LUMEN ET VIRTUS
ISSN: 2177-2789

ENDOMETRIOSIS: AN UP-TO-DATE REVIEW ON DIAGNOSIS, TREATMENT, AND ITS RELATIONSHIP TO INFERTILITY

https://doi.org/10.56238/levv15n41-033

Submitted on: 08/09/2024 **Publication date:** 08/10/2024

Isabela Padovan Necklace[1], Karine Emanuele da Silva[2] and Henrique Abreu Dall'Agnol[3]

ABSTRACT

The objective of the present study is to present a comprehensive analysis of endometriosis and its relationship with infertility. Methodology: this is an integrative literature review, with articles published between 2019 and 2024, in national and international databases, performing searches in the databases: PubMed, Scielo and Nature. The results demonstrate that endometriosis is a disease strongly related to infertility that affects both the quality of life and the economy of affected women. Early diagnosis with imaging methods is critical for effective management of the disease. The treatment is presented in a personalized way, depending on the complaints and desires of the patients.

Keywords: Endometriosis. Pain. Challenges. Infertility.

[1] Medical Student
UNICESUMAR
E-mail: isabelapadovan@hotmail.com
[2] Medical Student
UNICESUMAR
E-mail: karinemanuele_@hotmail.com
[3] Gynecologist and Obstetrician/ Fertileutic
UNICESUMAR
E-mail: henrique_dallagnol@hotmail.com

INTRODUCTION

Endometriosis is a complex and often debilitating condition that affects a significant portion of women of childbearing age, and it is estimated that about 10% of the global female population is affected by this disease (BLAMBLE et al, 2021). Defined as a chronic hormone-dependent inflammatory disease, endometriosis is characterized by the presence of endometrial tissue outside the uterine cavity, leading to symptoms such as chronic pelvic pain, dysmenorrhea, and, in many cases, infertility (FILHO, 2019). The etiopathogenesis of endometriosis is multifactorial and involves several theories that seek to explain the formation and location of lesions, from the retrograde menstrual flow proposed by Sampson to coelomic metaplasia and hematogenous dissemination. Although multiple biological, hormonal, immunological, and genetic factors are implicated in the disease, the interaction between them is not yet fully understood, which makes early diagnosis and proper management difficult (FEBRASGO, 2021).

The clinical manifestations of endometriosis are varied and have a profound impact on the quality of life of patients, interfering not only with physical health, but also with the emotional, social, and professional spheres. Pain and other frequently reported symptoms lead women on a challenging journey in search of diagnosis and treatment, often accompanied by a social stigma that minimizes their complaints. In addition, the disease is associated with a significant cost, both in terms of treatment and loss of productivity, which further underscores the need for a multidisciplinary approach and health policies that ensure adequate support for affected women (RODRIGUES et al., 2022).

Its diagnosis is a complex process that requires a careful and comprehensive approach, given that the condition can manifest asymptomatically in up to 22% of women and present symptoms that often overlap with other gynecological diseases. Early identification of endometriosis is essential for effective management of the disease and personalization of treatment, which must be tailored to the needs and preferences of each patient (FEBRASGO, 2021). Diagnosis involves a combination of a detailed clinical history, thorough physical examination, and the use of imaging tests, such as transvaginal ultrasound and magnetic resonance imaging, as well as serum markers that may indicate the presence of the disease (CRUMP et al, 2024).

The clinical evaluation begins with the collection of a comprehensive medical history, where symptoms such as dysmenorrhea, dyspareunia, pelvic pain, among others, are investigated. However, the absence of a specific symptom for endometriosis and the high prevalence of asymptomatic cases complicate the recognition of the disease. Thus, the

identification of high-risk groups becomes a crucial strategy, allowing patients to be directed to more in-depth diagnostic tests. (CHAPRON et al, 2019).

Physical investigation also plays an important role, where the doctor can identify signs suggestive of endometriosis, such as nodules or adhesions (PODGAEC et al, 2018). In the case of complementary exams, ultrasonography offers a dynamic and accessible evaluation, and magnetic resonance imaging stands out for its ability to detect occult subperitoneal lesions and assess the extent of the disease. (RBGO, 2013; OLIVEIRA et al, 2019; COUTINHO JUNIOR et al, 2008).

Endometriosis and infertility are interlinked conditions that affect a significant portion of the female population of reproductive age, generating a profound impact on the physical and emotional health of patients, which raises questions about the underlying mechanisms that connect these two realities (VASSILOPOULOU et al, 2018). The phenomenon of infertility is defined, according to Vila (2007), as the inability of a couple to conceive after a year of regular attempts without the use of contraceptive methods. This problem, which affects approximately 16% of couples, can be classified as primary or secondary, depending on the reproductive history of the couple (SANTOS, 2005). In the context of endometriosis, the factors that contribute to infertility are the most varied, and may involve mechanical obstructions, inflammatory processes, hormonal changes, and genetic changes (VASSILOPOULOU et al, 2018).

In this work, we will explore the etiopathogenesis of endometriosis, its clinical manifestations, and the challenges faced by patients. Through this analysis, we seek not only to elucidate the challenges faced by patients, but also to understand the complexity of this condition and the importance of a diagnosis, from anamnesis and physical examination to imaging methods and biological markers, as well as effective and personalized treatments to improve the quality of life of affected women and restore their reproductive capacity.

Given the complexity of the interaction between endometriosis and infertility, it is essential to understand the mechanisms that connect them, as well as the available treatment approaches. This work also proposes to explore the nuances of this connection, analyzing the pathophysiological factors that influence fertility in women with endometriosis.

METHODOLOGY

This is an integrative literature review, with articles published between 2019 and 2024, in national and international databases, performing searches in the following databases: PubMed, Scielo and Nature.

RESULTS

The literature collected confirms the high prevalence of the disease, estimated at 10% of the female population. However, its cause is not fully understood, and probably involves a complex interaction between the multiple theories developed to date that try to explain its genesis.

Complementary imaging tests (Magnetic Resonance and Ultrasound) are of great importance in the face of clinical suspicion, and have similar sensitivity and specificity for detecting the disease, but the confirmatory diagnosis is obtained with excision of the lesions and anatomopathological study. The CA125 marker, although not specific, also seems to be a reasonable parameter to measure disease activity, and is widely used in daily clinical practice.

The treatment of the disease is directed to the patient's complaint, ranging from hormonal blockade with hormonal contraceptives or the use of GnRh Agonists to laparoscopic surgery for lysis of adhesions in patients with pelvic pain/dysmenorrhea/dyspareunia. In cases related to infertility, in vitro fertilization seems to be an interesting alternative, either for immediate pregnancy or used later in patients who froze eggs before the laparoscopic approach due to pelvic pain.

DISCUSSION

ETIOPATOGENIA

Endometriosis is defined as a chronic hormone-dependent inflammatory disease where endometrial and stromal glands are found outside the uterine cavity. The action of estrogen is a condition for the development of the disease, since it acts on the endometrial tissue, which can result in chronic pelvic pain, dysmenorrhea, and infertility (FILHO, 2019). It is an often painful disease that affects about 10% of women of childbearing age worldwide (BLAMBLE et al, 2021).

Endometriosis is a disease of complex etiology, explained by several theories, involving the histogenesis of endometriosis. The most accepted theory postulated by Sampson, in 1927, suggests that retrograde menstrual flow transports endometrial tissue to the peritoneal cavity and other organs, associated with other factors would be able to allow the implantation of endometrial tissue outside the uterine cavity and coelomic metaplasia, which justifies cases in men, children and atypical sites. The presence of viable endometrial cells in the lumen of blood and lymphatic vessels suggests possible hematogenous and lymphatic dissemination, thus explaining lesions in the pleura, umbilical scar, retroperitoneal space, vagina and cervix (FEBRASGO, 2011).

The susceptibility of women suffering from endometriosis depends on the interaction of genetic, immunological, hormonal and environmental factors. Therefore, we have an enigmatic disease that is difficult to understand, whose complex etiopathogenesis imposes on us the need for in-depth knowledge of different pathophysiological aspects (FEBRASGO, 2021).

The mechanisms involved in associating endometriosis and infertility have not yet been fully understood; The proposals include: changes in the follicular microenvironment or oocyte, changes in the embryonic implantation mechanism, ovulatory dysfunction, immunological defects, hyperactivation of peritoneal macrophages, changes in cytokines in follicular fluid and blood circulation, unruptured follicle syndrome, changes in early embryonic development, increased cellular apoptosis in granulosa cells, in addition to endocrine changes such as inadequate luteal phase and hyperprolactinemia.

There is a tendency to genetic and constitutional predisposition to the disease. In addition to the alterations mentioned, it is plausible that pelvic anatomical distortions are related to the reduction in fertility found in patients with endometriosis. Some observational studies of in vitro fertilization have shown that the follicular phase is significantly longer and the fertilization rate is lower in patients with minimal or mild endometriosis, when compared to those with tubal factor and infertility with no apparent cause.

CLINICAL MANIFESTATIONS OF ENDOMETRIOSIS

Signs and symptoms related to endometriosis include pelvic pain and/or lower abdominal pain, abnormal menstrual bleeding pattern (either by quantity or by irregularity), family history of the disease, history of infertility, previous pelvic surgery, and history of ovarian tumor (WANG et al, 2022).

Most women suffer from neglect or lack of interest on the part of professionals, who do not value their complaints as they should, and often end up considering the symptoms as normal, relating the physiology of the menstrual cycle, a result of how health services see gender stereotypes, a reflection of a distorted social view of the female sex. On other occasions they relate the symptoms to sexually transmitted infections or any other type of infection, these situations cause patients to migrate between doctors and private network exams to be able to pay attention to their complaints and discover their diagnoses, which entails a great financial cost.

Certain symptoms of endometriosis, such as infertility, attract more attention from doctors. However, when the patient does not report this complaint, it is common for professionals not to give due importance to the condition. Given the difficulties that some

physicians face in diagnosing, professional competence and experience become essential for the correct identification of endometriosis (SILVA et al, 2021).

The clinical manifestations have a direct impact on the quality of life of the affected patients, both psychologically, bringing effects on their relationships, and on their productivity, impairing their performance at work and at home. Regarding the impairment of their work activity, most women report that they find it difficult to effectively exercise their profession, which generates frustration, indisposition, shame and concern. A significant portion of the patients reported needing to be absent from their work activities due to the pain presented.

With regard to the sexual sphere, a significant portion of the women reported avoiding the practice of sex due to deep dyspareunia, which generates feelings of guilt and frustration. On the other hand, some women report sexual activity even in the presence of pain, with the sole intention of satisfying their partner, fearing that marital relations will be weakened. The sexual act without pleasure and with pain is a strong cause of anxiety and depression.

These losses, both in the sphere of work and in the sphere of relationships, show that the disease goes far beyond pain, causing losses in the quality of life of women, psychologically affecting these women around the world as a result of their limitations (RODRIGUES et al, 2022).

According to Blamble et al (2021) approximately 50% of women with severe endometriosis report spending full days in bed due to the symptoms of this condition, on average, these women spend about 18 days a year in this way. In addition, medical costs are more than three times higher in these women than in women without endometriosis.

Brazilian Bill 1069/23 includes endometriosis with a disabling manifestation in the list of diseases that do not depend on a grace period for the granting of sickness benefit and disability retirement. The text determines that women affected by the disease have comprehensive treatment by the Unified Health System (SUS) with multidisciplinary care, access to complementary exams, pharmaceutical assistance and access to recognized therapeutic modalities, including physiotherapy and physical activity.

Depression is reported in more than half of women with chronic pain, most patients complain of irritability, fatigue and somatic worry. This association is mainly due to the way each patient uses their cognitive structure to adapt to pain, but it is also related to the emotional and cognitive characteristics of each patient, making it difficult to adhere to the proposed treatment.

Social, cultural, and psychological factors are as important as biological factors in mediating pain processing. Although it is a subjective experience, pain is not an abstraction. It is experienced by someone who must be respected and understood in its reality and totality for the treatment to be effective, with this being important for multidisciplinary care, with psychology having the role of rescuing the quality of life that was affected in the patient's life (LORENÇATTO et al, 2002).

In the case of local symptoms, in cases of bladder endometriosis (presence of glands and/or stroma in the bladder peritoneum, in the bladder serosa, or invading the bladder detrusor muscle) the present is often severe, being manifested in the form of suprapubic discomfort, dysuria, frequency, urinary urgency and hematuria (TOBIAS-MACHADO et al, 2001).

Like bladder endometriosis, the presence of foci of the disease in the intestinal wall may not generate symptoms. However, when reported, they usually include abdominal or pelvic pain, rectal pain, diarrhea, constipation, tenesmus, rectal bleeding (cyclical or not), and symptoms of bowel obstruction. Generally, these symptoms are more intense during the menstrual period (MAGNO-JUNIOR et al, 2011).

According to Anvisa's Health and Economy Bulletin published in December 2014, the treatment costs per semester taking into account the dosage of GNRH analogues, such as goserrelin, leuporrelin and triptorelin, for the relief of symptoms is approximately 4 thousand reais. In addition, the difference between the most expensive (reference) and the cheapest (similar) medicine per semester reaches 40%.

Therefore, regardless of the site of the disease, endometriosis has a considerable economic impact on society as a result of the delay in diagnosis after the onset of symptoms, expensive clinical and surgical medical treatments, and the chronicity of the disease, which can lead to several hospitalizations, and the indirect costs associated with the reduction in quality of life and work ability (BANDEIRA et al, 2024).

DIAGNOSIS OF ENDOMETRIOSIS

The diagnosis of endometriosis is often delayed because symptoms, such as pelvic pain and/or infertility, are also associated with other conditions (HORNE & SAUNDERS, 2019; ZONDERVAN et al., 2020). Although the diagnosis of some types of endometriosis can be accelerated by the use of imaging techniques, to date, progress towards the validation of a robust non-invasive blood test has been slow and much discussed (RIŽNER, 2014).

To treat endometriosis effectively, it is crucial to identify the problem quickly so that a comprehensive treatment approach can be initiated according to the patient's needs and preferences. This involves a thorough review of the medical history, physical examination when appropriate, and referral for tests such as transvaginal ultrasound and/or MRI (CRUMP et al, 2024).

CLINICAL HISTORY

Endometriosis can be asymptomatic in up to 22% of women, but in most cases, the symptoms involve dysmenorrhea, dyspareunia, non-cyclic pelvic pain, dyschesia, dysuria, changes in bowel habits, and often infertility.

However, the clinical presentation is very variable and none of these symptoms are specific to endometriosis, making it difficult to diagnose. Initially, endometriosis is investigated based on the patient's clinical history, asking about symptoms, personal and family history. However, because of the varied symptomatology, the similarity of symptoms among various gynecological diseases, the lack of a pathognomonic clinical finding, the high prevalence of asymptomatic endometriosis, and its weak correlation with disease severity, this type of diagnosis is inconclusive.

A complete history with the identification of symptoms highly suggestive of endometriosis, although not of great diagnostic significance, may be important to determine a high-risk group for endometriosis. Thus, only this group will be conducted for detailed diagnostic procedures. In addition, identifying the high-risk population will increase the specificity and sensitivity of subsequent diagnostic tests of endometriosis (FEBRASGO, 2021).

PHYSICAL EXAMINATION

Physical evaluation is essential when endometriosis is suspected, helps the physician further refine the differential diagnosis for the presenting complaint(s), and helps direct the appropriate imaging that may be required. Findings such as bulges or darkened areas in the posterior cul-de-sac after a speculum examination may indicate the presence of the disease. If the uterus has poor mobility with bimanual digital touch, this may suggest pelvic adhesions. Painful nodules, usually located in the posterior cul-de-sac, associated with retrocervical lesions, in the uterosacral ligaments, or even in intestinal organs, may also be observed. The presence of fixed and painful adnexa, along with the detection of adnexal masses, may be indicative of endometriomas in the ovaries (PODGAEC et al, 2018).

SUCKER EXAMS

There are different serum markers raised by the scientific community that could help the attending physician to identify patients in the early stages of endometriosis. One of these markers is interleukin-6 (IL-6), a glycoprotein secreted by several cell types, including peritoneal macrophages, endometrial stromal cells, and adipose tissue. IL-6 is a marker of acute phase inflammation and affects several biological activities, such as the induction of vascular endothelial growth factor expression and the growth and differentiation of B lymphocytes, as well as activating T lymphocytes. In addition, IL-6 plays an important role in reproductive physiology, as it regulates folliculogenesis, ovarian steroid production, and various early events associated with implantation.

Another serum marker is the CA-125 antigen, which serves as a biological marker of ovarian cancer, but other neoplasms can also present an elevation of Ca-125, including those originating in the endometrium, fallopian tubes, lungs, breast, and gastrointestinal tract. In normal women, plasma concentrations of Ca-125 are slightly higher at ovulation and significantly higher during menstruation. Serum levels of Ca-125 may be elevated in women with moderate and severe endometriosis in the presence of ovarian endometriomas and/or deep endometriosis lesions. Despite being a non-specific marker for the disease, increased levels associated with a good anamnesis and physical examination suggest the presence of endometriosis (RBGO, 2013).

Therefore, it is suggested that the CA-125 antigen, in addition to being a biological marker for several neoplasms, is also used as a nonspecific marker for the presence of deep endometriosis and disease activity.

IMAGING TESTS

Transvaginal ultrasound (SVT) and magnetic resonance imaging (MRI) are the imaging tests classically used for the detection of endometriotic lesions. In a study that aimed to evaluate the sensitivity and diagnostic specificity of both in the detection of ovarian endometriomas in patients with suspected endometriosis, high accuracy was shown in both diagnostic methods, in addition to the absence of a statistically significant difference between the two modalities (ALCÁZAR et al, 2023; KANTI et al, 2024).

SVT has as a positive factor its low cost, being widely accessible, and enabling preoperative planning in cases where surgical treatment is necessary. The evaluation of SVT is performed with standardized and well-established protocols, the most used technique is based on four stages. In the first stage, the uterus and the adnexa were evaluated by suprapubic approach, in the second stage, the mobility of the uterus and the

ovaries was verified. The third step is to look for markers: fixation of the ovaries and local sensitivity, then the "sliding signal" is evaluated (observation of the sliding of the anterior rectum freely on the posterior aspect of the cervix and posterior of the vagina). Finally, the fourth stage is to look for hypoechoic nodules or irregularities in the anterior and posterior compartments. Transvaginal ultrasound exams are done with bowel preparation, so oral laxatives are recommended the day before the exam and/or fleet enema a few hours before the procedure (OLIVEIRA et al, 2019).

MRI allows the identification of lesions hidden between adhesions and the extent of subperitoneal lesions, which cannot be visualized laparoscopically. Its accuracy, sensitivity, and specificity for detecting deep endometriosis exceed 90%. MRI follows specific protocols, and is usually performed during the menstrual period, with the bladder full. Before the exam, intravenous antispasmodic drugs are administered, and vaginal and rectal aqueous gel are introduced. The sequences include T1- and T2-weighted images in different planes, with fat suppression, and after gadolinium administration, more T1-weighted images with fat suppression are made (COUTINHO JUNIOR et al, 2008).

A study by Berger et al (2019) conducted the use of MRI after TVUS by evaluating the percentage change in the sensitivity and specificity of lesion diagnosis in patients with suspected endometriosis. An advantage of TVUS was observed, as it is dynamic and capable of assessing pelvic organ mobility and specific pain sites, which contributes to disease staging compared to MRI. Despite this, the study highlights that US is more operator-dependent, so this advantage may vary.

TVUS has excellent sensitivity and specificity in the diagnosis of ovarian endometrioma, especially in lesions larger than 2 cm. In a study by Guerriero et al (2018), they reported sensitivity of 97%, specificity of 90%, and positive and negative predictive value of 95%.

The usual appearance of endometriomas on TVUS is in the form of a cyst with thick content, with multiple points of medium intensity distributed homogeneously ("ground-glass" pattern); amorphous hyperechoic areas in the periphery, without Doppler flow and with poorly defined boundaries (older blood organized); parietal hyperechoic points (about 50% of cases); and septa.

The main differential diagnoses are: functional cysts (especially hemorrhagic cysts); abscess and neoplasm. The content aspect is the most important criterion for differentiating between the various types of cysts. Color Doppler mainly helps to detect or rule out vascularized solid areas, which are a strong indication of neoplasia. In cases that are

doubtful to TVUS, MRI is the indicated test to continue the investigation (FEBRASGO, 2018).

Studies have shown that magnetic resonance imaging and transvaginal ultrasound with preparation should be taken into account once the diagnosis is being made, since they help even in minimal lesions. Thus, these imaging tests can help and have the same accuracy, with ultrasonography being more operator-dependent and resonance imaging is more expensive and more complex to be performed.

Therefore, disease work-up is based on a thorough history, accurate physical examination, plasma markers (especially CA125) that suggest disease activity and chronic inflammation, and imaging (MRI and TVUS). The definitive diagnosis is obtained through the anatomopathological examination of the lesions.

ENDOMETRIOSIS AND INFERTILITY, A UNIVERSE APART

Endometriosis is a condition strongly related to infertility, and the mechanisms that explain this relationship follow four main paths: mechanical obstruction by pelvic adhesions; local/systemic inflammatory processes accompanied by elevation of cytokines in the peritoneal fluid; altered hormonal profile and genetic polymorphisms. (VASSILOPOULOU et al, 2018).

When it comes to local inflammation, studies suggest that it favors the formation of adhesions, generating a vicious cycle of inflammation. In women with endometriosis, retrograde blood flow during menstruation causes the release of inflammatory mediators by macrophages, dendritic cells, and mast cells, causing vasodilation and increased vessel permeability. This leads to leukocyte infiltration into the tissue, creating an unfavorable environment that affects folliculogenesis, sperm transport, and implantation. In addition, increasing IL-6 in follicles reduces the conversion of androgens to estrogens (TANBO & FEDORCSAK, 2017).

In pelvic endometriosis, activated macrophages in the peritoneal cavity produce cytokines, growth factors, and prostaglandins, the resulting oxidative stress causes lipid hyperoxidation, generating substances such as malondialdehyde, which can be recognized as foreign and trigger the production of antibodies. This leads to the destruction of red blood cells and endometrial cells in the peritoneum, reinforcing the process. Through circulation, these substances can reach the ovaries, affecting the maturation of oocytes.

In women with endometriosis, the hormonal profile is altered by various mechanisms, the function of the pituitary-ovarian axis is impaired, with a prolonged follicular phase and changes in luteinizing hormone (LH) secretion, including delayed or biphasic LH spikes. In

these patients, the number of preovulatory follicles, follicular development, and estradiol levels are lower. In addition, the follicular fluid has altered hormone levels, with a reduction in estrogen, androgen and progesterone, and an increase in activin. (VASSILOPOULOU et al, 2018).

Progesterone resistance can be caused by genetic polymorphisms, changes in microRNA expression, and epigenetic changes (such as toxin exposure and retinoid resistance). It has been suggested that increased progesterone signal generates a pro-inflammatory phenotype, while chronic inflammation, in turn, contributes to progesterone resistance, establishing a bidirectional relationship between these processes (VASSILOPOULOU et al, 2018).

Additionally, it is important to highlight that endometriosis is associated with low ovarian response, characterized by a reduction in antral follicle count and in the number of oocytes recovered in IVF cycles. The competence of the oocyte indicates its ability to mature and be fertilized. Ovarian endometrioma, unlike other endometriosis phenotypes, directly affects the ovaries, causing mechanical stress, stiffness, and distortion of the anatomy, which impairs blood flow and innervation. This is related to decreased oocyte quality and ovarian reserve.

In patients with ovarian endometrioma who want to start assisted reproduction treatment, surgery to remove the ovarian endometrioma before IVF/ICSI has not shown clear benefits in embryo transfer outcomes. The endometriotic tissue present in the endometrioma can release substances such as cytokines, chemokines, and growth factors, activating signaling pathways in follicular cells that result in premature follicle development and accelerated atresia. As the number of viable embryos influences the chances of transfer, this reduction decreases the chances of pregnancy. (LI et al, 2020).

Studies also show a higher risk of miscarriage in women with endometriosis who become pregnant with spontaneous conception or in vitro fertilization when compared to the population free of the disease (HORTON et al, 2019; HUANG et al, 2020).

Thus, it can be concluded that endometriosis exerts a significant impact on female fertility through several mechanisms. Mechanical obstruction caused by pelvic adhesions and the presence of ovarian endometriomas directly compromise oocyte quality and ovarian reserve. In addition, inflammatory processes and hormonal changes contribute to an environment that is less favorable to fertilization and embryo implantation. Oxidative stress is also a relevant factor that impairs the proper maturation of oocytes. Thus, advanced endometriosis is associated with a reduction in the probability of conception, highlighting the need for effective diagnosis and management to minimize these adverse effects.

ADENOMIOSE

Adenomyosis is a benign alteration of the uterus that histologically is characterized by benign invasion of the endometrium into the myometrium, in addition to 2.5 mm in depth with the presence of endometrial glands and stroma surrounded by hyperplasia and hypertrophy of the myometrial cells. Classically, diagnostic confirmation of adenomyosis is performed in hysterectomy specimens. However, without a consensus established in the medical literature, currently with the advancement of imaging studies, some groups have proposed that the diagnosis of the disease can be radiological. The clinical presentation of the disease is variable, as well as its impact on the woman's life. Progress in research is hampered by the need for histological diagnosis and the absence of consensus regarding its classification (FEBRASGO, 2021).

Adenomyosis presents a heterogeneous clinical picture, with increased uterine bleeding and dysmenorrhea as the most frequent symptoms, affecting 65% of cases. Classified by FIGO (International Federation of Gynecology and Obstetrics) as a cause of abnormal uterine bleeding, adenomyosis can be associated with infertility due to the impairment of the uterine wall, the decrease in ovarian reserve and the reduced endometrial receptivity to the embryo. In addition, women with adenomyosis may have other conditions, such as leiomyomas and pelvic endometriosis. Although many have nonspecific symptoms, about one-third of patients may be asymptomatic. The severity of symptoms, such as bleeding and pain, may correlate with the depth of myometrial infiltration.

The association between adenomyosis and infertility has been proven in multiple studies, with a prevalence of 1% to 14% of infertile patients according to the literature. Functional and structural alterations resulting from adenomyosis seem to be related to embryonic implantation failure and consequent infertility. Therefore, adenomyosis is a disease with a negative impact on fertility.

Several mechanisms negatively affect women's reproductive health, from molecular changes to changes in uterine structure. Some studies suggest that destruction of the architecture of the myometrial junction zone may impair sperm transport, while others point to changes in endometrial vascularization that affect implantation. In addition, molecular abnormalities, failures in the expression of adhesion proteins, genetic alterations, and elevated levels of free radicals in the uterine cavity are reported. Assisted reproduction techniques are an effective way to mitigate the impact of adenomyosis on fertility, and it is sometimes recommended to use GnRH agonists or contraceptives continuously prior to embryo transfer in an attempt to optimize reproductive outcomes.

In addition, adenomyosis has been linked to higher chances of miscarriage in women who have undergone IVF, significantly affecting embryo implantation. Endometriosis and adenomyosis often occur together, and oxidative stress and problems in free radical metabolism can compromise uterine receptivity in both conditions. The abnormal endometrial environment and endometrial dysfunction in these diseases contribute to adverse pregnancy outcomes due to hormonal, metabolic, and inflammatory changes. (HUANG Y et al, 2020).

TREATMENT OF ENDOMETRIOSIS

The approach to dealing with pain needs to be individualized for each patient, the goal is to relieve pain by reducing inflammation, as well as hormonal activity in the affected area. In general, medical treatment is not aimed at cure, but rather at suppression of symptoms, and often symptoms return when therapy is stopped. The rate of reappearance of endometriosis varies considerably, ranging from 4% to 74% (NEZHAT et al, 2019).

Conservative treatment

The use of oral hormonal contraceptives (ACHO) on a continuous basis is a first-line treatment in the management of the disease, as it blocks the menstrual cycle and stops the production of ovarian estrogen, inhibiting the growth and development of endometrial lesions (PAŠALIĆ et al, 2023). Pharmacologically, the (ACHO) act by blocking the development of endometriosis lesions by reducing the production of estrogen in the ovaries, through a process of negative feedback in the hormonal system that involves the hypothalamus, the pituitary gland and the reproductive organs. This leads to a decrease in the production of prostaglandins, which play a crucial role in the inflammatory response associated with endometriosis (YONG et al, 2020). It is worth noting that these therapies have a contraceptive effect and, therefore, are not recommended for women who wish to become pregnant (ALLAIRE et al, 2023).

On the other hand, Dienogest, a fourth-generation progestogen, which has received approval for the treatment of endometriosis in many countries, has been recommended for the treatment of painful symptoms of endometriosis lesions, the prevention of symptoms and the reduction of recurrence of the lesion.

From a pharmacological point of view, this progesterone acts mainly locally on endometriotic lesions, manifesting anti-estrogenic and, to a lesser extent, glucocorticoid or mineralocorticoid activity. In addition, it has anovulatory and antiproliferative effects. It also exerts a moderate inhibition on gonadotropin secretion, resulting in decreased natural

estradiol production. This reduction stimulates decidualization of the ectopic endometrium, leading to its subsequent atrophy.

In addition, the drug inhibits endometrial cell proliferation by modulating the expression of matrix metalloproteinases and aromatase, which play crucial roles in the ectopic endometrial response to endogenous estrogen. Studies have shown that it has comparable efficacy to GnRH agonists in reducing endometriosis-related pain and fewer side effects from hypoestrogenism. Therefore, its long-term use is considered viable. Still, some patients may experience some side effects such as changes in bleeding patterns and various symptoms related to hormones (such as weight gain, mood swings, and androgenic effects). However, these are generally well tolerated and are not the main causes of treatment interruption (LEE et al, 2023).

More recently, gestrinone has been shown to be an effective and well-tolerated drug for patients with endometriosis. This progesterone induces endometrial atrophy and/or amenorrhea, and results in decreased menstrual pain, pelvic discomfort, and changes in ovarian structure. As for the adverse effects recorded, gestrinone demonstrated a greater propensity to develop acne and skin oiliness compared to other therapeutic options, due to its andogenic effects. (DE SOUZA PINTO et al, 2023).

Therefore, it can be concluded that ACHO, especially when used continuously, is a first-line approach in the treatment of endometriosis, as they inhibit the menstrual cycle and estrogen production, reducing the growth of endometrial lesions. Combined hormonal contraceptives and Dienogest (DNG) have been shown to be effective in reducing pain and preventing recurrence of lesions. Acting locally, diegnost modulates the endometrial response to estrogen and has fewer side effects compared to GnRH agonists, although it can still cause some adverse reactions. Gestrone, an anti-estrogen, is also effective, promoting endometrial atrophy and pain relief, but it may be associated with side effects such as acne. These hormone therapies are effective in managing endometriosis, although they are not recommended for women who want to become pregnant.

Invasive treatment

According to Ordinance No. 879, of July 12, 2016 of the Ministry of Health, surgery is recommended when symptoms are intense and disabling, when there is no response to conservative treatment, or in cases of endometriomas, changes in pelvic anatomy, adhesions, intestinal or urinary obstructions, and for patients with infertility linked to endometriosis.

The surgery is divided into conservative or definitive, conservative surgery consists of eliminating the foci of endometriosis and removing adhesions, restoring the pelvic anatomy. This procedure results in a significant reduction in pain within 6 months for patients undergoing therapeutic laparoscopy, compared to those who are only monitored, regardless of the severity of endometriosis. Definitive surgery, on the other hand, includes a hysterectomy, with or without oophorectomy, depending on the patient's age. Hysterectomy with bilateral salpingoophorectomy and removal of all endometriosis foci is recommended in cases of severe disease, disabling symptoms that persist after drug treatment or conservative surgery, presence of other pelvic conditions that warrant hysterectomy, and when the patient no longer wishes to become pregnant.

Surgeries to treat endometriosis have historically been performed through open surgery, but in recent decades videolaparoscopy has become the predominant technique. Endometriotic lesions can be eliminated or removed through excision, diathermy or ablation/vaporization. The main goal of these interventions is to reduce and release adhesions to restore normal pelvic anatomy. In addition, some doctors use the interruption of the pelvic nerve pathway to try to reduce the intensity of pain (SADLOCHA et al, 2024). The treatment of endometriosis by videolaparoscopy is feasible and safe, with low recurrence rates (COSTA et al, 2010).

Thus, studies suggest that surgery is a crucial approach in the treatment of endometriosis, especially when the symptoms are intense and do not respond to conservative treatments. This intervention can be conservative, focusing on the removal of lesions, or definitive, such as hysterectomy, indicated in severe cases or when the patient does not wish to become pregnant. Videolaparoscopy is the preferred technique, with good results in pain reduction and recovery of pelvic anatomy, with variable recurrence rates, making it a viable and safe option in the management of endometriosis.

Treatment for Infertility

The management of endometriosis in patients with infertility is controversial, considering factors such as clinical presentation, age, and duration of infertility. Long-term hormone treatment to suppress ovulation is not recommended as it does not improve fertility. Surgery is an alternative to improve fertility, especially by removing the foci of the disease in stages I and II. In stages III and IV, the surgical indication is well established, although it can increase the chances of success in the face of in vitro fertilization. In cases of ovarian endometriomas, surgery is indicated for large cysts, uncertain diagnoses, pain control, or to facilitate egg retrieval, with a preference for removing the cyst capsule

(FEBRASGO, 2021). With everything it is suggested that the most effective treatment is GnRH analogues or combined oral contraceptives used for reduced periods prior to IVF, and surgery is an alternative to remove the foci of the disease, especially in stages I and II to improve infertility.

The laparoscopic surgical approach has traditionally been seen as the treatment of choice for endometriosis-associated infertility. Its goal is to eliminate the visible lesions of endometriosis and restore the normal anatomy of the pelvis. Without intervention, it is estimated that about half of women with mild endometriosis manage to get pregnant, while only about a quarter of women with moderate endometriosis and a few with severe endometriosis succeed in their reproductive journey (COCCIA et al, 2022).

Although videolaparoscopy guarantees better results in terms of quality of life for patients, these results require the complete removal of the disease, which can often lead to intra- and postoperative complications, especially when any type of intestinal surgery must be performed. The incidence of complications will vary in relation to the degree of classification of the disease and the type of surgery that is performed (KONDO et al., 2010).

However, it is concluded that about half of women with mild endometriosis manage to become pregnant, and with the progression of the disease this chance decreases, so the performance of videolaparoscopy to remove the disease with intra and postoperative complications varies according to their classification and type of surgery.

The rate of intraoperative and postoperative complications is different, although both depend on the severity of the disease and the experience of the surgeon and the service. Intraoperative complications happen more rarely, while postoperative complications are a little more frequent. Regarding the types of procedures performed, the rates are higher when there is excision of rectovaginal nodules associated with resection and intestinal anastomosis, which will cause rectovaginal fistulas, stenosis of intestinal anastomosis and use of ostomies. Other complications are: bleeding requiring conversion to open surgery, ureteral injury/fistula, nerve injuries, vaginal/uterine perforation, low anterior resection syndrome (LARS), pelvic abscess, non-pathological fever, postoperative abdominal pain, urinary tract infection, emptying pain, and urinary retention (KONDO et al., 2010; PANEL et al., 2016; DUBERNARD et al., 2006).

Initially, assisted reproductive therapy (ART) to treat endometriosis-linked infertility was recommended mainly in cases of tubal problems. However, recent advances in ultrasound diagnosis and improvements in ART laboratories have impacted the way infertility-related endometriosis is approached. Currently, ART is considered one of the first treatment options and plays a crucial role in this context (COCCIA et al, 2022).

When it comes to the effect of endometriosis on the IVF/ICSI outcome, women with stage III/IV endometriosis had lower IVF/ICSI results compared to those with milder forms of the disease or tubal infertility. More than half of women with minimal or mild endometriosis were able to have a baby, while only 40% of women with stage III/IV endometriosis gave birth after one to four cycles of IVF/ICSI. Treatment success tends to increase slowly, but the discomfort caused by ovarian stimulation can be an obstacle, especially when disease activity worsens during treatment (KUIVASAARI P et al, 2005).

Thus, a contemporary worldwide trend is observed regarding the indication of IVF for patients with moderate/severe endometriosis, either in isolation in search of conception or after videolaparoscopy.

CONCLUSION

Through the present review, endometriosis poses a significant challenge not only for affected women, but also for society as a whole, due to its economic impact and quality of life. Early diagnosis is hampered by the variability of symptoms and the lack of specificity, which requires a careful and comprehensive approach in the investigation of the disease. The identification of high-risk groups and the use of diagnostic markers, in addition to imaging methods, are essential for effective management.

Hormone treatment, while effective in reducing symptoms, should be carefully considered, especially in women who wish to become pregnant. Therefore, raising awareness about endometriosis and improving diagnostic and treatment protocols are essential to minimize the adverse effects of the disease and provide adequate support to affected women.

Surgery for endometriosis is a crucial intervention when symptoms are severe and do not respond to conservative treatments, especially in cases of endometriomas, adhesions, or infertility. The choice between conservative and definitive surgery depends on the severity of the condition and the patient's needs. Videolaparoscopy stands out as the preferred technique, providing good results in pain reduction and restoration of pelvic anatomy, with low recurrence rates.

Although surgery can improve fertility in early stages of the disease, the approach must be carefully planned, considering potential complications and the classification of endometriosis. Assisted reproductive therapy also plays an essential role in the management of endometriosis-associated infertility, especially in more advanced cases. Therefore, an integrated approach that considers both surgical intervention and fertility

options is critical for the effective care of affected women and improvement in their quality of life.

ACKNOWLEDGMENTS

To all those who contributed, in some way, to the realization of this work.

REFERENCES

1. Alcázar, J. L., Vara, J., Usandizaga, C., Ajossa, S., Pascual, M. Á., & Guerriero, S. (2023). Transvaginal ultrasound versus magnetic resonance imaging for diagnosing adenomyosis: A systematic review and head-to-head meta-analysis. *International Journal of Gynaecology and Obstetrics, 161*(2), 397-405. https://doi.org/10.1002/ijgo.14609

2. Allaire, C., Bedaiwy, M. A., & Yong, P. J. (2023). Diagnóstico e tratamento da endometriose. *CMAJ, 195*(10), E363-E371. https://doi.org/10.1503/cmaj.220637

3. Aplicações de ultrassonografia no diagnóstico de endometriose. (2018). FEBRASGO.

4. Bandeira, C., Costa Filho, A., Maia, A. C., Azevedo, L. K. S. A. de, Ferreira, M. B. B., & Gomes, N. D. do B. (2024). Endometriose e o impacto na sexualidade feminina. *Research, Society and Development, 13*(4), e10013445591. https://doi.org/10.33448/rsd-v13i4.45591

5. Berger, J. P., Rhemrev, J., Smeets, M., Henneman, O., English, J., & Jansen, F. W. (2019). Limited added value of magnetic resonance imaging after dynamic transvaginal ultrasound for preoperative staging of endometriosis in daily practice: A prospective cohort study. *Journal of Ultrasound in Medicine, 38*(4), 989-996. https://doi.org/10.1002/jum.14783

6. Blamble, T., & Dickerson, L. (2021). Reconhecendo e tratando a endometriose. *JAAPA, 34*(6), 14-19. https://doi.org/10.1097/01.JAA.0000750940.47126.58

7. Chapron, C., Marcelino, L., Borghese, B., & Santulli, P. (2019). Repensando mecanismos, diagnóstico e manejo da endometriose. *Nature Reviews Endocrinology.* https://doi.org/10.1038/s41574-019-0245-z

8. Coccia, M. E., Nardone, L., & Rizzello, F. (2022). Endometriosis and infertility: A long-life approach to preserve reproductive integrity. *International Journal of Environmental Research and Public Health, 19*, 6162. https://doi.org/10.3390/ijerph19106162

9. Costa, L. M. P., Ávila, I. de, Filogonio, I. D. S., Machado, L. G. R., & Carneiro, M. M. (2010). Tratamento laparoscópico de 98 pacientes com endometriose intestinal. *Revista Brasileira de Colo-Proctologia, 30*(1), 31–36. https://doi.org/10.1590/S0101-98802010000100004

10. Coutinho Junior, A. C., Lima, C. M. A. de O., Coutinho, E. P. D., Ribeiro, É. B., Aidar, M. N., & Gasparetto, E. L. (2008). Ressonância magnética na endometriose pélvica profunda: Ensaio iconográfico. *Radiologia Brasileira, 41*(2), 129–134. https://doi.org/10.1590/S0100-39842008000200013

11. Crump, J., Suker, A., & White, L. (2024). Endometriose: Uma revisão de evidências e diretrizes recentes. *Australian Journal of General Practice, 53*(1-2), 11-18. https://doi.org/10.31128/AJGP/04-23-6805

12. de Souza Pinto, L. P., Ferrari, G., Dos Santos, I. K., de Mello Roesler, C. R., & de Mello Gindri, I. (2023). Avaliação da segurança e eficácia da gestrinona no tratamento da endometriose: Uma revisão sistemática e meta-análise. *Archives of Gynecology and Obstetrics, 307*(1), 21-37. https://doi.org/10.1007/s00404-022-06846-0

13. Dubernard, G., Piketty, M., Rouzier, R., Houry, S., Bazot, M., & Darai, E. (2006). Quality of life after laparoscopic colorectal resection for endometriosis. *Human Reproduction, 21*(5), 1243–1247. https://doi.org/10.1093/humrep/dei491
14. Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO). (2021). Adenomiose. São Paulo: FEBRASGO. (Protocolo FEBRASGO-Ginecologia, n. 77/Comissão Nacional Especializada em Endometriose).

15. Filho, A. L. S. (2019). *Tratado de Ginecologia FEBRASGO* (1. ed.). Rio de Janeiro: Elsevier.

16. Guerriero, S., Saba, L., Pascual, M. Á., Ajossa, S., Rodriguez, I., Mais, V., & Alcázar, J. L. (2018). Transvaginal ultrasound vs magnetic resonance imaging for diagnosing deep infiltrating endometriosis: Systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology, 51*(5), 586-595. https://doi.org/10.1002/uog.18961

17. Horne, A. W., & Saunders, P. T. K. (2019). SnapShot: Endometriosis. *Cell, 179*(7), 1677-1677.e1. https://doi.org/10.1016/j.cell.2019.11.033

18. Horton, J., Sterrenburg, M., Lane, S., Maheshwari, A., Li, T. C., Cheong, Y. (2019). Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: A systematic review and meta-analysis. *Human Reproduction Update.* https://doi.org/10.1093/humupd/dmz012

19. Huang, Y., Zhao, X., Chen, Y., Wang, J., Zheng, W., & Cao, L. (2020). Miscarriage on endometriosis and adenomyosis in women by assisted reproductive technology or with spontaneous conception: A systematic review and meta-analysis. *Biomedical Research International, 2020,* Article 4381346. https://doi.org/10.1155/2020/4381346

20. Kanti, F. S., Gorak Savard, R., Bergeron, F., Zomahoun, H. T. V., Netter, A., & Maheux-Lacroix, S. (2024). Ultrassonografia transvaginal e ressonância magnética no diagnóstico de endometrioma: Uma revisão sistemática e meta-análise de estudos de precisão de testes diagnósticos. *Journal of Obstetrics and Gynaecology, 44*(1), 2311664. https://doi.org/10.1080/01443615.2024.2311664

21. Kondo, W. et al. Endometriose pélvica – Uma pesquisa de conhecimento e prática entre ginecologistas.

22. Kuivasaari, P., Hippeläinen, M., Anttila, M., & Heinonen, S. (2005). Effect of endometriosis on IVF/ICSI outcome: Stage III/IV endometriosis worsens cumulative pregnancy and live-born rates. *Human Reproduction, 20*(11), 3130-3135. https://doi.org/10.1093/humrep/dei176

23. Lee, J., Park, H. J., & Yi, K. W. (2023). Dienogest no tratamento da endometriose: Uma revisão narrativa da literatura. *Clinical and Experimental Reproductive Medicine, 50*(4), 223-229. https://doi.org/10.5653/cerm.2023.06128

24. Levantamento revela diferença de 40% no custo do tratamento da endometriose - cosmetovigilancia - Anvisa. (n.d.). Gov.br. Retrieved September 25, 2024, from https://antigo.anvisa.gov.br/resultado-debusca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=colmn1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=223487&_101_type=content&_101_groupId=219201&_101_urlTitle=levantamento-reveladiferenca-de-40-no-custo-do

25. Li, A., Zhang, J., Kuang, Y., & Yu, C. (2020). Analysis of IVF/ICSI-FET outcomes in women with advanced endometriosis: Influence on ovarian response and oocyte competence. *Frontiers in Endocrinology, 11*, 427. https://doi.org/10.3389/fendo.2020.00427

26. Lorençatto, C., Vieira, M. J. N., Pinto, C. L. B., & Petta, C. A. (2002). Avaliação da frequência de depressão em pacientes com endometriose e dor pélvica. *Revista da Associação Médica Brasileira, 48*(3), 217–221. https://doi.org/10.1590/S0104-42302002000300033

27. Magno-Junior, C., Batista, C. A. M., Leite, G. F., Paula, J. F. de, Kim, M. P., Batista, A. L. E., et al. (2011). Obstrução intestinal causada por endometriose. *ABCD, Arquivos Brasileiros de Cirurgia Digestiva, 24*(4), 336–338. https://doi.org/10.1590/S0102-67202011000400017

28. Ministério da Saúde. (2016). *Portaria Nº 879, de 12 de julho de 2016*.

29. Nezhat, C., Vang, N., Tanaka, P. P., & Nezhat, C. (2019). Tratamento ideal da endometriose e da dor. *Obstetrícia e Ginecologia, 134*(4), 834–839. https://doi.org/10.1097/AOG.0000000000003461

30. Oliveira, J. G. A. de, Bonfada, V., Zanella, J. de F. P., & Coser, J. (2019). Transvaginal ultrasound in deep endometriosis: Pictorial essay. *Radiologia Brasileira, 52*(5), 337–341. https://doi.org/10.1590/0100-3984.2018.0019

31. Painel, P., Huchon, C., Estrade-Huchon, S., et al. (2016). Sintomas da bexiga e observações urodinâmicas de pacientes com endometriose confirmada por laparoscopia. *International Urogynecology Journal, 27*, 445–451. https://doi.org/10.1007/s00192-015-2848-9

32. Pašalić, E., Tambuwala, M. M., & Hromić-Jahjefendić, A. (2023). Endometriosis: Classification, pathophysiology, and treatment options. *Pathology Research and Practice, 251*, 154847. https://doi.org/10.1016/j.prp.2023.154847

33. Podgaec, S., Caraça, D. B., Lobel, A., Bellelis, P., Lasmar, B. P., Lino, C. A., et al. (2018). *Protocolo FEBRASGO - Ginecologia, no. 32/Comissão Nacional Especializada em Endometriose*. Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO).

34. Portal da Câmara dos Deputados. (n.d.). *Leg.br*. Retrieved September 25, 2024, from https://www.camara.leg.br/proposicoesWeb/fichadetramitacao?idProposicao=2351149

35. Publicação oficial da Federação Brasileira das Associações de Ginecologia e Obstetrícia, 49(3), 2021.

36. Revista Brasileira de Ginecologia e Obstetrícia. (2013). Correlação entre os níveis de Ca-125 séricos e os achados cirúrgicos em mulheres com sintomas sugestivos de endometriose. DOI: S0100-7203(13)03500600005, *35*, Junho.

37. Rižner, T. L. (2014). Noninvasive biomarkers of endometriosis: Myth or reality? *Expert Review of Molecular Diagnostics, 14*(3), 365–385. https://doi.org/10.1586/14737159.2014.899905

38. Rodrigues, L. A., Almeida, S. A. de, Ferreira, G. N., Nunes, E. F. C., & Avila, P. E. S. (2022).

39. Sadłocha, M., Toczek, J., Major, K., Staniczek, J., & Stojko, R. (2024). Endometriosis: Molecular pathophysiology and recent treatment strategies—comprehensive literature review. *Pharmaceuticals (Basel), 17*(7), 827. https://doi.org/10.3390/ph17070827

40. Silva, C. M., Cunha, C. F. da, Neves, K. R., Mascarenhas, V. H. A., & Caroci-Becker, A. (2021). Experiências das mulheres quanto às suas trajetórias até o diagnóstico de endometriose. *Esc Anna Nery, 25*(4), e20200374. https://doi.org/10.1590/2177-9465-EAN-2020-0374

41. Santos, M. A. Modesto dos. (2005). *Terminologia em enfermagem*. São Paulo: Martinari.

42. Tanbo, T., & Fedorcsak, P. (2017). Infertilidade associada à endometriose: Aspectos dos mecanismos fisiopatológicos e opções de tratamento. *Acta Obstetricia et Gynecologica Scandinavica, 96*(6), 659–667. https://doi.org/10.1111/aogs.13082

43. Tobias-Machado, M., Di Giuseppe, R., Barbosa, C. P., Borrelli, M., & Wroclawski, E. R. (2001). Endometriose vesical: Aspectos diagnósticos e terapêuticos. *Revista da Associação Médica Brasileira, 47*(1), 37–40. https://doi.org/10.1590/S0104-42302001000100028

44. Vassilopoulou, L., Matalliotakis, M., Zervou, M., Matalliotaki, C., Spandidos, D., Matalliotakis, I., & Goulielmos, G. (2018). Endometriosis and in vitro fertilisation (Review). *Experimental and Therapeutic Medicine*. https://doi.org/10.3892/etm.2018.6307

45. Vila, A. C. D. (2007). A endometriose e sua relação com a infertilidade feminina e fatores ambientais.

46. Wang, P. H., Yang, S. T., Chang, W. H., Liu, C. H., Lee, F. K., & Lee, W. L. (2022). Endometriose: Parte I. Conceito básico. *Taiwanese Journal of Obstetrics and Gynecology, 61*(6), 927–934. https://doi.org/10.1016/j.tjog.2022.08.002

47. Yong, P. J., Alsowayan, N., Noga, H., Williams, C., Allaire, C., Lisonkova, S., & Bedaiwy, M. A. (2020). CHC for pelvic pain in women with endometriosis: Ineffectiveness or discontinuation due to side effects. *Human Reproduction Open, 2020*(2), hoz040. https://doi.org/10.1093/hropen/hoz040

48. Zondervan, K. T., Becker, C. M., & Missmer, S. A. (2020). Endometriosis. *New England Journal of Medicine, 382*(13), 1244–1256. https://doi.org/10.1056/nejmra1810764