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Understanding the pathogenesis of infertility in endometriosis - literature review

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Abstract:

Introduction and objective

Endometriosis is a complex systemic condition characterized by the growth of functional endometrial tissue outside the uterine cavity, affecting 10-15% of women of reproductive age. Up to 50% of these women face infertility challenges. Although there is a scientifically established connection between endometriosis and infertility, the underlying mechanisms remain not fully understood.

Review methods

The PubMed database was searched using phrases related to the topic of endometriosis-associated infertility. The search included original research articles, review papers, and guidelines, including the Polish guideline on managing women with endometriosis. Ultimately, 25 relevant sources presenting the latest knowledge were selected.

Abbreviated description of the state of knowledge

The pathogenesis of infertility associated with endometriosis is complex and involves multiple factors. The most frequently cited contributors in the scientific literature include pain and dyspareunia, mechanical factors, reduced ovarian reserve, oxidative stress, changes in embryo and oocyte quality, impaired ovulation, and compromised endometrial receptivity.

Summary

Endometriosis affects a growing number of women worldwide, with nearly half experiencing infertility. The complexity and involvement of multiple organ systems make it difficult to pinpoint a single cause, posing a challenge for clinicians. Addressing these diverse factors is essential for improving fertility management in women with endometriosis.

Keywords: endometriosis, infertility, pathogenesis

Introduction

Endometriosis is a complex reproductive disorder marked by the presence of functional endometrial tissue outside the uterine cavity, often on the outer walls of the uterus, ovaries, and sometimes as far as the diaphragm [1]. In rare instances, it can also be found in distant organs such as the liver, lungs, brain, and other locations [2]. Most diagnosed cases fall into three subtypes within the pelvic cavity: superficial peritoneal endometriosis (around 80% of cases), ovarian endometriomas (cysts), and deep endometriosis [2,3,4]. Common symptoms include pelvic pain, cyclic bowel and bladder pain, progressive dysmenorrhea, chronic pelvic pain, deep dyspareunia, dyschezia, and dysuria [1,2,3]. Due to its diffuse nature, endometriosis often leads to misdiagnosis and requires a thorough, clinically-based approach, including careful consideration of patient history. Given that the symptoms often involve multiple organ systems and are generally non-specific, endometriosis is not usually the first condition considered during diagnosis. Additionally, the current reliance on surgical identification—typically through diagnostic laparoscopy—poses a challenge to early detection and treatment. Surgical diagnosis is not an ideal gold standard, as diagnostic laparoscopy is sometimes inaccurate and may fail to detect the disease. [3].

According to the Polish Society of Gynecologists and Obstetricians, factors that increase the risk of developing endometriosis include low BMI, a positive family history, and high BMI associated with infertility [2]. Currently, the American Society for Reproductive Medicine (ASRM) system, established in 1985 and updated in 1997, is the global standard for staging endometriosis (Tab.1). However, this system has limitations, as it poorly correlates with pain symptoms, infertility, and does not account for extra-pelvic lesions. To improve classification, the Enzian system was developed for deep-infiltrating endometriosis, but the World Endometriosis Society's consensus statement emphasizes that both systems fail to adequately correlate with pain and calls for a broader understanding of endometriosis classification [3,4].

Despite the recognized connection between endometriosis and infertility, the mechanisms are not fully understood, and the condition is considered multifactorial. Endometriosis-associated infertility results from a complex interplay of factors, including the subtype of endometriosis, pain, inflammation, changes in pelvic anatomy, adhesions, disrupted ovarian reserve or function, compromised endometrial receptivity, and the systemic effects of the disease [5].

Table 1. Stages of endometriosis severity according to the ASRM staging system.

I	minimal
II	mild
III	moderate
IV	severe

Objective

The aim of this study is to review scientific literature on the pathogenesis of endometriosis-associated infertility. With the knowledge coming from reputable sources of information, it intends to summarize the current research in this matter and evaluate the latest approach to understanding the complex mechanisms underlying the infertility problems that women with endometriosis suffer from.

Materials and methods

A literature review was performed using the PubMed database to identify publications from 2020 to 2024, focusing on the pathogenesis of infertility in endometriosis. Keywords used in the search included: “endometriosis”, “infertility” and “pathogenesis”. The review sought to compile studies exploring the mechanisms involved in the development of infertility amongst women suffering from endometriosis. Original papers, review papers, meta-analyses and guidelines were included in the review. One of such taken into consideration was the Recommendations from the Polish Society of Gynecologists and Obstetricians on the management of women with endometriosis, which gave insight into the situation of endometriosis-associated infertility among the population of Polish women. Finally, a total of 25 items of literature and websites were selected.

Description of the state of knowledge

Endometriosis is a common gynecological condition worldwide, affecting 10–15% of women of reproductive age [2,5,6]. Infertility is a frequent symptom, with 30-50% of affected women potentially experiencing difficulty conceiving [2,6,7]. Conception rates are significantly lower for women with endometriosis: 2–5% for those with mild endometriosis,

compared to 15–25% for healthy, fertile women [8,9]. For women with deep endometriosis, the spontaneous fertility rate ranges from 2% to 10% [10]. Conception rates decrease with the severity of the condition: about 50% of women with mild endometriosis, 25% with moderate, and very few with severe endometriosis can conceive without intervention [8]. While women with superficial peritoneal and ovarian endometriosis do not appear to have a significantly increased risk of obstetric and neonatal complications (such as placenta previa, preterm birth and hypertensive disorders [11]), those with severe endometriosis face a markedly higher risk of placenta previa, regardless of surgical history. Deep infiltrating endometriosis is also a risk factor for spontaneous hemoperitoneum during pregnancy and is linked to surgical complications during cesarean sections [12].

Pain and dyspareunia

For successful natural conception, the ability to engage in sexual intercourse is crucial, but this aspect is often overlooked in discussions about endometriosis-related infertility. Pain from endometriosis, including superficial dyspareunia (pain around the vaginal opening) and deep dyspareunia (pain during intercourse), can hinder sexual activity, which may contribute to infertility. Endometriosis significantly increases the risk of deep dyspareunia, particularly in advanced stages affecting areas like the posterior vaginal fornix and rectum. Chronic pelvic pain from endometriosis can also reduce sexual desire, frequency, arousal, and orgasm, negatively impacting intimate relationships, emotional well-being, and overall quality of life [2,5]. Accurate diagnosis and management require understanding the nature and distribution of lesions, necessitating a multidisciplinary approach to address pain, fertility issues, and the need for specialized treatments [13].

Anatomical and genetic aberrations

Pelvic adhesions and anatomical distortions may impact the conception process in cases of endometriosis. The primary pathophysiologic processes involved are inflammation, fibrosis, adhesions, and the after-effects of surgery. Anatomical changes and mechanical factors can hinder the release of the oocyte from the ovary, obstruct the fallopian tube's ability to pick up or transport the ovum, or prevent sperm from reaching the fallopian tube [5,14]. Histopathological and biological evaluations of oocytes from women with endometriosis reveal several morphological abnormalities, including hardening of the zona pellucida, nuclear anomalies, cytoplasmic granularity, spindle disruption, and mitochondrial

irregularities. These women also demonstrate impaired expansion of the cumulus-oocyte complex (COC) and reduced extrusion of the first polar body. The affected oocytes show features such as decentralized chromatin, prominent nucleoli, cytoplasmic granularity, and the presence of vacuoles. There are also signs of spindle disassembly or disruption in oocytes undergoing in vitro maturation. Moreover, these oocytes often have a reduced mitochondrial content in the cytoplasm, fewer mitochondrial DNA (mtDNA) copies, and may fail to mature in vitro [15,16]. Notably, in a non-human primate model of induced endometriosis, no full-term pregnancies were observed when adnexal adhesions were present on the same side as ovulation [2].

Ovarian reserve

Endometriosis damages ovarian tissue and interferes with follicle development, resulting in a reduced ovarian reserve. While the antral follicle count (AFC) has traditionally been used to evaluate ovarian reserve, anti-Müllerian hormone (AMH) levels are now favored because they can be measured at any point in the menstrual cycle and are not affected by hormonal medications. Research has shown a correlation between the severity of endometriosis, as determined by the American Society for Reproductive Medicine (ASRM) scoring system, and ovarian reserve. Women with moderate to severe endometriosis often have significantly lower AMH levels than those with milder forms of the condition or other benign ovarian cysts [8]. Endometriomas, or ovarian cysts associated with endometriosis, are suspected to damage ovarian function. They may do this through mechanical damage, oxidative stress, or a combination of both. Studies have shown reduced follicle numbers and increased fibrosis around endometriomas. This inflammation and fibrosis can lead to premature activation of primordial follicles, depleting the ovarian reserve [5]. Studies suggest that endometriosis, especially in its advanced stages, leads to a marked reduction in ovarian reserve and may accelerate the decline of ovarian reserve over time compared to healthy controls. This accelerated decline could contribute to an earlier onset of menopause in women with a history of endometriosis or endometriosis-related infertility [8].

Oxidative stress

Oxidative stress contributes to infertility by directly damaging sperm and embryo viability and interfering with implantation. It can also cause structural changes to the peritoneal mesothelium, promoting adhesion sites for endometrial cell implantation, further

worsening the disease. Additionally, oxidative stress stimulates the production of angiogenic factors like vascular endothelial growth factor (VEGF), promoting new blood vessel growth that supports the proliferation of endometrial lesions. The resulting inflammatory environment, characterized by high levels of malondialdehyde (MDA), pro-inflammatory cytokines, and oxidized LDL, damages the peritoneal cavity and impairs sperm function. The elevated nitric oxide (NO) levels in the peritoneal fluid of infertile women with endometriosis further inhibit embryo implantation, compounding the fertility issues [14,17,18].

In the topic of oxidative stress particular emphasis is put on iron overload. While iron is essential for various biological functions, an excess can elevate oxidative stress through the Fenton reaction, causing cellular damage and cytotoxicity [16]. In endometriosis, retrograde menstruation and recurrent bleeding from ectopic lesions contribute to iron overload, which further intensifies oxidative stress [19]. Elevated iron levels in endometriotic lesions and surrounding tissues have been associated with increased proliferation of endometriotic cells and lesion growth. Research indicates that iron concentrations in endometriotic cysts are significantly higher than in other types of cysts or in peripheral blood. This iron excess, along with altered iron metabolism and decreased transferrin levels, can harm both the quality and quantity of oocytes, thereby affecting fertility. Additionally, macrophages in endometriotic tissue accumulate iron and produce reactive oxygen species (ROS), further contributing to oxidative stress. In summary, iron overload in endometriosis adversely affects oocyte health and fertility due to oxidative damage [5,16].

Oocyte, follicular fluid and embryo quality

Women with endometriosis show disrupted immune responses, including difficulties in clearing endometrial debris and altered cytokine profiles in follicular fluid (FF). Elevated cytokine levels, such as IL-6, IL-8, IL-12, and TNF-α, in FF are associated with inflammation and poor oocyte quality, which may impact fertility outcomes. Increased levels of MCP-1 and other inflammatory markers suggest heightened inflammation and immune cell recruitment [20,21]. Additionally, FF in endometriosis often has elevated phosphatidylcholines and sphingolipids, with deficiencies in other phospholipids. These imbalances can affect follicular maturation, embryo quality, and fetal development. Lipids like lysophosphatidic acid and lysophosphatidylcholine play roles in cell proliferation and inflammation, which are pertinent to endometriosis and fertility. Furthermore, proteins involved in apoptosis, such as CASP3

and BCL2, are altered in endometriosis, impacting granulosa cell survival. Women with endometriosis often have low levels of various metabolites in FF, including acetate, β-hydroxybutyrate, citrate, ascorbate, and several amino acids. Elevated homocysteine levels in FF and blood are linked to inflammatory and autoimmune disorders, potentially increasing the risk of miscarriage and affecting gametogenesis [20].

Several studies have investigated the impact of endometriosis on embryo quality, with varying results. A systematic review indicates that endometriosis does not significantly affect embryo morphology. However, standardized criteria for embryo grading are needed to resolve inconsistencies in study findings. Exposure to endometriosis fluid from women with stage III/IV endometriosis has been shown to negatively affect embryo morphology, leading to increased cellular fragmentation and potentially hindering embryo development. Women with advanced endometriosis (stage III/IV) typically have embryos with fewer blastomeres, a higher rate of arrested embryos, and greater nuclear and cytoplasmic abnormalities [15,22].

On the other hand, despite having fewer oocytes and mature oocytes, women with endometriomas undergoing IVF often achieve similar numbers of total embryos, high-quality embryos, and comparable rates of clinical pregnancy, implantation, and live births as women with other types of infertility. Studies indicate that when age is accounted for, there is no significant difference in the incidence of embryonic aneuploidy between women with and without endometriosis. In summary, while endometriosis may cause certain abnormalities in embryos, the overall outcomes, such as pregnancy and live birth rates, can remain comparable to those of women without endometriosis [15].

Impaired ovulation

Prolactin levels are notably elevated in women with endometriosis compared to those without the condition. Elevated prolactin levels disrupt the pulsatility of luteinizing hormone and impair hypothalamic function by blocking estrogen receptors, which can lead to anovulation. Additionally, another possible reason for ovulation failure in women with endometriosis is luteinized unruptured follicle syndrome, a condition that is difficult to assess clinically. In this syndrome, the dominant follicle undergoes luteinization but does not rupture or release the oocyte [5].

Endometrial receptivity

In women with endometriosis, defective implantation may stem from reduced endometrial receptivity or impaired decidualization. The eutopic endometrium in these women shows various molecular and functional abnormalities compared to healthy endometrium. The key issues include hormonal dysregulation, altered gene expression and pro-inflammatory microenvironment [5].

A review by Miller et al. (2016) highlights that estrogen stimulates cyclooxygenase-2 (COX-2) expression, which synthesizes prostaglandin E2 (PGE2). Both estrogen and PGE2, through continuous local production in endometriosis, create a state of estrogen dominance, affecting reproductive events like the transition from the proliferative to the secretory phase. This estrogen dominance also interferes with markers of endometrial receptivity, such as αvβ3 integrin. In endometrial stromal cells, the levels of estrogen receptor-β are 142 times higher, and estrogen receptor-α levels are nine times lower compared to normal endometrium, due to epigenetic changes [23]. This leads to improper transformation of decidualized cells observed in vitro. Additionally, progesterone receptors are altered; inflammatory cytokines like TNF-α and IL-1β decrease the expression of progesterone receptor B (PRB), leading to a relative increase in progesterone receptor A (PRA). This imbalance causes progesterone resistance, a hallmark of implantation failure, as progesterone is essential for endometrial receptivity [24,22].

The molecular basis of unsuccessful implantation in women with endometriosis involves altered gene expression in the endometrium, particularly during the implantation window. Studies have identified numerous genes with abnormal expression patterns in women with endometriosis, affecting processes such as immune function, inflammation, and apoptosis, which can reduce reproductive potential. Key findings include decreased expression of markers like leukemia inhibitory factor (LIF), interleukin 11 (IL-11R), and integrin αvβ3, and aberrant regulation of genes like HOXA10 and EMX2, all of which impair endometrial receptivity. Epigenetic changes, such as hypermethylation of the HOXA10 gene, contribute to these abnormalities and are linked to progesterone resistance. Further exploration of the role of endometrial matrix cells and their interactions may provide insights into the pathology of endometriosis-related infertility [25].

The inflammation in the eutopic endometrium is hypothesized to either generate or

sustain endometriosis by spreading activated endometrial progenitor cells through retrograde menstruation [23], with type I macrophages secreting proinflammatory factors throughout the menstrual cycle, creating an inhospitable environment for embryo implantation [5].

Impaired sperm motility

Mast cells are recognized as crucial components of the immune system and have recently been linked to both endometriosis and infertility, as their mediators can directly impair sperm motility. Key mediators such as interleukins (IL-6, IL-8), macrophage migration inhibitory factor (MIF), and TNF-alpha present in peritoneal fluids are known to inhibit sperm motility. Additionally, these mediators affect sperm DNA and impair sperm-oocyte binding and fusion. It is hypothesized that mast cells negatively impact sperm motility through their mediators, including the tryptase enzyme. However, Borelli et al. conducted a study suggesting that tryptase is unlikely to affect sperm motility. Instead, the significant degranulation observed from strong interactions between sperm and mast cell surface molecules might contribute to endometriosis-related infertility by impacting sperm in ways other than motility [21].

Conclusions

Endometriosis is a disease affecting an increasing population of women all over the world. Almost half of them deal with infertility problems. The pathogenesis of infertility in endometriosis is based on multiple mechanisms, including pain, anatomical alterations, impaired ovarian function, oxidative stress, and disruptions in endometrial receptivity and immune responses. Endometriosis is often associated with significant pain, particularly during ovulation and intercourse. This can lead to reduced sexual activity and, consequently, lower chances of conception. There are structural changes that can block or damage the fallopian tubes, making it difficult for the egg and sperm to meet. Adhesions and scar tissue can also cause organs like the ovaries, fallopian tubes, and uterus to stick to each other or to the pelvic wall, impairing their normal function. The inflammatory environment and the oxidative stress caused by endometriosis may negatively affect the quality of the oocytes, reducing their ability to be fertilized or to develop into healthy embryos. What is more, changes in the uterine lining may hinder the embryo from properly attaching, leading to lower implantation rates. Nevertheless, given the current medical knowledge, it is difficult to identify a single factor that most significantly contributes to the development of infertility in endometriosis.

This is due to the complexity of the underlying mechanisms, the fact that symptoms often originate from multiple organ systems, and the limited and costly diagnostic options, all of which make understanding the pathogenesis of infertility a continuing challenge for clinicians. However addressing these diverse factors one by one is crucial for optimizing fertility management in women with endometriosis.

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