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Review Article

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Endometriosis Impact on Fertility: A Review of Pathogenesis, Diagnosis and Treatment

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Abstract

Endometriosis is a common problem affecting 5-10% of women of childbearing age. It is a condition with unknown pathology, leaving us with several theories. However, about half of women with endometriosis complain of difficulty conceiving. The exact mechanism remains unclear. In severe cases, infertility is associated with anatomical disturbances, but the pathophysiology of infertility in mild cases of endometriosis is not understood. From the balance of available evidence, medical treatment of endometriosis does not improve fertility and should not be given to patients wishing to conceive. However, surgical ablation or excision of minimal and mild endometriosis does improve fertility chances.

Methods of assisted reproductive technology can be used in combination with hormonal treatment in women with mild endometriosis.

Endometriosis treatment is yet to be considered effective. This article is a review of the literature on endometriosis-a disease affecting the quality of life in women all over the globe.

Keywords: Endometriosis, Pathogenesis, Impact on fertility, Diagnosis management

Introduction

EM is defined as endometrial tissue lying outside the uterine cavity; it can be described as ectopic growth of both endometrial glands and stroma within the peritoneum or internal abdominal and pelvic organs.

Endometriosis can affect almost any organ or structure, although most endometriosis implants are located in the pelvic cavity. Pelvic endometriosis has a somewhat predictable and repetitive distribution pattern most frequently affecting retro cervical space, vagina, ovaries, bladder dome, rectosigmoid colon, and round ligaments [1]. This endometrial tissue can induce fibrosis in deeper sites such as the rectovaginal septum and the bladder. According to the epidemiological data, 10-15% of women of reproductive age and up to 30% of those with pelvic pain are affected [2]. The prevalence of EM was found to be 18% in a recent systemic review by Moradi Y et al. Published studies from January 1990 to December 2018 reporting the prevalence of EM were reviewed displaying that EM is very common in developing countries [3]. As the prevalence of EM varied by stage, ranging from 2% (95% CI: 1-4) for stage I 4-20% (95% CI: 11-28) for stage II. The prevalence rates of EM in women with infertility, chronic pelvic pain, and asymptomatic were 31% (95% CI: 15-48), 42% (95% CI: 25-58), and 23% (95% CI: 19-26), respectively. Despite the high prevalence rates, scarce is considered to be known about the underlying causes of this condition [4].

Pathogenesis of EM

The key to understanding the pathophysiology of EM is to have a decent insight into its origin. Mechanisms behind the pathology of endometriosis are still unclear, yet various theories are postulated about the origin of endometrioses lesions, only two of them are widely acknowledged, which are:

Sampson's Implantation Theory

This theory claims that endometriosis lesions arise as a result of retrograde menstrual regurgitation of viable endometrial tissue and glands through the patent ovarian ducts, followed by implantation on the peritoneal surface that causes EM. Menstrual blood can be seen in the pelvic cavity by laparoscopy during the time of menses. The implantation of endometrial tissue within cesarean section surgical scars lends credence to this notion. Immune tolerance to

the transplanted tissue is hypothesized to facilitate the development of endometrial lesions [5].

Coelemic Metaplasia Theory

This theory suggests that the cells lining Müllerian ducts dedifferentiate back into their primitive origin, and then transform into endometrial cells, this transformation is thought to be driven by hormonal stimuli or inflammatory irritation [6].

In some instances, EM may be present in unusual settings; a few cases of EM were reported in patients with Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) syndrome, some of them showing complete uterine agenesis, and other cases of EM in patients with MRKH syndrome showing rudimentary uterus were reported as well [7, 8]. EM can occur in teenagers before menarche and in women who have never menstruated before; interestingly it can occur in castrated men on estrogen therapy. All of these cases support the coelomic metaplasia theory in the explanation of endometriosis lesions development [9-11].

Looking at both of the theories it is obvious that a single theory is unlikely to explain the pathophysiology of EM sufficiently.

There is a strong suggestion that genetic &immunological factors may alter the women's susceptibility and allow them to develop EM: it is well recognized that components of the immune system of women with EM are abnormal; multiple cell types including macrophages, neutrophils, lymphocytes, and dendritic cells are found to be deregulated; it seems like some cellular components are not doing well at surveillance of peritoneal fluid it appears as if the immune system develops tolerance to the abnormally located endometrial tissue allowing the establishment of lesions [5, 12-15].

Ectopic endometrial tissue secretes estradiol, progesterone, monocyte chemoattractant protein (MCP)-1, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), and proinflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8, tumor necrosis factor-alpha (TNF-α) and others.

Women who are impacted have higher levels of inflammatory markers in their peritoneal fluid, highlighting a background immunological reaction with inflammation [16]. This active inflammation is probably responsible for pain and infertility symptoms seen in EM patients [17,18]. Estradiol levels rising and stimulating the formation of endometrial tissue are caused by increased prostaglandin E2 levels and aromatase activity. This finding is revealing a complex interaction between hormonal and immunological factors. This combination of variables creates an inflammatory environment that fosters a long-lasting angiogenic environment that accelerates the development and progression of EM [19].

A systemic review and meta-analysis by Nina shegisi et al. have reviewed published articles that reported an association between endometriosis and autoimmune diseases [20]. The results demonstrated a level of association between EM and some auto-immune disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), and inflammatory bowel disease (IBD); however, the quality of evidence was generally poor. The results of this study implicate that clinicians should be aware of the possibility of EM and autoimmune illnesses coexisting when either condition is identified according to the observed connection between EM and autoimmune disorders. Autoantibodies have been detected in women with EM but only anti-endometrium antibodies and interleukin -6 have shown to be useful in EM detection however they are not as accurate as the traditional surgical diagnosis [21]. EM is heritable in about half of the cases, this was shown by twin studies but there is still no clear proof of associated gene mutations [22, 23]. Incidence of EM appears to be increased in first-degree relatives of patients, this fact suggests a polygenetic-polyepigenetic mechanism behind EM, this theory is going along with findings on EM [24].

Persistent micro trauma at the junctional zone between endometrium and myometrium, which can be visualized by 3D ultrasound-forms the basis of the "tissue injury and repair" theory the context of which is: At the time mechanical alterations during wound healing, stem cells are activated and leave their niche traveling to the pelvic cavity by the mean of retrograde menstruation(backward reflux through the ovarian ducts), this is followed by the establishment of lesions as the stem cells differentiate into endometrial tissue [25-27]. Endometrial implants consist of stroma and epithelial cells as well as smooth muscles. this cluster of cells expresses receptors for estrogen, vasopressin, and oxytocin making the ectopic tissue behave just like normal endometrium in response to hormonal stimuli. [28, 29].

EM-specific exosomes were detected in peritoneal fluid and thought to have a role in disease development [30] for the findings about biomarkers to be of clinical use further evaluation is required.

Classification

Several classification systems of EM have been proposed to assess the disease in terms of severity, extent, location, and expected clinical outcome. Accurate classification enables for better communication between care providers and useful comparing clinical intervention, in fertility studies, two systems are commonly used in these are:

Revised American Society for Reproductive Medicine classification

The classification was developed by the American Society of Reproductive Medicine (ASRM), which is based on gross findings (open surgery or laparoscopy). This system is mainly used for EM patients complaining of infertility. The first ASRM IS was released in 1979 and revised most recently in 1996 [31]. The revised ASRM scoring system distinguishes four classes or stages EM: minimal,

mild, moderate, and severe. Unfortunately, it does not consider the depth or level of invasion of the lesion, and the role of this system in the prediction of fertility potential remains unclear [32].

Endometriosis fertility index EFI

Is another system that is focused on the prediction of fertility status associated with EM and is based on post-surgical results and other factors that affect fertility [33]. Women with high scores i.e., 9-10 have a 75% chance of getting conception [34]. Similar results were found on external validation of EFI.

EM Impact on Fertility

EM is a heterogeneous disease with complex pathogenesis that may affect fertility by altering a wide range of molecular mechanisms, for a single model is not sufficient to describe EM-related infertility.

Approximately 50% of women with EM will be able to conceive without treatment, whereas in women with moderate disease, only 25% will conceive spontaneously, and few spontaneous conceptions occur in the case of severe disease [35].

It is easy to see that anatomical distortion of pelvic organs especially the tubes and ovaries is directly associated with subfertility. But this is not always the case other mechanisms that take a role in the pathogenesis of infertility are listed in the table below

Table 1: Possible causes of subfertility in women with EM [36].

Possible causes of subfertility in women with EM
Adhesions
Chronic intraperitoneal inflammation
Disturbed folliculogenesis
Luteinized unruptured follicle (LUF)
Luteal phase defects
Progesterone resistance
Detrimental effects on spermatozoa
Anti-endometrial antibodies
Dysfunctional uterotubal motility
Idiopathic

It is only logical to think that numerous factors and pathways are involved in reducing fertility in women with EM; women with infertility are most likely to be at a late stage of EM development although some infertile women are mildly affected by EM [37]. The changes caused by abnormal endometrial tissue in the: peritoneal environment, ovarian function, endometrium, and uterine tubes, are most likely responsible for the reduced fertility status.

Effect On Germ Cells and The Embryo

Peritoneal fluid in affected women contains increased numbers of inflammatory cells and mediators i.e., macrophages, interleukin -1B, IL-8, IL-10, and tumor necrosis factor Alfa TNF-a. These factors are thought to alter the ovarian function and reduce ovulation by reducing ovarian response [38, 39]. Sperm motility and quality are both reduced in women with EM due to the inflammatory\toxic effect of the peritoneal environment. IL-6 role has been described in reducing sperm motility [40-41].

EM can cause luteal phase disruption as a result of progesterone receptors alterations manifested by reduced expression of progesterone receptors leading to progesterone resistance also the inflammatory medium may have a toxic effect on the embryo possibly by free radicals and oxidative stress in the endometrial environment [42, 43]. In addition, oxidative stress, prostaglandins, and cytokines may interfere with oocyte–sperm interactions, impair embryo development, and disrupt implantation [44]. Studies have shown that women with EM are at increased risk of developing luteinized non ruptured follicle syndrome (LUF), LUF syndrome can be diagnosed by ultrasound and tend to have a higher prevalence in women with EM increasing the ratio of infertility in this population [45].

Tubal Abnormalities

In EM, disordered peristalsis may contribute to infertility because of disturbed transport of gametes and embryos to the uterine cavity [46-47].

Effect On Endometrium

Pituitary dysfunction in EM patients may reduce endometrium receptivity in EM the endometrium may express reduced numbers of progesterone receptors making the endometrium resistant to progesterone stimuli and thus reducing receptivity [48, 49].

Anti-endometrial antibodies are thought to have a role in disrupting the implantation process [50]. There is an enzyme responsible for the conversion of androstenedione and testosterone to estrone and estradiol. The levels of this enzyme known as aromatase are increased in EM, resulting in increased estradiol production [51]. The role of aromatase in the pathophysiology of endometriosis is clear given that it is an estrogen-dependent disease; increased es-

trogen production in the endometrium may also affect endometrial development and receptivity. An altered concentration of MMPs is seen in EM patients, MMPs are normally inhibited by progesterone however in the setting of endometriosis, they remain elevated which may lead to disruption of implantation [52].

clinical trials of oocyte donation were conducted to showcase the difference in effect between distorted endometrium receptivity and oocyte abnormalities in EM patients, recent reviews of these trials revealed that women who receive oocytes from EM-affected donors are showing reduced implantation rates regardless of the recipient state, these findings suggest that reduced oocyte quality is more associated with infertility rather than defective endometrium function [53]. From the evidence above it is clear that a multi-factorial explanation of EM association with infertility is appropriate.

Diagnosis

Diagnosing endometriosis is a seemingly difficult process, which is usually delayed by an average of 4 to 11 years following the initial onset of symptoms [54]. This is highly due to the symptoms and signs being nonspecific and non-pathognomonic, which will both negatively affect the early detection rates and also for a proper diagnosis to take place [55]. This usually results in the progression of the disease into a more severe form before treatment initiation [56].

Since the clinical presentation of endometriosis can mimic physiological menstrual symptoms, a preliminary diagnosis should be based on detailed history and clinical examination to raise the suspicion high enough for other more complicated means of diagnosis [54].

Clinical Diagnosis

As mentioned earlier, no specific sign can be an absolute indicator of endometriosis, so cyclic or intermenstrual pain may be a vague indication of the presence of endometriosis. The pain can differ according to the location and perhaps the severity of the disease [57].

Endometriosis should be suspected whenever there is severe dyschezia, menstrual blood on stools, menstrual diarrhea, severe menstrual mastalgia, and radiation of pain to the perineum [58]. Some abnormalities during the physical examination can be useful to reach the diagnosis, such as visible bluish lesions on the vaginal fornix; palpable sensitive nodules, or a thickened area involving any of several pelvic locations (the torus uterus, uterosacral ligament(s), the upper third of the posterior vaginal wall, the pouch of Douglas; adnexal masses; fixed retroverted uterus; or pelvic pain upon mobilization [59-62].

Some studies revealed that doing bimanual examination is of low accuracy for the diagnosis of endometriosis and overall poor predictive value [57].

Biomarkers

As another proposed modality for diagnosis, over 100 putative biomarkers for endometriosis have been proposed (Such as CA125); a systematic review found that none have consistently been shown to be clinically useful [63].

Future research on biomarkers is emerging to provide a valid and reliable non-invasive diagnostic test [64].

Biomarkers tests with other blood tests can be useful in ruling out differential diagnoses like other inflammatory processes or malignancy [65].

A biomarker to some extent can individually characterize the progression of the disease or the effect of a given treatment [66].

Imaging Techniques

Although Imaging techniques have a limited role in the diagnosis of endometriosis as it lacks the adequate resolution to identify certain lesions, they are often used as a way to locate endometrioses foci and identify their depth and number before surgery, especially in the presence of deep infiltrative lesions [57, 67].

1. Ultrasonography

Ultrasound can vary greatly accuracy-wise, as it mainly depends on the skills of the operator, and the location of the lesion. For instance, when diagnosing endometriosis lesions in the detrusor muscle, performing an ultrasound with Doppler can be beneficial in determining the patency of the ureters with the lesion [68].

2. Magnetic Resonance Imaging

MRI is more sensitive than other imaging modalities for identifying deep infiltrative lesions and endometrium [55, 65]. But some studies suggest that it is overall less accurate than transvaginal ultrasound in detecting endometriosis [69].

3. CT Scan

Since CT scan can't visualize pelvic organs very well, it has no role in the diagnosis of endometriosis [57].

Laparoscopy:

Although Laparoscopy isn't normally used as a first-line diagnostic tool for its invasive nature, a combination of histological examination is still considered the gold standard for diagnosis of endometriosis [55, 70-72]. Yet some experts suggest that a diagnosis of endometriosis can be made even in the absence of histological confirmation [73, 74].

Laparoscopy is indicated whenever there are severe symptoms, or in case of investigating the cause of infertility even in asymptomatic women [60].

Accuracy of diagnosis by visual means such as laparoscopy increases with the severity of the disease [75].

Treatment

EM treatment aims to enhance the quality of life through the man-

agement of EM-related symptoms restoring fertility is a major goal for women of reproductive age. For normal reproductive function, a combination of functional pelvic organs and normal hormonal regulation is needed, medical and surgical options of treatment are focused on removing pathological changes in this system, another approach is to bypass obstacles by the means of assisted reproduction.

Medical Treatment

Medications are available for EM acting by inhibiting follicle growth to reduce the progress of EM. Unfortunately, most medications have some contraceptive characteristics i.e.: inhibition of ovulation [74].

Medical treatment may also be complementary to other procedures as the use of ovulation induction with clomiphene citrate or letrozole following laparoscopy has shown to improve the fertility of women with minimal to mild EM [75].

Surgical Management

Pain, dyspareunia, dyschezia, and dysmenorrhea, there is a lot of debate about the usefulness of the surgical approach to treating EM-related infertility.

There are some similarities between the principles of laparoscopic surgery for infertility and those for other symptoms, with surgical training being a key factor for the outcome of surgery and the ovarian reserve must be checked before surgery. Data from different studies suggested that there was a benefit of surgical treatment compared to diagnostic laparoscopy alone for a clinical pregnancy, and Surgical management is used to enhance symptoms of EM such as complaints of chronic pelvic ongoing pregnancy after 20 weeks (OR 1.66, 95% CI 1.09–2.51 and OR 1.64 95% CI 1.05–2.57, respectively) [76, 77].

Surgical laparoscopy is related to a considerable fertility outcome compared to diagnostic laparoscopy in mild to moderate cases ‘ this result was reached through a large multicenter trial; in these trials the possibility of conceiving increased by 2.4% to 17.7%, respectively after performing diagnostic laparoscopy to 4.7% and 30.7% after laparoscopic surgery this suggest that surgical laparoscopy is associated with better fertility outcome compared to diagnostic laparoscopy in patients with mild to moderate EM [78].

However, the role of the surgical approach in moderate to severe cases of infertility is not supported by enough data and the efficacy of improving fertility outcomes is questionable; in this group of patients, surgery aims to restore normal pelvic anatomy and to remove large endometriomas [79]. excision of endometrioma is thought to be reducing the ovarian reserve which may negatively affect fertility, therefore routine removal is not recommended to improve fertility chances, it is thought to be beneficial to suggest oocyte cryopreservation for young patients before ovarian surgeries [80]. systemic reviews have not identified the benefits of endometrioma removal on IVF outcome [81]. Surgical procedures and ART must be considered as complementary strategies [82].

Assisted Reproduction

Different kinds of reproductive technology are used to bypass pathological limitations of reproduction .intra uterine insemination is the most commonly used method with or without follicle stimulation .this is a simple in vivo procedure where gametes are transferred through fallopian tubes .another type of procedure is IVF where one or more embryos are being transferred to the uterus, this is a common practice in couples with normal sperm count, in those with reduced sperm quality or the previous failure of IVF intracytoplasmic sperm injection is recommended.

Intra Uterine Insemination

It is performed by introducing a small sample of prepared sperm into the uterine cavity with a fine uterine catheter. IUI may be helpful in cases of mild EM, this procedure is usually preceded by several days of ovarian stimulation .as this might be convenient but the presence of EM is considered to be a risk factor for treatment failure expectedly this procedure is not to be recommended for women with severe disease as the tubes would be damaged [83]. Studies showed that women with mild to moderate disease have a lower success rate of IUI than women with unexplained infertility and that the success rate of both groups would be similar after ablation treatment [84-85].

In Vitro Fertilization

Originally IVF was designed for couples with tubal factor infertility but it is now used in almost all cases of infertility including tubal disease, endometriosis failed ovulation induction, or failed IUI.

Control of ovarian stimulation by gonadotrophins has made IVF more efficient .data collected by ASRM showed similar or slightly higher live birth rate compared to other cases of infertility a meta-analysis including over 2000 IVF for EM and over 4000 IVF for other causes revealed that pregnancy rates are much lower in women with EM, particularly in those with severe cases as fertilization and implantation rates were lower [86, 87]. This contradiction with the ASRM results can be explained by the fact that meta-analysis might be less able to control confounding factors in women where endometriosis coexist with other causes of infertility

Possible advances in the treatment of EM

Discoveries of new therapeutic agents and the development of existing ones are important to achieve satisfactory results for EM patients in the future. EM is associated with inflammatory damage and altered angiogenesis which may be correlated with poor IVF outcomes, and thus implantation and clinical pregnancy rates can be modified by using anti-inflammatory and antioxidant agents [88]. the future therapy for EM-associated infertility seems to be oriented toward targeting the altered molecular pathways involved in the mechanism of EM pathogenesis. Other methods work by replacing damaged endometrium with stem cells [89, 90].

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