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Endometriosis - A Medical Challenge: Impact on Fertility and Treatment Method

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Abstract:

Aim of study:

The subject of this review is to highlight the complexity of the disease known as endometriosis. This disease affects 10% of women of reproductive age, causing a number of symptoms of various origins, and additionally affects women's fertility, mental health and role in society. The work aims to systematize knowledge about endometriosis, the mechanism by which it affects fertility and possible therapies, including surgical methods and assisted reproductive technology (ART.). The issue of infertility associated with endometriosis is has not been fully explored yet. A personalized treatment plan including medication, surgical assisted reproductive techniques and psychological support should be developed to improve the quality of life of patients with endometriosis and enable them to become pregnant.

Material and methods:
A systematic review of scientific and medical literature from the PubMed and Google Scholar databases was conducted.

Results:
Currently, the most effective treatment for infertility is in vitro fertilization (IVF). Successful treatment of endometriosis-related infertility should be discussed in detail with each patient and the decision on the therapy plan should be individual and comprehensive.

Keywords: endometriosis, infertility, chronic pelvic pain, gynecology, IVF, IVI

Introduction

Endometriosis is a chronic and progressive disease. It affects approximately 10% of women of reproductive age worldwide. It leads to a heavy economic and social burden, causes pain, infertility, impaired quality of life and limits patients in many aspects of life. [1]
Endometriosis was first reported as early as 1860, and still remains a major diagnostic challenge for clinicians and patients. Unfortunately, because of various factors, women suffering from endometriosis often go undiagnosed for an average of about 7 to 12 years[1,2]. Approximately 60% of affected women will see 3 or more physicians before an accurate diagnosis is made [3]. Additionally, they often have to make an average of 7 visits to their primary care physician before they get a referral to a specialist. [4]
Unfortunately, teenage girls also suffer from increased symptoms - painful menstruation and chronic pelvic pain. Endometriosis has been diagnosed in 62-75% of young women undergoing laparoscopy for chronic pelvic pain (CPP) and/or painful menstruation. [5]

Definition

The pathophysiology of endometriosis stems from tissue similar to that of the endometrium existing outside of endometrial cavity. It is an estrogen-dependent condition that causes cyclic bleeding at the site of the ectopic tissue. During menstrual bleeding, the endometrial focus is subjected to a chronic inflammatory response. [1] Inflammatory lesions can occur in various locations. There are 3 types of endometriosis: superficial peritoneal endometriosis (SE), ovarian endometriosis (OE) and deep endometriosis (DE). In some cases, foci of endometriosis can occur on distant organs including the lungs, liver, brain. [3]

Symptoms and clinical implications

The symptoms of endometriosis are nonspecific and the disease may present differently in each patient. Symptoms can be troublesome cyclically or chronically. They include pelvic pain, painful and heavy menstrual bleeding, painful ovulation, dyspareunia, dysuria and infertility. Patients also report gastrointestinal symptoms that are difficult to diagnose, such as nausea, vomiting, constipation, diarrhea, flatulence, and pain during defecation. When foci of endometriosis are present in the lungs, diaphragm or pleura, patients may experience cyclic hemoptysis, pneumothorax and pulmonary nodules. Those symptoms are referred to as "thoracic endometriosis syndrome (TES)". Symptoms from the urinary system can also be present in patients. Endometriosis most often affects the bladder, and rarely occurs around the ureters or kidneys. Patients report dysuria, urinary urgency, frequent urination, and discomfort in the rectopubic region during urination. [5,6,7]

Common comorbidities include migraine, irritable bowel syndrome (IBS), chronic fatigue syndrome, fibromyalgia, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, uterine myomas and ovarian cysts. [3,8]

Endometriosis also significantly affects patients' relationships. Approximately 50-56% patients report that the disease has affected their intimate lives, and for 8-10% of patients it has caused the end of their relationships. [8]

Patients also suffer mental health consequences. Rates of anxiety and depression are higher than in a control group of healthy, non-endometriosis sufferers, increasing the risk of developing chronic pain. [6] Affected women report experiencing high fatigue, decreased productivity, and social isolation. Findings report that endometriosis is associated with greater use of pain medications and antidepressants. A 1.75-fold increase in direct medical costs in endometriosis patients has been reported. [4,9]

Diagnostics

Previously, the gold standard for diagnosing endometriosis was the commonly used laparoscopy, which allowed physicians to assess the extent of the lesions and preform a biopsy necessary for histopathological examination of the tissue to confirm its histological origin.

Unfortunately, this method generated a delay in diagnosing patients. Currently, in order to avoid prolonged waiting and possible complications after laparoscopy, non-invasive imaging techniques, i.e. transvaginal ultrasonography (TVS), transrectal ultrasonography (TRS) and magnetic resonance imaging (MRI) are used. These techniques have the advantage of being safer, as well as more accessible and quicker in terms of waiting time for the patients. With ultrasound, physicians can assess tenderness, mobility and localization of endometriosis foci. However, diagnostic methods also suffer from various disadvantages, such as the high false-negative rate of TVS and TRS. This may be due to fact that the ultrasound technicians or radiologists interpreting those imaging tests may not have sufficient experience in diagnosing endometriosis.

To make the diagnosis of endometriosis, it is necessary to take a thorough history from the patient, assess the level of pain with the Visual Analogue Scale(VAS scale), and perform a physical examination including pelvic and abdominal examination, speculum examination to evaluate posterior vaginal fornix (PVF), digital vaginal examination to assess the presence or absence of nodules within the uterosacral ligaments (USLs), torus uterinus, PVF, rectovaginal septum (RVS), low rectum and parametrium, as well as bimanual examination.

The results of physical examination depend on the experience of the examining physician in diagnosing endometriosis. Pelvic examination for endometriosis detection on its own has a low success rate.

Laparoscopic methods should be considered for patients with negative imaging results, persistent symptoms and ineffective treatment. They should no longer be considered the gold standard for the diagnosis of endometriosis. [10,11]

Classification

Symptoms do not correspond to the severity of the lesions. Some patients, despite the diagnosis of endometriosis, do not report any symptoms, There are currently 3 scales that are used in daily practice to describe endometriosis. [12]

The American Society of Reproductive Medicine's r-ASRM classification assesses the extent and severity of lesions. Stages I and II are mild types of endometriosis, while III and IV refer to advanced stages of the disease.

The #ENZIAN scale is a descriptive tool for assessing deep endometriosis. It evaluates the depth of lesion invasion, assigns grades to anatomical compartments, and categorizes ectopic foci based on their location.

EFI - the endometriosis fertility index, assessing the chance of spontaneous pregnancy after laparoscopy in women struggling with infertility associated with endometriosis. [13,14]

Infertility

One of the symptoms of endometriosis is infertility in patients with a multifactorial etiology. The association between endometriosis and infertility is well documented, with 30-50% of women with endometriosis struggling with infertility. Fertility rates in women with untreated endometriosis range from 2 to 10%. [15]

Women with severe endometriosis have a significantly higher risk of developing placenta previa, and deep infiltrating endometriosis is a risk factor for spontaneous bleeding and surgical complications during cesarean section. [16]

Infertility mechanisms

The inflammation resulting from endometriosis adversely affects oocyte production and ovulation in the affected ovary. This is due to the presence of cytokines, growth factors, prostaglandins and reactive oxygen species in the peritoneal fluid. The presence of peritoneal macrophages, which have the ability to produce pro-inflammatory mediators, promotes the recruitment of other immune cells. In addition, there is dysregulation of the progesterone receptor which reduces endometrial receptivity.

Inflammatory cells in the peritoneal fluid have a toxic effect on the embryo, as well as damaging oocytes and sperm. The presence of inflammation and increased number of cytokines impair the normal transport of gametes, disrupts the function and motility of the fallopian tubes. In addition, disturbances in the contractile function of the uterine muscle can adversely affect the transport and implantation of the embryo. [15,16,17]

The impact of endometriosis on ovarian reserve appears to be significant. To assess ovarian function, AMH (Anti-Müllerian Hormone) levels and AFC (antral follicle count) are commonly used. A time-dependent faster decline in serum levels of AMH in women with untreated endometriosis than in healthy controls has been observed. Study shows that inoperable women

with endometriosis had reduced serum AMH and AFC levels compared to non-endometriosis patients with benign ovarian cysts. Prolactin levels are elevated in women with endometriosis, which disrupts hypothalamic function by blocking estrogen receptors, causing a lack of ovulation.

Altered pelvic anatomy due to the presence of adhesions also impacts the patient's comfort. Closely related is the effect of pain on potential fertility. The ability to engage in intercourse is a critical factor in the mechanism of fertility. Endometriosis is associated with a 9-fold increased risk of dyspareunia. Infiltrates affect the posterior vaginal fornix, the uterosacral ligaments, the pouch of Douglas and the rectum, which can cause significant discomfort during intercourse. [18,19,20]

Treatment of infertility

The treatment of endometriosis is highly complex. Each patient and their case should be treated individually, taking into account their maternity plans, age, stage of the disease, ovarian reserve and available resources. Patients with endometriosis-associated infertility should be treated in multidisciplinary referral centers. Currently, we distinguish 3 approaches to the treatment of endometriosis and associated infertility: pharmacological treatment, surgical treatment and assisted reproductive technology (ART). [21]

Pharmacological treatment of endometriosis

The use of GnRH antagonists, progestogens, combined oral contraceptives and danazol is an effective treatment for the symptoms of endometriosis, but there is currently no evidence of a beneficial effect of such treatment on fertility. The use of ovulation-blocking treatment does not improve future chances of pregnancy. In addition, postoperative pharmacotherapy has not been proven to improve pregnancy rates. To summarize the studies to date, no advantage of pharmacotherapy was observed in terms of pregnancies achieved. [21,22]

Surgical treatment of endometriosis

Surgical treatment options include laparotomy, laparoscopy and robotic surgery. The preferred surgical method currently is laparoscopy, which has the advantage of shorter recovery time, hospitalization and relatively low cost. Surgical intervention is aimed at removing endometriosis foci, adhesions and restoring normal pelvic anatomy. The procedure consequently reduces inflammation. Data has shown that performing laparoscopy for mild to moderate endometriosis improves fertility and live birth rates. However, there is insufficient

evidence to support the beneficial effect of laparoscopy on postoperative pregnancy rates for moderate and severe endometriosis. Surgical treatment of deep endometriosis in infertile women should be considered only in cases of severe pain. [23,24]

Surgical treatment also has a number of disadvantages, which include potential surgical complications, formation of new postoperative adhesions and a decrease in ovarian reserve. A 2020 meta-analysis showed that there was a significant decrease in AMH levels at 3 and 6 months after surgical intervention. [25]

In summary, surgical planning should also consider likely prognosis of outcome based on various factors such as ones included in EFI endometriosis fertility index, which assesses the likelihood of spontaneous pregnancy after surgery for endometriosis. The probability of spontaneous pregnancy after endometriosis surgery is higher in women with a higher EFI. [26,27]

ART assisted reproductive technology

Today, assisted reproductive techniques are one of the first-choice approaches for endometriosis-related infertility.

In patients in stage I and II according to rASRM, the use of ovulation stimulation and IUI home insemination increases the rate of live births. This management is more effective than wait-and-see management or the use of IUI without ovulation induction.

For stage III and IV endometriosis, especially in women over age 35, IUI along with insemination induction are usually proposed. [28]

In vitro fertilization (IVF) is the most effective treatment for infertility in women with endometriosis. Currently, up to 25% of IVF procedures are performed on patients with endometriosis. IVF should be used when current infertility treatment is not effective, especially for women over 35 with an unfavorable prognosis and a low EFI.

The choice of treatment should be decided on a case-by-case basis and in consultation with the patient. [15,29,30]

Conclusions

Endometriosis is an insidious disease that takes away the comfort of patients' lives, affecting their daily lives, relationships, finances, ability to start a family, and causing mental health issues. There is a strong link between endometriosis and infertility. IVF is the most effective method of treatment for patients struggling with infertility. The patient's care should be comprehensive and provide access to fast and effective diagnostics to enable the patient to live

a life without pain, discomforts and enable pregnancy. The choice of treatment method for a patient struggling with infertility should be thoughtful, assuming a long-term treatment plan. Depending on the severity of the disease, the physician may implement a specific treatment protocol using assisted reproductive techniques or a surgical approach. Every patient should have access to psychological care to prevent damage to mental health and, consequently, issues in personal and professional life.

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