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Vulvodynia – a multidisciplinary problem

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ABSTRACT

This literature review is devoted to the problem of vulvodynia. The article summarizes information about the etiology and pathogenetic factors of this syndrome, touches the aspects of diagnosis and treatment of this form of chronic genital pain. Despite the prevalence of this pathology, women with pain in the vulva often remain undiagnosed and do not receive adequate therapeutic and psycho-emotional support. Currently, the focus is in searching of the definition, classification, prevalence, pathophysiological factors of occurrence and adequate personalized therapy of this nosology.

Key words: vestibulodynia, dyspareunia, sexual dysfunction, provoked vulvodynia, unprovoked vulvodynia, generalized vulvodynia, clitorodynia

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Вульводиния – мультидисциплинарная проблема

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РЕЗЮМЕ

Обзор литературы посвящен проблеме вульводинии как мультидисциплинарной проблеме. В статье обобщены сведения об этиологии и патогенетических факторах развития заболевания, затронуты аспекты диагностики и лечения данной формы хронической генитальной боли. Несмотря на распространенность патологии, женщины с болью в области вульвы нередко остаются не диагностированными и не получают адекватную терапевтическую и психоэмоциональную поддержку. В на-

стоящее время актуальность представляет поиск определения, классификации, распространенности, патофизиологических факторов возникновения и адекватной персонализированной терапии данной нозологии.

Ключевые слова: вестибулодиния, диспареуния, сексуальная дисфункция, спровоцированная вульводиния, неспровоцированная вульводиния, генерализованная вульводиния, клитородиния.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Vulvodynia is a chronic vulvar discomfort that lasts more than 3 months and is manifested mainly by symptoms such as burning sensation and itching, as well as pain. At present, vulvodynia is a common but still poorly understood problem with multifactorial etiology. According to literature sources, an increasing number of patients seek medical help with the symptoms of this disease annually, while it is quite difficult to determine the exact cause of their condition. The problem of treating vulvodynia is extremely urgent due to the chronic course of this process and the difficulty in achieving the therapeutic effect due to the presence of a psycho-emotional component. This pathology was first outlined in the literature in the 1880s as “excessive sensitivity of nerves innervating the mucous membrane of the vulva” [1] or “hypersensitivity of the vulva” [2]. According to the type of condition, professionals distinguish generalized or localized forms of vulvodynia, each of which in turn is classified into provoked, unprovoked, independent of the presence of an irritant, and mixed types. The localized form includes vestibulodynia and clitorodynia [3]. Portuguese scientists have proposed a classification of vulvodynia based on 3 main groups of trigger factors: 1) local inflammatory factors (urinary tract infections, candidiasis, herpetic infection); 2) general pain susceptibility (fibromyalgia, irritable bladder syndrome, etc.); and 3) pinched/damaged pelvic nerve (scoliosis, pelvic surgery). It is assumed that such systematization could explain the differences between generalized and localized vulvodynia, as well as the difference in treatment responses [4]. In recent years, the term “vulvodynia” has been increasingly used in domestic medicine. It means

a chronic pain syndrome or discomfort of a different nature, such as burning or itching, which occurs in the vulvar area and the entrance to the vagina [5]. According to the classification of chronic pain syndromes, the so-called «gynecological pain» is distinguished, which includes pain syndrome associated with endometriosis, vaginal, vestibular, generalized and localized vulvar pain syndrome and pain in the clitoral area [6]. This classification defines vulvodynia as «a syndrome of unexplained pain in the vulva, sexual dysfunction, and mental instability». There are similar terms, such as vulvar dyskinesia, provoked vestibulodynia, and dyspareunia. However, all of them have nuances and do not characterize the whole concept of vulvodynia [7].

PREVALENCE

For a long time, vulvodynia had been considered a rare disease. However, recent large epidemiological studies speak of a high incidence (17%) and prevalence (7%) of this pathology in the population [8-9]. Vulvodynia affects women of all age groups, from adolescence to menopause [10]. In the United States, 8.3% to 16% of women suffer from vulvodynia. According to estimates by the National Institute of Health, about 13 million women may have symptoms of the disease at some point in their lives, and in 6% of women symptoms of the disease occur before the age of 25 years. These indicators are considered significantly underestimated due to the absence of visible pathologies of the vulva [9, 11]. In Portugal, according to studies by Vieira-Baptista [4], the prevalence rate is 16%. Spanish researchers speak about the prevalence of vulvodynia in 7–8% of women by the age of 40, while 30% to 48% of them have never sought medical

help [12]. A study conducted in Michigan revealed an incidence rate of 4.2% among women, with a prevalence rate ranging from 3.3% for women over 60 to 7.6% for girls under 20; pain syndrome that does not meet the criteria for vulvodynia was observed in 11.5% of women [13]. According to Reed [9] et al., the prevalence of vulvodynia differs depending on ethnicity: 4.3% of African women report symptoms compared with 9.3% of European women and 15.6% of Hispanic women. Other sources speak of an equivalent risk of developing vulvodynia in European and African American women [8]. Difficulties in diagnosing vulvodynia, in general, are associated with possible ethnic differences in the level of pain threshold, pain perception, and description of symptoms, as well as with possible poor accessibility of medical care [14].

ETIOLOGY AND PATHOGENESIS

Vulvodynia has a multifactorial etiology, however, not all causes are known today. One can assume that somatic, psycho-emotional, and psychosexual aspects (high levels of anxiety, depression, disturbances in emotional and sexual relations with a partner, etc.), as well as their combination, take part in the development of vulvodynia [15]. Despite the multicomponent state, the emphasis is laid on the somatic causes of this pathology, among which chronic inflammation in the vulva and vagina, atrophic processes, chronic contact dermatitis of the vulva, dermatosis of the vulva (lichen sclerosus and lichen planus) are distinguished [16]. The root cause of vulvodynia may also be improper development during embryogenesis [17–18], immune/genetic factors [19–20], and abnormal development of the female genital organs and their innervating nerve pathways [21–24]. The influence of environmental factors is not excluded: infections (human papillomavirus, chronic candida process), irritating substances (oxalates and products of its metabolism), injuries and microtraumas in the pelvic area. Currently, most vulvologists do not share this view. However, the results of a cross-sectional study in Portugal indicate a direct positive correlation between oral contraceptives, the presence of chronic candidiasis, genital herpes, urinary tract infections, depression, premenstrual syndrome and the development of vulvodynia. Pregnancy and childbirth were not associated with this pathology [4]. Pathophysiological changes in the mucous membranes in vulvodynia manifest themselves

in an increase in sensitive innervation and local blood flow, which suggests the presence of a neurogenic inflammatory process [25]. The trigger mechanisms in the development of the chronic inflammatory process of the nerves innervating the vulva are contact irritants, recurring vulvovaginal infections, hormonal changes, and chronic skin diseases. During the outcome of chronic inflammation, normal sensations are perceived as abnormal, which leads to the occurrence of hypersensitivity and pain [21–22]. Histological biopsies from the vulva revealed an increase in the number of mast cells and hyperproliferation of nerve receptors [26]. It is also believed that abnormalities in the development of the pelvic floor, in particular, weak muscular skeleton, can cause tension of the nerves that pass through this area. Due to pressure or friction of irritated muscles, pain can be radiated to the vulva [27]. Pelvic floor muscle dysfunction is almost always present in women with vulvodynia. The role of these disorders in the occurrence of pain in vulvodynia is also confirmed by the improvement of symptoms along with the normalization of the function of the pelvic floor through physiotherapy. The quality of the pain and its response to drug treatment indicate its relationship with neuropathic pain. Whether the pain is peripheral or central in origin is unknown.

NEURAL PROLIFERATIVE (VULVAR) FACTORS

Although hypersensitivity to the vulvar vestibule is one of the defining characteristics of vulvodynia, in particular, provoked vulvodynia, the mechanism underlying this allodynia was not clarified until 1998. Westrum, Willén, Bohm-Starke, et al. [21] used immunohistochemical (IHC) staining to visualize an increase in the density of nerve endings in the vestibule endodermis in women with provoked vulvodynia who underwent vestibulectomy compared with the control group. Additionally, the neural proliferation of nociceptors was investigated, which explained the onset of allodynia. Quantitative sensory testing by Pukall et al. [28], showed that women with provoked vulvodynia are more sensitive to tactile and painful stimuli of punctate in comparison with control women. The similar results are observed in response to other forms of stimulation, for example, thermal and pressure pain. Hypersensitivity is not limited to static stimuli or vestibule.

EMBRYOLOGICAL AND CONGENITAL FACTORS

Vulvodynia has been described in young girls with or without concomitant interstitial cystitis and irritable bladder syndrome. One of the possible explanations for the coexistence of vulvodynia and interstitial cystitis is that these two conditions are congenital endothelial disorders of the urogenital sinus. Some cases of provoked vulvodynia may be associated with a congenital defect in hyperplasia of the neurons of the vulvar tissue. Women with vulvodynia have significantly more nerve fibers in the vaginal vestibule compared with the control group [23]. It has also been hypothesized that there is a correlation between the number of vanilloid receptors (VR1) and the further development of vulvodynia [29].

GENETIC FACTORS

Several studies have suggested a genetic predisposition to the development of provoked vulvodynia (for example, Babula et al. [30], Lev-Sagie et al. [31], Foster et al. [26], Gerber et al. [32], Goldstein et al. [33]). Genetic studies have focused on three possible (but potentially overlapping) mechanisms: genetic polymorphisms that increase the risk of developing chronic candida and other infections [31], genetic changes that affect the nature of inflammation [32] and increased susceptibility to hormonal changes caused by oral contraceptives. The genetic predisposition to vulvodynia associated with the polymorphism of interleukin (IL)-1 β genes, which affects the nature of the inflammatory reaction, is proved. Women with vulvodynia are more often homozygous for the second allele of the IL-1 β gene and the second allele of the IL-1 β receptor antagonist gene compared to healthy women [32, 34].

HORMONAL FACTORS

It has been believed for decades that the vulvar and vaginal tissues respond to and depend on steroid hormones to ensure proper health and functioning, and that circulating estrogen deficiency leads to anatomical and physiological changes in the vagina. There are many reasons for the decrease in sex steroids, natural and iatrogenic, leading to physiological changes and symptoms of the disease. The most common cause of decreased sex steroids in women is menopause. Other natural causes of anovulation include lactation or anorexia, hypothalamic amenorrhea due to biological stress factors, such

as excessive physical activity or physiological stress and hyperprolactinemia [35]. Iatrogenic causes of decreased circulating sex steroids include surgical factors such as ovariectomies and hysterectomies [36], combined oral contraceptives (COCs) (estrogen and progestin-containing oral contraceptives), used by 82% of North American women at some point in their lives [37]. It has been shown that COCs induce morphological changes in the mucous membrane of the vestibule, increasing its vulnerability to mechanical deformations [38]. In addition, the use of COCs is associated with a decrease in the pain threshold, a decrease in the size of the clitoris, the thickness of the labia, and introital diameter. The latest prospective randomized experimental study by Battaglia et al. [39] showed desensitization of orgasm, a decrease in lubricant production, and an increase in dyspareunia associated with COC intake. Bazin et al. [40] in a controlled study showed that women who started taking COC before age 17 had a relative risk of developing provoked vulvodynia. In addition, Bouchard et al. [41] and Harlow et al. [42] confirmed that early use of COCs significantly increases the risk of vulvodynia. Greenstein et al. [43] reported that the use of COCs containing ethinyl estradiol in a dose not exceeding 20 mg significantly increases the risk of provoked vulvodynia. Goldstein et al. [44] revealed polymorphism in androgen receptors, which significantly increased the risk of developing COC-induced provoked vulvodynia. Many medical practitioners believe that hormonal changes affect vulvodynia. Symptoms often occur just before menstruation, and there is evidence that early use of hormonal contraception may predispose to vulvodynia. However, other studies and clinical experience do not support this hypothesis [45]. Starting or stopping oral contraceptives and increasing estrogen levels usually do not improve symptoms. The study by Reed also disproved the hypothesis that oral contraceptives are associated with the further development of vulvodynia in women under 50 [46].

PSYCHO-EMOTIONAL FACTORS

Patients do not consciously associate vulvodynia with their psycho-emotional problems. There are several pathogenetic variants, depending on the ratio of somatic and mental factors:

1. Vulvodynia as a somatoform disorder – the predominance of psychogenic mechanisms in the absence of organic changes in the vulva or their

inconsequentiality. In this case, the presence of concomitant pain syndromes, such as fibromyalgia, irritable bladder syndrome, irritable bowel syndrome, is often observed;

2. Vulvodynia as a psychogenic reaction due to the effect on the patient's mental status of gynecological diseases and related symptoms. Ineffective therapy, relapses of the disease, anxiety often become trigger factors for the deterioration of the patient's psycho-emotional status and, as a consequence, the development of vulvodynia;

3. Vulvodynia as iatrogeny, often a similar condition develops against the background of the presence of sexually transmitted diseases in patients;

4. Vulvodynia as a psychosomatic disorder – the presence of a set of symptoms, including the presence of both mental and somatic pathologies [47].

CLINICAL EVIDENCE

Vulvodynia is characterized by the presence of burning, itching, pulsation, pain in the vulva. The pain may be constant or intermittent, localized or diffuse. Symptoms occur during friction on underwear or physical exertion, and in a sitting position or during rest [48]. The classification of vulvodynia is based on the location of the pain: localized and generalized. The localized form of vulvodynia and vestibulodynia occurs in contact with a sensitive area of the vulva. Usually, this form is projected in the vestibular gland in the vestibule of the vagina, possible irradiation into the clitoris (clitorodynia), and unilateral localization (hemivulvodynia). Pain is described as a sensation of burning, throbbing, tearing, “razor blade”. Often, women with localized vulvodynia complain of dyspareunia and avoid sexual intercourse; pain can last from several hours to a day after intercourse, during it and when the penis penetrates the vagina. The use of tampons, playing sports or other active activities, wearing tight clothing can cause discomfort. Localized vulvodynia is divided into primary, when pain occurs after the first penetration into the vagina, and secondary, arising after a while [49]. Generalized vulvodynia is characterized by the localization of pain in the area of the vulva or around it, including the pubic area, the labia, the vestibule, and the perineum. Pain can be permanent or intermittent in nature and range from a sensation of slight discomfort to unbearable pain, greatly reducing the quality of life. Sym-

toms can be diffuse or localized in several areas at once, occur alternately, fade and worsen, and not depend on external irritation. The nature of pain does not differ from those with a localized form. Often there is dyspareunia, painful urination, a change in the nature of vaginal discharge [50]. A study by Sadownik et al. [51] revealed that 71% of women have dyspareunia, 64% have recurrent candidiasis, 57% and 46% have a sensation of burning and itching in the vulva, and 33% have sexual dysfunction. A study by Brown et al. [52] showed that European women describe the symptoms of burning pain 19 times more often than African-American women who describe the pain as “aching”, which is less consistent with the classic manifestation of vulvodynia. Gansky et al. [53], while studying a group of women with fibromyalgia, found that European women have a lower pain threshold and a predominantly localized nature of the spread of pain compared to African-American women, mainly complaining about the generalized nature of the pain syndrome. Along with vulvodynia, the presence of other pain syndromes is often observed. Reed and his colleagues examined 24 women in his study for interstitial cystitis, irritable bowel syndrome, fibromyalgia, and vulvodynia. The incidence ranged from 7.5% to 11.8%; in 27% of patients, the presence of vulvodynia was significantly associated with other pain syndromes [54]. The chronic nature of vulvodynia can negatively affect a woman's self-esteem and cause depression and anxiety disorders. Vulvodynia is not considered a psychopathological condition. However, Tribo et al. [55] reported anxiety syndrome in more than 50% of women. Further studies have shown that women with anxiety disorders are 4 times more likely to develop vulvodynia. In addition, women can experience significant sexual and psychological problems in their relationship with a partner. Many of them use psychological support, sex therapy and/or counseling from a psychotherapist or sexologist. Pain caused by vulvodynia can ultimately lead to decreased sexual activity; fear and expectation of pain during intercourse can lead to sexual dysfunction such as disorders of sexual arousal, decreased libido, problems with orgasm/anorgasmia, phobic avoidance of sexual activity [56].

DIAGNOSTICS

One of the diagnostic methods for detecting vulvodynia is the “Cotton swab test” used to identify sensitive areas in the vulva. The test

is carried out strictly sequentially, starting from the outer edge of the thigh to the inside, from top to bottom along the labia majora, and then the labia minora, to the frenum of the labia, perianal region and ending with the vestibule of the vagina and the area of periurethral and Bartholin glands. The right and left side of the vestibule should be examined separately. During the test, the patient evaluates each of the studied areas on a 10-point Likert pain scale, where 0 is its absence, and 10 is severe pain. A localized form of vulvodynia can be diagnosed if the patient experiences discomfort at individual points, and a generalized form – if pain covers a vast area. If the patient does not experience a burning sensation or pain in any of the areas, then vulvodynia cannot be considered as a differential diagnosis [48]. Friederich proposed local diagnostic criteria for vulvodynia, including soreness during the Q-tip test (point symmetrical palpation of the vaginal area with a cotton swab), erythema of the vulva of varying severity and pain when touching the vestibule of the vagina. However, only the last criterion is often positive and is the only diagnostic symptom. In addition, IMMPACT recommendations [57] are of great significance in the diagnosis of vulvodynia, used to evaluate such criteria as pain, physical/sexual functioning, emotional functioning, treatment efficacy and treatment satisfaction, symptoms and adverse events, and patient compliance.

DIFFERENTIAL DIAGNOSIS

Vulvodynia is a diagnosis of exclusion. The main diseases of differential diagnosis include atrophic vaginitis, introital or vaginal lichen planus, desquamative inflammatory vaginitis. The symptoms of genital neuralgia are similar to vulvar pain, however, pain, in this case, has characteristic clinical signs. The patient feels better in a standing position while sitting or lying there is great discomfort. Candidiasis infections, with the exception of *Candida albicans*, in particular, *Candida glabrata*, *Candida krusei* (*Issatchenkia orientalis*) can cause itching and feeling of abrasion than classical itching but are usually asymptomatic [45]. The diagnosis of vulvodynia requires the exclusion of an obvious somatic pathology that can cause pain. The identification of the psychogenic component through the collection of anamnesis, including a pain history of life, is important; the sexual function, the level of stress, depressive episodes, if any, are studied. The clinical signs in the presence of a psychogen-

ic component are characterized by a mismatch of the nature of pain and clinical manifestations, the dynamics of the pathology non-typical for gynecological diseases – sudden appearance and disappearance, changes correlated with relationships with a partner, sexual function (conflicts with a partner, lack of awareness of one's own sexuality, sensation of sexual inferiority), the level of mood and the lack of effect of the therapy [25]. For differential diagnosis, the pelvic floor muscles are examined by palpation in the projection of the muscle that raises the anus and the internal obstructive muscle for painful sensations [58].

TREATMENT

Therapy of vulvodynia requires an interdisciplinary approach and combines an individually selected ratio of drug therapy, psychopharmacotherapy, psychotherapy, sexuality counseling, and surgical interventions. It is important to understand the presumed root cause of the symptoms and perform a comprehensive differential diagnosis. The creation of awareness is important in the treatment of vulvodynia. Confidence and awareness of patients about their problem and further therapy helps to cope with the psycho-emotional aspects of vulvodynia and leads to recovery. Women need to realize that vulvodynia is a separate nosology, neither contagious nor associated with serious or life-threatening conditions, such as oncology, sexually transmitted diseases, or immunodeficiencies. However, it is worthwhile to inform women in advance that vulvodynia usually responds to treatment, but cannot be completely treatable, and requires high patient compliance. Lack of compliance nullifies the effect of the therapy. More often, improvements come slowly, by trial and error with an individually selected treatment program. Psychotherapeutic measures include cognitive-behavioral therapy, analysis of interpersonal relationships, and relationships with a partner. Often, training in relaxation techniques, self-examination with the study of the pelvic floor muscles and the techniques of their training, consultations of a psychotherapist and sexologist, including paired methods of sexual therapy give good results.

NON-SPECIFIC METHODS OF TREATMENT

Local care of the affected area and avoidance of potential irritants can improve the quality of life. Occasionally, a significant improvement in

condition occurs when you refuse to use non-specific detergents, excessive washing, taking medications and local anti-candidiasis therapy and lubricants. 2% Lidocaine gel is a safe and non-irritating local anesthetic that can relieve discomfort [45]. Non-pharmacological treatment also includes physiotherapy of the pelvic floor muscles. Muscle relaxation subsequently leads to a decrease in pain. However, according to research, from 60% to 80% of successful physiotherapeutic outcomes are achieved only with treatment by pelvic-focusing physiotherapists [59]. Common methods of therapy include soft tissue mobilization, ultrasound, surface electromyography, and the use of vaginal dilators. As additional methods, electrical stimulation can be used; some involve electrical stimulation, exercises for the pelvic floor muscles (including Kegel), methods of thermal exposure and neuromodulation of the sacral plexus, and electric muscle stimulation, devices [60]. Hypnosis has been used with some limited success [61]. A study by Schlaeger et al. [62] addressed the issue of acupuncture in women with vulvodynia. 36 women received acupuncture 2 times a week for 5 weeks. It was found that pain and dyspareunia reduced significantly, while the sexual activity of women, on the contrary, increased. Coady et al. [63] put forward a hypothesis about the relationship of vulvodynia with impingement syndrome of the hip joint. 26 patients with generalized unprovoked vulvodynia or clitorodynia underwent arthroscopy of the hip. The study revealed significant symptomatology improvements in women under 30 almost 3–5 years after surgery. A review by Frigo N.V. [64] reported successful therapy with Neogyn vulvar soothing cream. 24 women aged 53–80 years were examined and treated with Neogyn cream for 12 weeks; after the therapy, 60.9% of patients had a significant decrease in discomfort, dyspareunia, and 65.26% improved the quality of their sexual life. G. Donders et al. [65] conducted a placebo-controlled, cross-sectional study of 30 patients with vulvodynia who were prescribed this cream. These studies showed a decrease in symptoms of provoked vestibulodynia. Narcotic pain killers should be used with caution; the combination of tramadol and hydrocodone was used in the short term for acute pain [50].

SURGICAL TREATMENT

Currently, vestibulectomy is the gold standard for the treatment of vestibulodynia, but only if the pain is localized only in the vestibule.

The treatment efficacy ranges from 65% to 90%. Very often surgery causes damage to the vaginal mucosa, leading to the removal of a more extensive area than the focus of pain; in the post-operative period, symptoms may be preserved due to incomplete preoperative diagnosis and inaccurate pain map. Taking neuropathic pain killers usually continues after surgery to maximize the quality of life and promote the recovery of sexual functioning. Novocaine blockade is feasible only when other treatment methods do not provide positive dynamics to relieve pain and improve the patient's quality of life [66].

PAIN MODULATORS

The use of tricyclic antidepressants, such as Amitriptyline or Desipramine, can help reduce chronic neuropathic pain due to the central mechanism of action, which alters the transmission of pain impulses to the brain through the spinal cord. Brown et al. [67] studied the effect of Amitriptyline C with/without Triamcinolone; the efficacy of this method has not been proven. A randomized controlled trial by Foster et al. [68] showed that the effects of oral Desipramine were not superior to those in the placebo group. The efficacy of other antidepressants, such as Duloxetine and Venlafaxine, has also not been proven. A randomized controlled trial of Gabapentin – a drug that helps control epileptic seizures, has been shown to trigger symptoms of vestibulodynia. However, studies of Pregabalin anticonvulsant drug showed improvement in symptoms, and the use of Lamotrigine reduced pain within 8 weeks [69]. Hydroxyzine and Cetirizine have been used to reduce itching. Combinations of neuropathic pain killers (for example, Amitriptyline, Gabapentin, Pregabalin) can also be used for some women since they have different mechanisms of action [50].

CONCLUSION

Vulvodynia is a relevant multidisciplinary problem, causing both physical and psychological discomfort. This pathology reduces the quality of life not only of the patient herself but also of her partner, contributing to the development of a wide range of psycho-emotional and sexual problems. Vulvodynia requires careful diagnosis; often being a symptom of a number of serious diseases of the vulva, vulvodynia can also act as an independent nosology, and it can be difficult to establish the exact cause of this condition.

Treatment of vulvodynia must be client-oriented, in accordance with the potential predictors of the onset of the disease. It is very important not only to choose the appropriate therapy for a particular woman but also to provide psychological support in order to achieve the highest possible increase in the quality of life of such patients and their partners.

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