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Chapter

Introductory Chapter: Changes in the Approach of the Patient with Endometriosis and the Development of Genetics and Molecular Biology in Gynecology

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1. Introduction

Endometriosis is characterized by the presence of endometrial-like functional tissue located outside the uterine cavity, most commonly in the pelvic peritoneum, ovaries and rectovaginal septum, and more rarely in the pericardium, pleura and central nervous system. The studies indicate a prevalence of up to 20% of women of reproductive age [1] and 30–50% of infertile women with endometriosis [1].

2. Clinical condition

The clinical condition of the patient with endometriosis is quite variable. The patient may be asymptomatic, refer only to infertility, or have symptoms such as severe dysmenorrhea, profound dyspareunia, chronic pelvic pain, ovulatory pain, urinary symptoms or peri-menstrual bowel movements, and chronic fatigue. Gynecological examination may be normal, but the presence of pain in uterine mobilization, uterine retroversion, or increase in ovarian volume is suggestive of endometriosis, although it is not specific. Other conditions, such as irritable bowel syndrome, pelvic inflammatory disease, and interstitial cystitis may present similar symptoms and should be included in the differential diagnosis. Signs suggestive of deep infiltrative endometriosis are palpable nodulations in the posterior vaginal fornix or rectovaginal septum, thickening of the uterosacral ligaments, or violaceous lesions in the vagina [2].

3. Diagnostic evaluation of endometriosis

Although the definitive diagnosis of endometriosis requires surgical intervention, preferably through videolaparoscopy, several findings in physical, imaging, and laboratory tests can already predict, with a high degree of reliability, that the patient has endometriosis. To date, no biochemical marker can be considered as an endometriosis endpoint, but Ca-125, when collected on the first or second day of the menstrual cycle, may be useful for the diagnosis of advanced stage endometriosis when the values are higher than 100 IU/mL [3]. Although normal

concentrations do not exclude the disease, cases with elevated preoperative levels may aid in patient follow-up and clinical suspicion of recurrence of endometriosis. More recently, some cytokines have been studied as new nonsurgical endometriosis markers. Interleukin-6 (IL-6) appears to perform better than other cytokines in discriminating patients with endometriosis [4]. The first imaging test to be applied to the patient with a history and physical examination suggestive of endometriosis is transvaginal pelvic ultrasound, preferably with intestinal preparation. A study by Abrão et al. [5], evaluating the accuracy of this test, demonstrated a sensitivity of 94% and a specificity of 98% in the identification of foci of deep endometriosis. If the test is normal, the patient may not have endometriosis or have noninfiltrative initial disease. On the other hand, if the test is conclusive for ovarian endometriosis, rectovaginal septum or rectosigmoid, or urinary tract, treatment may be indicated without additional imaging tests. For evaluation of endometriomas larger than 2 cm, transvaginal ultrasonography is an efficient method, according to Moore et al. [6]. The presence of ovarian masses with a doubtful diagnostic hypothesis can be better evaluated with magnetic resonance imaging (MRI). Changes suggestive of rectovaginal septum disease, uterosacral, or rectosigmoid ligaments may be confirmed by rectal echoendoscopy or MRI. Rectal echoendoscopy allows the identification of the distance between the lesion and the rectal lumen as well as extrinsic compressions and submucosal lesions of the rectum [7]. MRI also allows the identification of deep disease with invasion of the intestinal tract, but it does not make it possible to specify the intestinal layer affected by the lesion [8]. Transvaginal ultrasonography for the diagnosis of bladder endometriosis has been reported as an effective method, with sensitivity of 71.4% and specificity of 100% [9]. Ultrasonography suggestive of bladder or ureteral endometriosis can be complemented with excretory urography, which may show ureteral narrowing. Uro-resonance can be used as an alternative method to excretory urography for evaluation of renal collecting system dilatations. Although the available imaging exams presented good accuracy in the diagnosis of endometriosis, laparoscopy with lesion biopsy for anatomopathological analysis is still the gold standard in the diagnosis of endometriosis.

4. Classification of endometriosis

After videolaparoscopy, endometriosis can be classified according to the histological type of the implants, with the anatomical location of the disease—peritoneum, ovary or rectum—or by the extension of the disease to the pelvic organs. The most commonly used classification is that of the American Society of Reproductive Medicine—revised in 1996 [10]. This classification rates minimal, mild, moderate, or severe endometriosis due to the extent of disease in the peritoneum and ovaries, as well as the presence of tube-ovarian and Douglas sack bottom block. This classification, although with some limitations, is quite useful in the orientation of postsurgical treatment, especially when the patient's complaint is infertility.

5. Critical analysis of treatments for endometriosis

The therapeutic approach to endometriosis varies, depending on the patient's complaint, pelvic pain or infertility, although such complaints are often associated. Gonadotropin-releasing hormone (GnRH) analogues, GnRHa, may be indicated for three months and then continue with oral contraceptives. If the patient has

recurrence of pain, or an image suggestive of endometrioma greater than 3 cm or suspected of adherence, surgery should be indicated.

6. Surgical treatment of endometriosis

Surgical treatment of endometriosis involves procedures of low complexity, such as the treatment of superficial foci and the release of tendon adhesions, to complex interventions in the ovaries, Douglas sacs, intestines, bladder, and ureters, requiring, in some cases, a multidisciplinary team. For several years, the surgical treatment of endometriosis was based on the oncological principles of radical removal of the lesions. This principle is still used when it comes to cases of intestinal or ureteral stenosis or ovarian masses of doubtful characteristics. However, we currently know that there is no correlation between the disease with the severity of the symptoms, as well as the reproductive prognosis and long-term recurrence of pain [11]. In addition, many patients present infertility associated with pain, requiring that the surgical procedure be conservative. Based on these considerations, some authors recommend surgical treatment only for patients who do not respond to drug treatment, as well as for those who wish to become pregnant spontaneously [12]. There are few published randomized clinical trials evaluating the outcome of surgical treatment of symptomatic endometriosis. A review by Vercellini et al. [12] describes symptomatic improvement after conservative treatment of around 60–80%, with recurrence of symptoms and reoperation rate ranging from 12 to 58% between studies.

For the patient with infertility, follicle ablation and adhesiolysis appear to improve fertility in the minimal and mild degrees of disease [1]. In cases of moderate or severe degrees, there are no randomized clinical trials or meta-analyses available to answer if resection of foci would increase gestation rates.

7. Molecular genetics and endometriosis

Endometriosis exhibits similarity with cancer since endometrial cell implants require neovascularization to establish, grow, and invade tissues. In addition, the etiopathogenic theories of endometriosis involve growth factors and cytokines associated with regulation of cell multiplication and neoangiogenesis that may act on carcinogenesis. It is estimated that 1% of cases of endometriosis is related to cancer, and for some types of endometriosis, its benign nature has been questionable [13, 14].

Although the definitive diagnosis of endometriosis necessitates a surgical intervention, called video-laparoscopy, several findings in the physical, imaging and laboratory examinations can already predict, with a high degree of reliability, that the patient has this disease. During this surgical procedure, it is possible to visualize lesions suggestive of the disease and to obtain a tissue specimen for anatomopathological analysis and confirmation of the diagnosis of endometriosis [15]. The classification used for endometriosis is that of the American Society of Reproductive Medicine (ASRM), revised in 1996, which rates this disease in minimal (stage I), mild (stage II), moderate (stage III), or severe (stage IV) [16]. Currently, the most common treatments are surgery, ovarian suppression therapy, or the association of both [13, 15].

The cause of endometriosis remains unknown. However, there is evidence of immunological [17, 18], environmental [19], and genetic [18, 20] factors involved in its pathogenesis.

Regarding the immune response, the role of cytokines in the development of endometriosis [21–23] is highlighted, and elevated levels of several of them have been found in patients with endometriosis [23, 25]. The same group of investigators [24, 26] evaluated the levels of cytokines involved in the Th1 immune response patterns (interleukin (IL)-2, tumor necrosis factor (TNF)-alpha and interferon (IFN) and Th2 (IL-4 and IL-10) in patients with endometriosis (n = 65) and in those without the disease (n = 33). Podgaec et al. [24] observed elevation in IFN-gamma and IL-10 levels in patients with endometriosis, evidencing the coexistence of both responses. However, when considering the ratio of cytokine levels to these responses, IL-4 and IL-10 predominated, thus reflecting a possible shift to the Th2 immune response component. In the subsequent study, 18 cytokine levels were associated with the clinical symptoms of endometriosis. Patients with endometriosis who had depth dyspareunia and infertility exhibited elevated levels of TNF-alpha and IL-2, respectively. These cytokines are related to the Th1 immune response, and almost 70% of the patients who presented these results exhibited deep endometriosis. The authors conclude that when specific clinical data are associated with elevated production of certain cytokines, there is a Th1 response pattern that may be associated with deep endometriosis. Induction of Th1 immune response was also reported by Fairbanks et al. [25], who showed elevated levels of IL-12 in patients with severe endometriosis.

The contribution of environmental factors to the development of endometriosis was reviewed by Bellelis et al. [19] who related their influence and diet to the genetics of this disease. They concluded that the mechanism by which dioxin and its similes (2,3,7,8-tetrachlorodibenzo-p-dioxin/TCDD and polychlorinated biphenyls/PCBs) act to alter endometrial physiology is uncertain and speculative. They also state that there is insufficient evidence regarding the use of diets as preventive factors or even adjuvants in the treatment of endometriosis.

The genetic and hereditary basis of endometriosis was evidenced in the study by Bellelis et al. [19] in which approximately 5.3% of the patients reported a first-degree family history with a history of endometriosis. Familial aggregation, a high concordance rate in monozygotic twins, and a 4–7% risk for first-degree relatives support a contribution of genetic factors to the pathogenesis of this disease [14]. In this context, the identification of genetic variants or single nucleotide polymorphisms (SNPs), responsible for susceptibility to endometriosis, has been the subject of investigation in recent years [26–28]. Different classifications were proposed for endometriosis candidate genes.

8. Conclusions

What are the objectives of the genetic study of individuals? There is a great interest of the medical community and also much concern of the lay press about the potential benefits and harms of genetic screening, gene therapy, and even the possibility of cloning individuals. The current use of genetic tests for the detection and treatment of endometriosis is still at an early stage, but very important. The determination of susceptibility markers will be increasingly explored in clinical studies, and their uses will be much more defined.

Still, it seems increasingly likely that major changes will occur over the next decade in how we evaluate and treat our patients. In particular, surgeons and clinicians will have the opportunity to use a number of new tests to predict the future appearance of endometriosis in patients still free of the disease. They may have the power to explore the best therapeutic modality for a particular patient according to their genetic makeup. And they will be able to more specifically target prevention

measures for family members of people already affected by the disease. It should be understood that molecular diagnosis, especially in asymptomatic individuals, does not mean disease, but an increased risk of developing this disease. Ethical implications exist and should not be underestimated. Patients should be advised about the likely implications of such tests not only after, but especially before the achievement of these.

A major step has already been overcome and we currently have basic tools for a new leap in understanding human pathologies responsible for much of the world's mortality. Bridging the great barrier that still separates this basic knowledge from clinical practice is still a much greater challenge.

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