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FORECASTING REPRODUCTIVE FUNCTION DISORDERS IN WOMEN POST-ABORTION ENDOMETRITIS.

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ABSTRACT

Research objective. Endometritis occurs mainly in reproductive age, is characterized by a prolonged and low-symptom course, leads to disruption of the menstrual cycle and reproductive function, as a rule, is one of the main causes of infertility, miscarriage, miscarriage, undeveloped pregnancy, complications of pregnancy and childbirth.

Materials and methods. A prospective study included 210 women who applied to the gynecological department of the maternity complex in Andijan with various gynecological complaints, as well as patients with an undeveloped pregnancy, spontaneous abortion and women who had an abortion.

Results. Analysis of clinical and anamnestic data showed that no statistically significant differences were revealed in the groups of examined patients by age ($p > 0.05$). The age ranged from 18 to 45 years.

Conclusion. Chronic endometritis is a cause of reproductive dysfunction and high reproductive loss in subsequent pregnancies. The high frequency of chronic endometritis in women with reproductive disorders and in modern conditions does not tend to decrease.

Key words: chronic endometritis, non-developing pregnancy, spontaneous abortion, reproductive system, prognosis, interleukins, inflammation, immunity.

INTRODUCTION

Chronic endometritis (Ch.E.) is a disease associated with various clinical manifestations, however, despite a large number of studies, pathognomonic symptoms have not been clearly identified. The prevalence of the inflammatory process of the endometrium has not been completely studied and amounts to an average of 15% [1,2]. The main role of inflammatory diseases of the internal genital organs in the structure of the reproductive function of women, as well as chronic endometritis (Ch.E), as the cause of infertility of uterine genesis, which tends to steadily grow, is described. The etiological risk factors for development and the trigger mechanism of chronic inflammatory processes in the endometrium, the features of the pathogenesis and clinical manifestations of cholesterol have been identified. Criteria for the morphological diagnosis of Ch.E., morphological features of Ch.E. with the autoimmune nature of the inflammatory process, various extra-nosological structural and functional disorders in the endometrium are determined.

Currently, question of uterine cavity sterility in healthy women is often debated. Some authors believe that the endometrium in women is predominantly sterile, despite the contamination of the endocervix, due to the ability of the endometrial functional layer to reject during menstruation. [3,4,5]. However, there is another point of view that the mucous membrane of the uterine cavity cannot be sterile, despite the fact that it is continuously exposed to various infectious agents from the lower genital tract [6,7,8]. Conditionally - pathogenic microorganisms (CPM) are present in the genital tract in almost all women, therefore, protective mechanisms should work not only at the level of introduction of microbial agents, but also on the path of their distribution. In this case, whether their penetration into the epithelial and stromal cover of the uterine mucosa occurs and whether the inflammatory process develops against this background, largely depends on the state of local and general immunity [9, 10, 11].

The disease develops mainly in women of reproductive age. According to our data, the maximum frequency of chronic endometritis falls on the age group of 18-45 years, i.e. on the age interval, the most important in the implementation of the reproductive function. Among women with chronic endometritis, 97.6% are women of reproductive age, which emphasizes the particular importance of this pathology in terms of the effect on reproductive function.

The frequency of chronic endometritis, according to various authors, varies from 2 to 73%, which is associated primarily with difficulties in morphological verification of the diagnosis, differences in the initially analyzed material and patient population, and significant variability in the number of observations. According to our data, the frequency of chronic endometritis in gynecological patients is $2.6 \pm 0.2\%$.

Data on the frequency of the disease in women with impaired reproductive system function is extremely important. In women with infertility, non-developing pregnancy, and spontaneous miscarriage, chronic endometritis occurs in 12-68% of cases, reaching its maximum in the presence of tubal-peritoneal infertility factor. According to our data, in patients with infertility, the frequency of chronic endometritis is on average $9.8 \pm 0.7\%$, i.e., the disease occurs 5 times more often than in the general cohort of gynecological patients. The highest prevalence rates of chronic endometritis were observed in patients with habitual miscarriage and accounted for more than 70% [12,13,14].

Given the frequency of various fetal losses - more than 40% of the first pregnancies are interrupted [15,16] - the statistics of unaccounted and untreated cases of Ch.E. determines a steady trend in future demographic losses [17]. This statement demonstrates the appropriateness of rethinking approaches to the veiled root cause of early reproductive loss – Ch.E., which provokes interruption of embryo implantation, cytotrophoblast invasion, villi vascularization and placenta formation at its early stages [18,19,20].

The morphological basis of the hypoplastic macrotypic of chronic endometritis is dystrophic-atrophic changes in the endometrium, mixed - alternation of sites of dystrophy and fibrosis, hyperplastic - the induction of microlipose growths on the background of a single mucosal lymphocytic infiltration [21].

The relevance of the predictive predictors of disorders of universal adaptive mechanisms in response to a chronic focus of inflammation determining the effectiveness of the pathogenetic stratification of rehabilitation therapy is relevant.

The aim of the study is to study and predict reproductive system disorders in women who underwent post-abortion endometritis, women who underwent uterine curettage for diagnostic purposes and to evaluate the effectiveness of therapy in women with reproductive disorders.

MATERIAL AND METHODS

In accordance with the objectives, a prospective study included 210 women who applied to the gynecological department of the maternity complex in Andijan with various gynecological complaints, as well as patients with an undeveloped pregnancy, spontaneous abortion and women who had an abortion. The work is based on the results of a comprehensive clinical and laboratory examination of patients of reproductive age. Laboratory studies of the polymerase chain reaction were carried out in the medical diagnostic center "Standard-Diagnostics".

Clinical and laboratory study of analyzes and ultrasound examination of women was carried out on the device "Akkon 98" in the maternity complex of the city of Andijan.

Indications for intrauterine interventions (hysteroscopy, diagnostic curettage (DC)) were spontaneous fetal loss, undeveloped pregnancy, artifact abortion, dysfunctional uterine bleeding (DUB), reproductive dysfunction, and suspected endometrial pathology according to ultrasound data.

The studies were conducted on the basis of endometrial scraping after curettage of the uterine cavity, biopsy material, vaginal discharge material. The presence of specific and conditionally pathogenic microorganisms in the endometrium, data on the immune status of women in the study of the cytokines IL1, IL10, transforming growth factor, TNF-alpha, and secretory immunoglobulin were studied. Especially valuable was the modern and informative methods of polymerase chain reaction (PCR), as well as data from morphological studies and ultrasound. It is also important to consider for the diagnosis of Ch.E.: anamnestic data, parity, age, gestational age, clinical manifestations of the disease, as well as morphological, hysteroscopic and ultrasound criteria for its verification, taking into account microbial contamination of the upper and lower genital tract.

According to our assumptions, the trigger for the development of Ch.E. is persistence in the endometrium of conditionally pathogenic aerobic-anaerobic microorganisms. In this case, absolute pathogens rarely reach the upper genital tract, which is associated with their early diagnosis and timely effective treatment.

The assumption that the presence of microorganisms in the uterine cavity does not always lead to the development of chronic inflammation, and that in healthy women in the absence of morphological signs of inflammation in most cases in the endometrium are determined by conditionally pathogenic microorganisms, led to the need for a more detailed study of the prerequisites of Ch.E, its diagnosis and the outgoing methods for predicting disorders of reproductive function of women.

The disadvantages of classical microbiological research include the long periods of cultivation of microorganisms, the need to maintain their viability until the biomaterial arrives in the laboratory. In recent years, a new approach to the study of the microbial spectrum has appeared - the real-time polymerase chain reaction (PCR) method. We used the modern PCR method (Femoflor 16), which allows us to study the presence, degree and nature of the imbalance of the vaginal microbiota. It is important to note that the drawbacks of the real-time PCR method include the inability to determine the sensitivity of microorganisms to antibiotics, as well as assess the presence and degree of local inflammatory reaction.

To date, the need has developed to use the real-time of PCR method to determine the microbial contamination of the mucous membrane of the uterine cavity by analogy with the test systems used to diagnose vaginal microbiocenosis. Thus, the etiological diagnosis of Ch.E. is associated with a number of difficulties and is a difficult task in modern conditions. For accurate determination of the pathogen, high-quality preparation of endometrial samples and the use of modern highly sensitive diagnostic methods are necessary.

Hysteroscopy is necessary to exclude various intrauterine pathologies, and for an accurate verification of the diagnosis of Ch.E, it is necessary to conduct a morphological study of the endometrial biopsy. Based on this, the main goal of our work was to study and predict reproductive dysfunctions.

RESULTS AND DISCUSSION

In the course of the work, a comprehensive examination was carried out of 210 women who applied to the maternity complex in Andijan for fetal loss, an undeveloped pregnancy, as well as complaints about menstrual irregularities and reproductive function, dysmenorrhea, as well as endometrial pathology according to ultrasound.

Out of 210 women, 167 patients with morphologically confirmed Ch.E.(group I) and women without endometrial pathology were included in the study; conditionally healthy women were the comparison group (group II). Analysis of clinical and anamnestic data showed that no statistically significant differences were revealed in the groups of examined patients by age ($p > 0.05$). The age ranged from 18 to 45 years: in group I, on average, it was 32.74 ± 0.7 years, in group II - 31.02 ± 0.6 years.

Table 1

Materials and research methods.

Biomaterial	Research Method, Diagnostic Markers	The number of samples in group I	The number of samples in group II
	Pelvic ultrasound	167	43
Endometrial scrapings	Hysteroscopy, diagnostic curettage of the endometrium	91	22
Vaginal discharge	Vaginal smear microscopy	167	43
Vaginal discharge and endometrial tissue biopsy	Cultural method (aerobic, anaerobic and microaerophilic cultivation conditions): facultative anaerobic, obligate anaerobic, microaerophilic microorganisms, yeast fungi, genital mycoplasmas.	84	25
Vaginal discharge and endometrial biopsy	Real-time polymerase chain reaction. Total bacterial mass, Lactobacillus spp, facultative anaerobic and obligate anaerobic microorganisms, absolute pathogens.	101	31
Vaginal discharge and endometrial biopsy	Conducting parallel studies: the cultural method and the polymerase chain reaction in real time to study the entire spectrum of genital tract microorganisms.	40	9
Endometrial biopsy	Real-time PCR: study of mRNA of IL1, IL10 cytokine genes, transforming growth factor, TNF-alpha, secretory immunoglobulin	79	31

For reasons of treatment, the patients were divided into two blocks. The first block of complaints was associated with various disorders of the menstrual cycle, and the second with pathology of reproductive function.

During the study, a thorough analysis of the reasons for the treatment of patients in both groups was carried out. Most often, patients with Ch.E. complained of various menstrual irregularities (87.4%). The leading among them were intermenstrual uterine bleeding (41.3%) (Table 2), the duration of which varied from 4 to 10 days. The basis of the pathology of this species is dysfunctional uterine bleeding in Ch.E. is the excessive secretion of proteolytic enzymes that damage subepithelial capillaries, increasing their permeability.

At the same time, 32 patients (46.4%) with intermenstrual uterine bleeding did not have any other gynecological pathology on the part of the myometrium of the endometrium, which suggests that dysfunctional uterine bleeding in these patients is due to the presence of Ch.E. At the same time, 53.6% of patients with this symptom showed a combination of Ch.E. with endometriosis (33%), uterine myoma (13.0%) and other gynecological diseases (14.5%).

Abundant menstrual dysfunctional uterine bleeding was noted in group I in 31.1% of cases, in group II - in 6.9% ($p = 0.001$). It is important to note that 19 patients (36.5%) with this symptom with morphologically confirmed Ch.E. did not have a combined gynecological pathology. Therefore, in these cases, it is likely that the inflammatory process in the endometrium led to a disruption in the normal desquamation and regeneration of the endometrium with the subsequent development of copious spotting. Moreover, in 63.5% of patients with this symptom, a combination of Ch.E. with myoma (28.8%), endometriosis (36.5%) and other gynecological diseases (23.1%) was revealed.

The combination of profuse menstrual and intermenstrual uterine bleeding in patients with Ch.E. was detected in 16.8%, while a combination of these symptoms was not found in any case in the comparison group ($p = 0.004$). Hypomenstrual syndrome was diagnosed in 28 women with Ch.E. (16.8%), while 21 patients (75%) of them confirmed the presence of intrauterine synechia of varying severity. Dysmenorrhea in group I is noted in every third case.

Thus, various violations of the nature of the menstrual cycle are a leading complaint in patients with Ch.E. An analysis of reproductive function showed that infertility revealed in every second patient (52.1%) prevails with Ch.E, while the duration of infertility varied from 1 to 17 years and averaged 4.5 ± 0.52 years. In group I, primary infertility was detected in 22.8% of cases, secondary - 29.3%. Habitual miscarriage occurred in 22.8% of cases.

On average, the number of pregnancy losses was 1.7 ± 0.12 per patient, varying from 1 to 6. An undeveloped pregnancy was detected in 15 women with Ch.E. (9%), on average 1.6 ± 0.14 per patient, varying from 1 to 5. The prevalence of infertility in the structure of complaints of women

with Ch.E. indicates the presence of structurally functional changes in the endometrium with chronic inflammation of the endometrium, which can probably be a barrier to the onset and development of pregnancy. It was not possible to assess the duration of the disease in patients with Ch.E, given that this diagnosis is made not only on the basis of the duration of clinical symptoms, but also during the morphological study of endometrial scraping. And in more than half of the cases, a histological study of the endometrial biopsy was performed by us for the first time.

Table 2

Reasons for the treatment of patients.

Groups		I group with Ch.E. (n=167)	II comparison group (n = 43)	p-level of significance (χ^2)
I Block The nature of the menstrual cycle:	Menstrual uterine bleeding	52/ (31,1%)	3/ (6,9%)	0,001
	Intermenstrual uterine bleeding	69/ (41,3%)	6/ (14,0%)	0,0008
	Lean menses	28/(16,8%)	0	0,004
	The combination of dysfunctional uterine bleeding (inter- and menstrual)	28/(16,8%)	0	0,004
	Dysmenorrhea	46/ (27,5%)	4/ (9,3%)	0,012
	Normal menstruation	21/ (12,6%)	32/ (74,4%)	$8,4 \times 10^{-12}$
II Block Reproductive function	Infertility:	87/(52,1%)	12/ (27,9%)	0,005
	1. Primary infertility	38/ (22,8%)	6/ (14 %)	0,206
	2.Secondary infertility	49/ (29,3%)	6/ (9,3%)	0,007
	Habitual Miscarriage (HM)	38/(22,8%)	4/ (9,3%)	0,049
	Two or more undeveloped	15/ (9,0%)	1/ (2,3%)	0,142

	pregnancies			
	Lack of complaints of reproductive dysfunction	30/ (18%)	29/ (67,4%)	<0,0001
	Chronic pelvic pain syndrome	43 (25,8%)	3 (7,0%)	0,008
	Endometrial pathology according to pelvic ultrasound with no complaints	8/(4,8%)	11/ (25,6%)	0,003
	A combination of the above complaints (2 or more)	120/(71,9%)	9/(21,0%)	<0,001

At present, in the course of the study, two productive foundations for the role of the infectious factor in the etiological genesis of Ch.E. are formed. The causative agents of specific chronic endometritis are absolute pathogens (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*), viruses (Herpes simplex types 1 and 2), *Mycobacterium tuberculosis*, *Treponema pallidum*, *Mycoplasma genitalium*, etc.

A special place in the structure of Ch.E. is occupied by herpetic damage to the endometrium. At the same time, against the background of herpetic lesion, the local protective functions of the endometrium decrease. Clinical signs of Ch.E. during viral damage are usually absent. Therefore, the study of the endometrium for the detection of viruses is extremely important.

With nonspecific Ch.E. only conditionally pathogenic microorganisms are detected or pathogens are not detected at all (Table 3).

Table 3

The frequency of occurrence of microorganisms in the endometrium

Specific microorganisms	
Microorganisms	Frequency of occurrence
<i>Chlamydia trachomatis</i>	2,7-2,8%
<i>Neisseria gonorrhoeae</i>	1,4%
<i>Trichomonas vaginalis</i>	0,2
<i>Mycoplasma genitalium</i>	3,8%

<i>Herpes simplex I type</i>	8%
<i>II type</i>	2,5%
Conditionally pathogenic microorganisms	
Conditionally pathogenic microorganisms	Frequency of occurrence
<i>Streptococcus spp</i>	14%
<i>Staphylococcus spp</i>	6%
<i>Enterococcus faecalis</i>	31 %
<i>Escherichia coli</i>	33%
<i>Enterococcus spp</i>	23%
<i>Candida</i>	24%
<i>Klebsiella pneumoniae</i>	2%
<i>Ureaplasma urealyticum</i>	30%

All studies on the microflora of the upper genital tract relied only on traditional cultural methods, etiological laboratory diagnostics of the infectious process. With the introduction of molecular genetic methods, new microorganisms (*Mycoplasma genitalium*, etc.) were discovered that are difficult to distinguish using standard techniques. By minimizing the unintentional contact of the uterine cavity with the microbial flora of the vaginal discharge, you can use specially developed methods for taking material, while the vaginal microflora is 2.7% contaminated.

In our work, when sampling the test material, mucus from the endocervix, after installing the Cuzco disposable vaginal speculum, we used a disposable sterile subclavian soft catheter and a 10.0 ml standard syringe, which made it easier to take the material.

In modern conditions, the diagnosis of Ch.E. is difficult due to the erased clinical picture of the disease, the lack of uniform pathognomonic clinical symptoms and generally accepted morphological criteria for Ch.E.

During the study, the basis of the morphological diagnosis of Ch.E. was the presence of sclerotically altered walls of the spiral vessels of the mucous membrane of the uterus, inflammatory lympho-plasmocyte infiltrates and focal fibrosis in the stroma of the endometrium.

The main hysteroscopic factor of Ch.E. are inflammatory, endometrial, vascularized outgrowths - micro-polyps with a diameter of about 1 mm, which contain plasma cells and lymphocytes. Micropolyps lead to the launch of active intrauterine reactions and the active

release of interleukins and local growth factors. Studies have shown that when micropolyps are detected in the endometrium, histological criteria for Ch.E. were confirmed in 91.5% of cases, and in the absence of them, Ch.E. was determined in 11.2%. Thus, analyzing these data, we can conclude that using only hysteroscopic criteria can lead to overdiagnosis, despite the fact that the predictive value in hysteroscopy is 56% sensitivity, 88% specificity, 95% positive and 85% negative.

Important signs of the inflammatory process are the presence of intrauterine micropolyps, diffuse or local hyperemia, and stromal edema of the uterine mucosa.

The combination of hyperemia, edema and micropolyps with this method has a diagnostic accuracy of 93.4%, confirming that hysteroscopy can be a useful method for the diagnosis of Ch.E. Hysteroscopy is necessary to exclude various intrauterine pathologies, and for an accurate verification of the diagnosis of Ch.E, it is necessary to conduct a morphological study of the endometrial biopsy.

Studies of cytokines in this pathology confirmed the presence of an inflammatory nature. The level of increase in the concentration of IL1 and IL10 in the test material clearly confirmed the presence of an inflammatory nature, which was a predictor of the base of Ch.E.

The results of the assessment of the cytological picture of metaspirates of women with various types of abortions in early pregnancy immediately after instrumental intervention allow us to conclude that the method is highly predictive.

When ascertaining the uncomplicated course of the postabortion period, the assessment of cytograms was carried out on days 3 and 5, and the identification of signs of the inflammatory process in the endometrium lasted up to 11 days.

In a detailed study of samples of biopsy samples obtained by curettage of the mucous membrane of the uterine wall in order to terminate pregnancy, we used a pathomorphological classification with the conditional allocation of three dominant types: autoimmune, inflammatory, hormonal.

Correlation of the results of the cytological evaluation of metaspirates with morphological data showed the presence of an inflammatory process of the uterine mucosa in 52 women without hysteroscopic control during emptying of the uterine cavity.

Ultrasound data for signs of Ch.E. carried out within the framework of macro types showed that the endometrium does not correspond to normal echographic criteria in more than half of cases. Hyper-echogenic formations in the basal layer of the endometrium (foci of fibrosis, calcification) are found in every fifth with a mixed and hypoplastic macrotype (23.4% on average), almost a third (29.8%) with hyperplastic. Varicose veins of parametria - in half (50.5%) with a mixed version, which is almost twice as often as hypoplastic (26.7%) ($p < 0.05$)

and almost a third (35.9%) - with hyperplastic. The hypoechoic uterine contour - both in isolation and in combination with varicose veins of the parametrium - mainly with a hypoplastic macrotype Ch.E. - in almost every second (60.8% and 50.8%), with a mixed one - a combination of symptoms is determined four times more often, than when registering one. Thinning of the endometrium (less than 8 mm) - with a hypoplastic macrotype - three times more often than with a mixed version (56.7% and 22.5%, respectively). The mismatch between the endometrial echostructure and the phase of the menstrual cycle is less common with a mixed macro type (28.8%) than with the rest - a hypoplastic (46.1%) ($p < 0.05$) and a hyperplastic macro type (36.5%) ($p < 0, 05$).

Despite the variety of proposed treatment options for Ch.E, the treatment of this disease is associated with significant methodological difficulties. When prescribing antimicrobial agents, it is necessary to take into account the species and quantitative composition of microorganisms found in the endometrium. It is probably not advisable to prescribe antibacterial drugs to patients for whom pathogens have not been identified, since inadequate use of antimicrobial agents can lead to the transformation of the disease into a latent form, to the development of flora resistance to the drugs used. In connection with the suppression of local immunity in Ch.E, it is advisable to prescribe immunocorrective therapy.

CONCLUSION

Chronic endometritis is a cause of reproductive dysfunction and high reproductive loss in subsequent pregnancies. The high frequency of chronic endometritis in women with reproductive disorders and in modern conditions does not tend to decrease. The prognostic scarcity of identifying violations of the reproductive function of women after invasive procedures in the uterine cavity pushes modern scientists to deeply study this nosology.

The urgent medical and social problem today remains the problem of chronic postabortion endometritis. Along with the high incidence of chronic pelvic inflammatory diseases, the frequency of chronic endometritis has recently increased. This, in turn, suggests that no clear diagnostic criteria and standards for the treatment, prevention of complications and rehabilitation of women with this pathology have been developed.

Ch.E. is diagnosed with the mandatory presence of its clinical markers and morphological features in the endometrium. Depending on the presentation of generally accepted criteria for inflammation in the endometrium, complete and incomplete morphological forms of Ch.E. are distinguished.

Additional visual criteria for Ch.E. are inflammatory micropolyps (41.8%), intrauterine synechia (31.9%), uneven thickness of the endometrium (36.3%), presented in various combinations and detected in 91.2% of cases with hysteroscopy.

The unfavorable prognosis of the course of Ch.E. is largely due to the lack of an algorithmized approach in the diagnosis and treatment of women with dysfunctional uterine bleeding, spontaneous miscarriage, and undeveloped pregnancy, while awareness of the immunological events accompanying various variants of chronic endometritis will allow differentially prescribed immunocorrective therapy.

The choice of anti-inflammatory therapy for Ch.E. depends on the presence of the pathogen in the endometrium and the degree of activity of the local immune response. Antibacterial therapy is indicated in all cases with the detection of infectious agents in the endometrium. At the same time, relief of dysfunctional uterine bleeding was noted in 70.3% of cases, normalization of the morphological structure of the endometrium - in 68.4%, reproductive function - in 42.1%. In the absence of microbial agents in endometrial biopsies, the administration of selective non-steroidal anti-inflammatory drugs is effective. All women should be prescribed immunomodulating therapy.

The treatment efficiency of patients with Ch.E. increases when hysteroscopy and curettage of the uterine cavity are used at the diagnostic stage, which is confirmed by normalization of the morphological picture of the endometrium in 80 and 46.2% ($p = 0.048$) cases, respectively, due to the removal of the affected endometrium and products from the uterine cavity inflammation supporting the chronization of the process.

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