagnosis of cervical diseases.

The results of the echographic examination of the examined women were entered into a special electronic database. When recording colposcopic data, the location of the revealed changes

was taken into account. By dividing the cervix into 4 quadrants, all detected changes were indicated by the clock of the dial (for example, at 6 o'clock).

Taking into account the clinical and echographic prognosis, women with significant discrepancies in the diagnosis were assigned to the group of active observation by a gynecological oncologist.

The pathological process was presented mainly by minor symptoms of inflammation $n = 41$ (80.4%), moderate inflammation was in $n = 7$ (13.7%) patients, and it was expressed only in $n = 3$ (5.9%) patients. (Fig. 2)

Fig 2. Distribution of patients (%) depending on the severity of clinical symptoms.

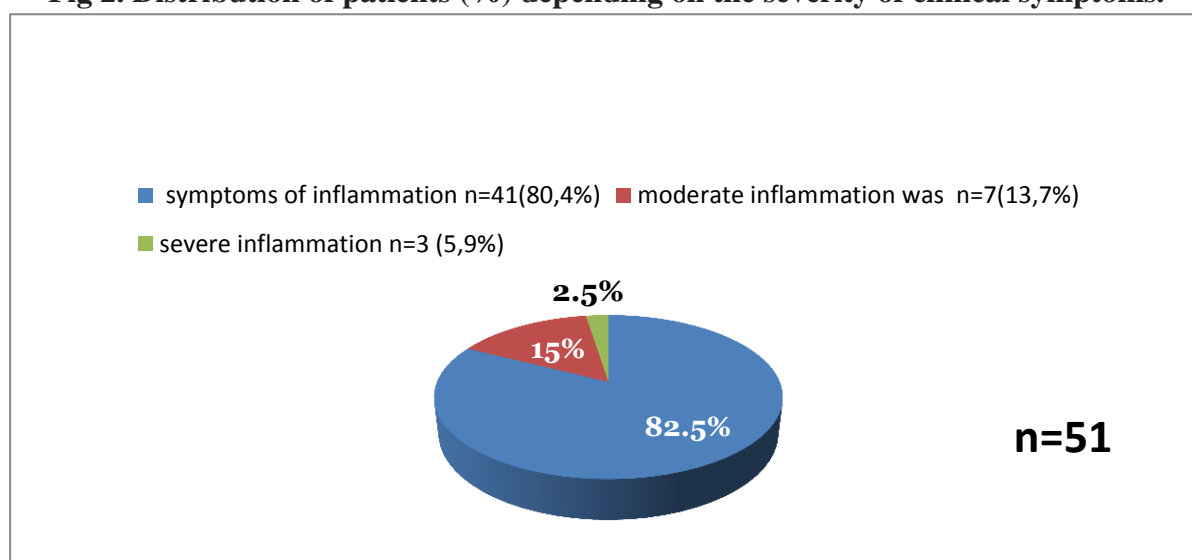


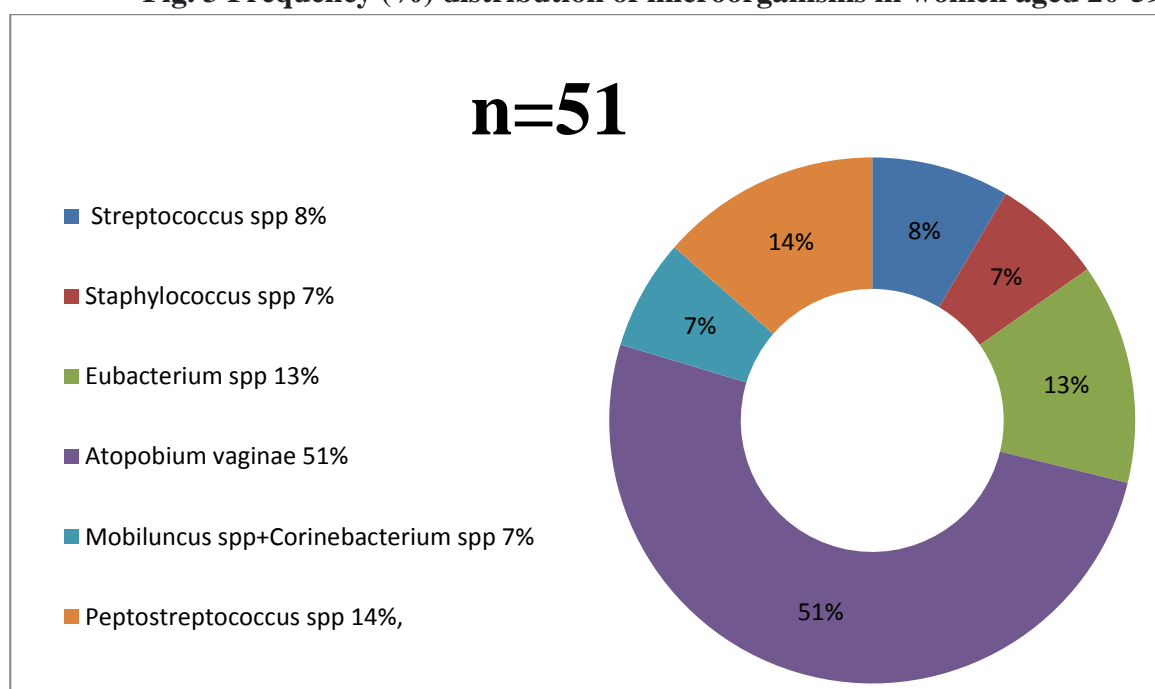
Table 10. Femoflor-16 test result. Woman D. - 26 years old. reproductive age.

Issue name	RESULTS	
	Quantitative	Relative
Material taking control	$10^{5,4}$	
Total bacterial mass	$10^{6,4}$	
Normoflora		
Lactobacillus spp	$10^{4,6}$	-1,8 (1,3-1,7%)
Facultative Anaerobic microorganisms		
Enterobacterium spp	$10^{3,2}$	-3,2 (<0,1%)
Streptococcus spp	$10^{6,4}$	0,0 (79-100%)
Staphylococcus spp	$10^{4,1}$	-2,3 (0,4-0,5%)
Obligate-Anaerobic microorganisms		
Gardnerella vaginalis+Prevotella bivia+Porphyromonas spp	$10^{5,1}$	-1,3 (4-5%)
Eubacterium spp	$10^{3,5}$	-2,9 (<0,1%)
Sneathia spp+Leptotrichia spp+Fusobacterium spp	Not found	
Megasphaera spp+Veillonella spp+Dialister spp	$10^{3,4}$	-3,0 (<0,1%)

Lachnobacterium spp+Clostridium spp	Not found	
Mobiluncus spp+Corinebacterium spp	$10^{3,2}$	-3,2(<0,1%)
Peptostreptococcus spp	Not found	
Atopobium vaginae	$10^{2,1}$	-4,3(<0,1%)
Yeast-like mushrooms		
Candida spp	$10^{3,6}$	
Mycoplasma		
Micoplasmahominis	$10^{2,5}$	
Ureplasma spp	$10^{2,2}$	
Pathogenic microorganisms		
Micoplasmagenitalium	Not found	

51 women were identified: Streptococcus spp-8%, Staphylococcus spp-7%, Eubacterium spp-13%, Mobiluncus spp+Corinebacterium spp-4%, Peptostreptococcus spp-13%, Atopobium vaginae-51%, Micoplasmahominis-7%, Ureplasma spp-1%.

Fig. 3 Frequency (%) distribution of microorganisms in women aged 20-59



CONCLUSIONS

Thus, the general clinical characteristics indicate a high frequency among the examined patients of chronic cervicitis, hereditary burden of oncological diseases, a combination of uterine fibroids with adenomyosis and or hyperplastic endometrial process, traumatic injuries of the cervix (postpartum, post-abortion). It is advisable to analyze the factors identified above in a comparative aspect in groups of patients with varying degrees of severity of the pathological process of the cervix with a detailed statistical analysis.

For all women with a burdened gynecological history, colposcopy is recommended for widespread introduction into the practice of obstetricians-gynecologists for the purpose of comprehensive diagnostic measures. Due to the use of digital video systems with software in

modern colposcopes, the effectiveness of this diagnostic method increases significantly, which allows for adequate timely treatment.

Comprehensive diagnostic measures with the inclusion of colposcopy in polyclinics, gynecological hospitals, more in-depth studies carried out in specialized oncological institutions are promising and expedient, as it improves the accuracy of diagnosing cervical diseases, provides adequate timely treatment and provides secondary prevention of cervical cancer.

The study "Femoflor" makes it possible to differentiate the state of microbiocenosis, verify the diagnosis and prescribe adequate therapy and avoids the difficulties associated with the cultivation of microorganisms in laboratory conditions, since the method is based on the process of determining fragments of the genetic material of microorganisms, which allows to determine the severity of the imbalance, and can be simple and easy to use.

Diagnosis of cervical diseases by RT-PCR using the Femoflor-16 test is an affordable, fast, effective, modern method that allows early initiation of adequate etiotropic therapy, monitoring its implementation, followed by restoration of normal microflora.

Given the multifactorial nature, as well as in connection with the above facts and the available materials of periodicals, it becomes obvious that at present, more and more study of this problem is aimed at the problems of studying genetic factors, indicating the relationship of polymorphisms of genes of folate cycle enzymes involved in the synthesis proteins, lipids and nucleic acids with the development and functioning of dysplasia of the stratified squamous epithelium of the cervix.

The most modern form of folate is calcium levomefolate (META FOLIN), which is structurally identical to the natural L-5-methyltetrahydrofolate, the main folate form found in food and contraceptives Yarina plus, or Jess plus, where women with neoplasia, or with cervical erosion wearing an IUD is not recommended.

For the prevention of diseases of the cervix, timely treatment of inflammatory processes of the vagina, cervix, uterus and its appendages is necessary; timely correction of menstrual irregularities; rational management of childbirth; prevention of abortion; promotion of the culture of sexual relations, the use of modern methods of contraception (Yarina plus, Jess plus) and, which is especially important, timely and correct tactics of managing patients with the use of screening research.

Yarina® Plus is a low-dose monophasic combined estrogen-gestagenic contraceptive preparation consisting of tablets containing hormones and calcium levomefolate, and tablets containing only calcium levomefolate. The contraceptive effect of combined oral contraceptive drugs is based on the interaction of various factors, the most important of which are suppression of ovulation, increased viscosity of cervical secretions and changes in the endometrium.

Jess® Plus (425 mcg Metafolin) is a low-dose monophasic combined estrogen-progestogen contraceptive preparation consisting of tablets containing hormones and calcium levomefolate, and auxiliary tablets containing only calcium levomefolate. The contraceptive effect of combined oral contraceptive drugs is based on the interaction of various factors, the most important of which are suppression of ovulation, increased viscosity of cervical secretions and changes in the endometrium.

Also in vitamins Elevit 1 - a trimester and antianemic drugs Ferlatum-fol, which contains from 400-800 mg of metapholin.

It is available separately in tablets, and is also part of multivitamins, vitamin-mineral complexes, some oral contraceptives, which is especially important for women who need contraception and pregravid preparation. Thus, for the prevention of diseases of the cervix, timely treatment of inflammatory processes of the vagina, cervix, uterus and its appendages is necessary;

timely correction of menstrual irregularities; rational management of childbirth; prevention of abortion; promotion of the culture of sexual relations, the use of modern methods of contraception (Yarina plus, Jess plus) and, which is especially important, timely and correct tactics of managing patients with the use of screening research.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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