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REVIEW

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Endometriosis and Subfertility: A Literature Review

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ABSTRACT

Introduction: *Endometriosis is a condition that mainly concerns women of reproductive age, which causes several problems, including subfertility. The phenotypic presentation of endometriosis is defined by a complex interplay between genetic profile, immunological and mechanical factors. In this literature review we examine the causality between endometriosis and subfertility, outlining possible mechanisms involved in the pathogenesis.*

Aim: *The purpose of this study was to conduct a literature review in order to identify the correlation between endometriosis and subfertility through possible mechanisms involved in the pathogenesis of endometriosis-associated subfertility and treatment.*

Methods: *A search in Medline/PubMed was done, using the terms "endometriosis" and "subfertility", to identify the most relevant studies that were published during the last six years.*

Results: *Pathogenesis of endometriosis-associated subfertility is not clear yet, although some data indicate that there are several factors that could affect a patient's fertility. Involved mechanisms include mechanical obstruction such as ovarian tubal dysfunction and the abnormal peritoneal microenvironment, genetic, and epigenetic mechanisms, and immunological traits. It is fundamental to better understand these mechanisms in order to improve the therapeutic approach.*

Conclusions: *The clinical management of endometiosis-related subfertility has to be improved. It is important to consider a change in the classification of endometriosis and, more importantly, an effort to avoid surgical procedures. There is a crucial need for effective protocols and novel targets for specific diagnosis and treatment. Consequently, the importance of understanding pathogenesis and genetic mechanisms is underlined. Future researchers should focus on novel non-invasive treatment methods that target specific pathogenic pathways.*

Keywords: endometriosis, subfertility, causality, etiopathogenesis, treatment.

INTRODUCTION

Endometriosis is a chronic disease that is characterized by the presence of endometrial glands and stroma-like lesions outside the uterus. It affects many sites, most commonly the pelvis, particularly the ovaries, peritoneum, pouch of Douglas, and uterosacral ligaments. It is mainly associated with pain and subfertility. Clinical manifestations of endometriosis include dysmenorrhea, non-cyclical pelvic pain, dyspareunia, and subfertility. Generally, endometriosis affects women of reproductive age,

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among which it has an estimated prevalence of 5%-7%, while studies examining infertile women reported a prevalence of up to 35%. This may be an indication of a causal relationship between endometriosis and subfertility (1, 2).

The pathophysiology of endometriosis is not thoroughly clear. According to Sampon's theory of implantation, which is the most widely accepted one among the many developed theories, an early lesion establishes in the uterus and serves as a nidus for the proliferation of endometrial tissue. Subsequently, the tissue spreads to other pelvic regions via retrograde menstruation, attaching to and invading the peritoneum, which leads to the establishment of ectopic endometrial tissues outside the uterus. Retrograde menstruation occurs in many women, while endometriosis lesions are not developed in every case. Furthermore, in some cases, the condition is developed in women without a uterus and some men. These facts are not consistent with the implantation theory, resulting in the need for a better explanation of endometriosis pathogenesis. More recently, the G-E (genetic–epigenetic) theory proposes that when a combination of specific genetic and/or epigenetic cellular incidents occurs, irrespective of the original cell, it may exceed a certain threshold leading to endometriosis (3).

It is important to investigate mechanisms involved in the pathogenesis of endometriosis in order to develop new treatment options, regarding endometriosis-associated subfertility. Until now, treatment involved surgery or medical therapy (4). It is crucial to find new therapeutic targets that can increase the chances of pregnancy and improve patients' quality of life.

Aim

The purpose of this study is to review the literature in order to identify the correlation between endometriosis and subfertility through possible mechanisms involved in the pathogenesis of endometriosis-associated subfertility and treatment. Medline and PubMed were searched using the terms "endometriosis" and "subfertility" and focusing on the most relevant studies that were published during the last six years. ❑

RESULTS

Subfertility in patients with endometriosis is thought to be caused by a variety of reasons. Mechanical factors play a major part in the process. By mechanically obstructing the transfer of oocytes, sperm, and embryos through the fallopian tubes, occlusion of the fallopian tubes and peritoneal adhesions prevent fertilization and implantation. Furthermore, gamete migration is hampered by tubal motility impedance caused by high cytokine levels (5).

Pelvic adhesion involving the ovaries and tubes may hinder egg release from the ovary, impair tubal ovum pick up or ovum transport, and/or block sperm transfer into the fallopian tube, concerning patients with moderate to severe endometriosis. The use of hysterosalpingoscintography (HSSG) revealed that patients with endometriosis had a substantial decrease in the physiologic utero-tubal transport capacity when compared to controls (6).

According to later investigators, subfertility in women with endometriosis may be due to poor oocyte quality, which might reflect embryo and/or endometrial aberrations or interactions between the endometrium and embryo. The importance of oocyte quality in subfertile patients has been emphasized by studies on oocyte donation cycles. In a retrospective analysis, researchers examined the outcomes of ovodonation cycles and reported that females with and without endometriosis, who received oocytes from donors without the disorder, had equal implantation and pregnancy rates, whereas females without endometriosis who acquired oocytes from women with endometriosis had much lower implantation rates. Therefore, these findings imply that endometriosis-related oocyte alteration results in worse quality embryos with a decreased chance of implantation (7).

Patients with endometriosis presented a reduced ovarian reserve. They also showed considerably lower levels of serum anti-Müllerian hormone (AMH) than healthy controls, which could be a marker of this condition. In contrast, no variations in follicular fluid (FF) AMH levels were found between females with endometriosis and healthy controls. When researchers compared IVF endometriosis patients to control subjects, they reported lower yields of rates of implantation and pregnancy, fertilization rates, high-quality day 3 embryos, and rates of blastocyst formation. A rise in the rate of spontaneous abortions has also been noted. In addition, the severeness of alterations relies on the stage of en-

dometriosis: those with stage III-IV endometriosis presented a poorer quality of embryos, fewer retrievable oocytes, lower rates of implantation, fewer fertilizable oocytes and fewer fetuses compared to patients with stage I-II endometriosis or without endometriosis (5).

While the follicular environment is important for oocyte maturation, changes in FF composition may impair oocyte quality, influencing fertilization, early embryonic development and future pregnancy. Follicular fluid is a metabolically active milieu in which granulosa cells, endothelial cells and leukocytes release steroid hormones, growth factors, cytokines, reactive oxygen species (ROS) and antioxidants. When ROS are exceeding, despite their essential role in some functions of the female reproductive tract, they can have a negative impact particularly on the levels of estradiol (E2), which represent a significant predictor of ovarian response, leading to steroidogenesis and oocyte maturation damage (7). It is seen that the number of preovulatory follicles, follicular growth, dominant size, and follicular estradiol concentrations are all decreased in women with endometriosis. In addition, a higher percentage of apoptotic cells in the granulosa cells of female patients is observed, indicating low oocyte quality (6).

Over the years, researchers have looked into the role of endometrium in endometriosis-related subfertility, suggesting that changes in endometrial receptivity due to late histological maturation or biochemical perturbations in the eutopic endometrium may impair embryo implantation in female patients with endometriosis (8).

Hormones, cytokines, adhesion molecules and other variables are all involved in endometrial receptivity, which allows the growing embryo to implant. In the endometrium of female patients with endometriosis, a defective "window of implantation" might be due to insufficient expression of several endometrial receptivity molecules. Integrins have been suggested as sensitive indicators of endometrial receptivity. In healthy controls, avβ3 integrin expression supervenes within the implantation window, and the absence is linked to poor reproductive results. A reduced endometrial expression of avb integrin has been reported in some women with endometriosis-associated subfertility and may impede embryo attachment during implantation. Furthermore, lower expression of four implantation indicators, including lysophosphatidic acid receptor 3, glycodelin A, HOXA10, and osteopontin in endometriosis patients indicates an impaired endometrial receptivity (6).

When comparing subfertile female patients with endometriosis to those without the disease, it is observed that the level of peritoneal fluid (PF) is much higher. Incubation with PF from women with moderate to severe endometriosis resulted in sperm motility decreases of approximately 40%, 50% and 80%. Furthermore, PF inhibits the sperm acrosome response, sperm attachment to the zona pellucida, and ciliary activity in the fallopian tube in individuals with endometriosis. Endometriotic implants were shown to produce estradiol and progesterone, which ulcerate VEGF, interleukin-8 (IL-8), and macrophages, which suggests that endometriosis may be caused by processes that change follicular growth and ovulatory failure (6).

Many studies regarding the genetic association of endometriosis aimed to reveal candidate genes and single nucleotide polymorphisms (SNPs), and hence to understand the pathogenesis and reveal possible therapeutic targets (9). Genes involved in inflammatory and detoxification processes, cell adhesion, and endocrine pathways are correlated with endometriosis (10).

Homeobox A (HOXA) is a sequence of signaling events involved in implantation. It is a transcription factor, a member of GATA family. Generally, it is proven that this gene is up-regulated during implantation, especially in the mid-secretory phase of the menstrual cycle. There are many studies examining the role of HOXA-10 gene expression patterns during endometriosis, with controversial results (11). Furthermore, some epigenetic changes in these genes have shown that hypomethylation and activation of GATA6 and hypermethylation and downregulation of GATA2 led to endometriosis–related changes (12). In another recent study, a comparison of HOXA-10 gene expression in fertile women without endometriosis, infertile women without endometriosis, and infertile women with endometriosis revealed that it is down-regulated in women with endometriosis, especially infertile ones (11).

Transforming growth factor β (TGF-β) is another gene superfamily related to endometriosis. In a recent study investigating the gene expression

for ligands, receptors and intracellular signaling, a reduced expression of BMP-6 and SMAD4 was noticed in females with peritoneal endometriosis (13). Genetic polymorphisms of matrix metalloproteinase (MMP)-12 and -13 are also correlated with superficial endometriosis (9).

Many other genes and polymorphisms have been associated with endometriosis-related subfertility. In a recent meta-analysis from 242 different genes, 28 were eligible and five of them – glutathione S-transferase pi 1 (GSTP1) rs1695, glutathione S-transferase mu 1 (GSTM1) null genotype, wingless-type MMTV integration site family member 4 (WNT4) rs16826658 and rs2235529 and interferon-gamma (IFNG) (CA) repeat – had a strong correlation with endometriosis (10).

Epigenetic modifications are considered important in endometriosis-related subfertility. These modifications involve histone modification, DNA methylation, microRNAs (miRNAs), and long non-coding RNAs (lnsRNAs). Changes in some estrogen receptors (ERs) and progesterone receptors (PRs) may have an important impact (14). In a recent study, it was reported that histone deacetylase 3 (HDAC3) was downregulated in females with endometriosis, which was related to increased fibrosis, hormonal signaling and impaired endometrial receptivity (15). Another study investigated aberrant aromatase expression (CYP19A1) in infertile women with endometriosis and demonstrated that its decrease might have resulted from epigenetic alterations, impairing follicular steroidogenesis and leading to poor oocyte and embryo condition (16). Also, a recent study investigated the role of many exosomal miRNAs. Many miRNAs were possibly involved in regulating the endometrial receptivity in infertile patients with endometriosis (17).

Oxidative stress is one of the most studied mechanisms connected to endometriosis-associated subfertility. Endometrial cells are affected by abnormally high amounts of ROS produced by oxygen metabolism, which results in the damage of proteins, lipids but also DNA structure, disrupting cellular cycle and function (4). Increased blood levels of advanced oxidation protein products together with nitrates were identified by a study focusing on the assessment of biochemical imbalances in women undergoing surgery for gynecological disorders, notably in those with late stages of endometriosis (18). Lin *et al* found increased ROS levels in endometriosis granulosa cells (GCs) as well as evidence that ROS-induced GCs senescence contributed to endometriosis-associated subfertility (19).

Endometriosis is characterized by a complex landscape of elevated amounts of immune factors such as cytokines, prostaglandins, and metalloproteinases, which contribute to the growth and progression of the disease. In patients with endometriosis, subfertility is caused by a persistent inflammatory condition brought on by an aberrant peritoneal environment. Some cytokines and chemokines observed in high quantities in the PF and sera of subfertile women with endometriosis are considered to play a role in the progression of the inflammatory state. The most investigated molecules include IL-1, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), RANTES, and vascular endothelial growth factor (VEGF) (20, 21).

In their study, Jorgensen *et al* detected the concentration of 48 separate cytokines from the PF among women undergoing laparoscopy for subfertility investigation with different immunoassays. They demonstrated that four cytokines, including SCGF-β, IL-8, HGF and MCP-1, had substantially greater concentrations in female patients with endometriosis than control persons without the condition, while IL-13 showed a decreased concentration in endometriosis patients (22). Another research, that evaluated the correlation between the level of four soluble immune checkpoints, including sHLA-G, sPD-1, sCTLA4 and sPD-L1, and the clinical characteristics of endometriosis-associated subfertility demonstrated that sPD-L1 was a potential biomarker. Furthermore, the research revealed that sPD-L1, sPD-1 and sCTLA-4 in the PF may be implicated in the pathogenesis as immune regulators (23). A meta-analysis conducted by Malvezzi *et al* supported the link between endometriosis-associated subfertility and high serum proinflammatory interleukins, including IL-6 and IL-8, while as far as IL-1 was concerned, it did not provide significant evidence of differences in concentration between endometriosis patients and controls in serum, FF and PF (24).

Endometriosis is characterized by an increased immune response as well as an enhancement in the number of B lymphocytes and the formation of autoantibodies. Endometriotic le-

sions were extensive in plasma cells and activated macrophages, with strongly expressed cytokine B lymphocyte stimulator (BLyS), according to immunohistochemistry and gene expression microarray evaluation. B lymphocytes produce high levels of autoantibodies in response to elevated levels of BLyS (20). Furthermore, women with endometriosis presented higher antinuclear (ANA), anti-SSA/Ro and antiphospholipid autoantibodies (aPL) compared to controls. In contrast to subfertile patients without endometriosis, anti-sperm and anti-cardiolipin antibodies were observed at higher numbers in the sera and peritoneal fluids among 323 women experiencing varying stages of endometriosis (21).

Generally, there are three strategies regarding the treatment of endometriosis-associated subfertility, surgery, assisted reproduction or medical treatment. Currently, assisted reproduction is often combined with medical treatment. Future perspectives include immunomodulatory and stem cell therapy (4).

Surgery is an important approach to the treatment of endometriosis-associated subfertility. It can be achieved by laparotomy, laparoscopy or robotic surgery (4). The stage of the disease plays an important role in the prediction of procedural outcome. Data from different studies regarding minimal/mild endometriosis suggests that there is an increase in pregnancy rate after surgery, but a 30% cumulative probability of pregnancy during 36 weeks may not be sufficient to justify the risk of surgery (25).

Medical treatment has two available directions, suppress follicle growth leading to amenorrhea or stimulate follicle growth and ovulation. The first strategy can be achieved by drugs like gonadotropin-releasing hormone agonists, progestins, danazol, or oral contraceptives, but they do not offer a solution to subfertility. Clomiphene citrate alone or in combination with gonadotropins can be used to stimulate follicle growth (25). ❑

DISCUSSION

Even though the association between subfertility and endometriosis is still debatable, clinical observations and a variety of studies support a causal link. The pathogenesis of endometriosis-associated subfertility is not clear yet, although some data indicate that several factors could affect a patient's fertility.

As shown by the present review, mechanisms involved include mechanical obstruction such as ovarian tubal dysfunction and the abnormal peritoneal microenvironment, genetic, and epigenetic mechanisms, and immunological traits. Cellular cycle-, proliferation- and apoptosis-related loci, genes involved in inflammatory and detoxification, angiogenesis-related genes, and hormonal function genes have been associated with endometriosis. Endometriosis is characterized by an increased immune response as well as an enhancement in the number of B lymphocytes and formation of autoantibodies. IL-1, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), RANTES, and vascular endothelial growth factor (VEGF) are among the most investigated molecules.

The usual treatment of endometriosis-associated subfertility consists of surgery and medical treatment. As regards surgery, it can be achieved by laparotomy, laparoscopy or robotic surgery. Finally, medical treatment has two available directions: either suppression of follicle growth leading to amenorrhea or stimulation of follicle growth and ovulation. There are conventional and emerging medical treatments for endometriosis. Conventional drugs include progestins, combined oral contraceptives, GnRH agonists/antagonists, nonsteroidal anti-inflammatory drugs, and aromatase inhibitors, while emerging medicines focus on disease-specific targets. ❑

CONCLUSIONS

Even though the association between subfertility and endometriosis is still debatable, clinical observations and a variety of studies support a causal link. New studies focus on understanding changes in women with endometriosis-related subfertility. There are changes in oocyte quality, like AMH levels, that can be used as markers of endometriosis. Moreover, endometrial and peritoneal alterations may suggest a pathogenetic mechanism, involving many molecules.

Regarding clinical management, starting with the classification of endometriotic lessons, there is a need for others systems like EFI systems, that can predict a more accurate pregnancy rate. Additionally, although laparoscopy is still the most

frequent intervention, recent studies reveal that surgical procedures may damage the ovary, leading to non-invasive treatment approaches. Subfertile women currently use IVF as the most common approach, although endometriosis lowers the success of the therapy. New studies support protocols than can increase pregnancy rates. Regarding medical treatment, there are many available hormonal treatments, that can be used as a pretreatment to ART, and non-hormonal medical agents that target inflammation or angiogenesis, although there is a crucial need for more effective drugs.

Future researchers should focus on novel non-invasive treatment methods that target specific pathogenic pathways. New protocols have to be investigated leading to a safer and more effective ovulation induction regimen. Furthermore, understanding the genetic, epigenetic and immunological differences can reveal new potential biomarkers and therapeutic targets. Consequently, uncovering candidate genes and single nucleotide polymorphisms (SNPs) is an important direction for investigation. ❑

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References

1. **Alimi Y, Iwanaga J, Loukas M, Tubbs RS.** The Clinical Anatomy of Endometriosis: A Review. *Cureus* 2018;10:e3361. doi:10.7759/cureus.3361.
2. **Lee SY, Koo YJ, Lee DH.** Classification of endometriosis. *Yeungnam Univ J Med* 2021;38:10-18. doi:10.12701/yujm.2020.00444.
3. **Koninckx PR, Ussia A, Adamyan L, et al.** The epidemiology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear. *Best Pract Res Clin Obstet Gynaecol* 2021;71:14-26. doi: 10.1016/j.bpobgyn.2020.08.005.
4. **Filip L, Duică F, Prădatu A, et al.** Endometriosis Associated Infertility: A Critical Review and Analysis on Etiopathogenesis and Therapeutic Approaches. *Medicina* (Kaunas) 2020;56:460. doi:10.3390/medicina56090460.
5. **Mate G, Bernstein LR, Torok AL.** Endometriosis is a cause of infertility. Does reactive oxygen damage to gametes and embryos play a key role in pathogenesis of infertility caused by endometriosis? *Front Endocrinol* 2018;9:1-16. doi:10.3389/fendo.2018.00725.
6. **Khine YM, Taniguchi F, Harada T.** Clinical management of endometriosis-associated infertility. *Reprod Med Biol* 2016;15:217-225. doi:10.1007/s12522-016-0237-9.
7. **Da Broi MG, Navarro PA.** Oxidative stress and oocyte quality: ethiopathogenic mechanisms of minimal/mild endometriosis-related infertility. *Cell Tissue Res* 2016;364:1-7. doi:10.1007/s00441-015-2339-9.
8. **Da Broi MG, Ferriani RA, Navarro PA.** Ethiopathogenic mechanisms of endometriosis-related infertility. *JBRA Assisted Reproduction* 2019;23:273-280. doi:10.5935/1518-0557.20190029.
9. **Vassilopoulou L, Matalliotakis M, Zervou MI, et al.** Defining the genetic profile of endometriosis. *Exp Ther Med* 2019;17:3267-3281. doi:10.3892/etm.2019.7346.
10. **Méar L, Herr M, Fauconnier A, et al.** Polymorphisms and endometriosis: a systematic review and meta-analyses. *Hum Reprod Update* 2020;26:73-102. doi:10.1093/humupd/dmz034.
11. **Özcan C, Özdamar Ö, Gökbayrak ME, et al.** HOXA-10 gene expression in ectopic and eutopic endometrium tissues: Does it differ between fertile and infertile women with endometriosis? *Eur J Obstet Gynecol Reprod Biol* 2019;233:43-48. doi:10.1016/j.ejogrb.2018.11.027.
12. **Yotova I, Hsu E, Do C, et al.** Epigenetic alterations affecting transcription factors and signaling pathways in stromal cells of endometriosis. *PLoS One* 2017;12:e0170859. doi:10.1371/journal.pone.0170859.
13. **De Conto E, Matte U, Cunha-Filho JS.** BMP-6 and SMAD4 gene expression is altered in cumulus cells from women with endometriosis-associated infertility. *Acta Obstet Gynecol Scand* 2021;100:868-875. doi:10.1111/aogs.13931
14. **Chen H, Malentacchi F, Fambrini M, et al.** Epigenetics of Estrogen and Progesterone Receptors in Endometriosis. *Reprod Sci* 2020;27:1967-1974. doi:10.1007/s43032-020-00226-2.
15. **Guo SW.** Genesis, genes and epigenetics of endometriosis-associated infertility. *Nat Rev Endocrinol* 2019, 15:259-60.10.1038/s41574-019-0191-9.
16. **Hosseini E, Mehraein F, Shahhoseini M, et al.** Epigenetic alterations of CYP19A1 gene in Cumulus cells and its relevance to infertility in endometriosis. *J Assist Reprod Genet* 2016;33:1105-1013. doi:10.1007/s10815-016-0727-z.
17. **Zhou W, Lian Y, Jiang J, et al.** Differential expression of microRNA in exosomes derived from endometrial stromal cells of women with endometriosis-associated infertility. *Reprod Biomed Online* 2020;41:170-181. doi:10.1016/j.rbmo.2020.04.010.
18. **Anastasiu CV, Moga MA, Neculau AE, et al.** Biomarkers for the noninvasive diagnosis of endometriosis: State of the art and future perspectives. *Int J Mol Sci* 2020;21:1750. doi:10.3390/ijms21051750.
19. **Lin X, Dai Y, Tong X, et al.** Excessive oxidative stress in cumulus granulosa cells induced cell senescence contributes to endometriosis-associated infertility. *Redox Biology* 2020;30:1-13. doi:10.1016/j.redox.2020.101431.
20. **Lin YH, Chen YH, Chang HY, et al.** Chronic niche inflammation in endometriosis-associated infertility: current understanding and future therapeutic strategies. *Int J Mol Sci* 2018;19:2385. doi:10.3390/ijms19082385.
21. **Kolanska K, Alijotas-Reig J, Cohen J, et al.** Endometriosis with infertility: A comprehensive review on the role of immune deregulation and immunomodulation therapy. *Am J Reprod Immunol* 2020;85:1-7. doi:10.1111/aji.13384.
22. **Jorgensen H, Hill AS, Beste MT, et al.** Peritoneal fluid cytokines related to endometriosis in patients evaluated for infertility. *Fertility and Sterility* 2017;107:1191-1199. doi:10.1016/j.fertnstert.2017.03.013 .
23. **Santoso B, Sa'adi A, Dwiningsih SR, et al.** Soluble immune checkpoints CTLA-4, HLA-G, PD-1, and PD-L1 are associated with endometriosis-related infertility. *Am J Reprod Immunol* 2020;84:1-7. doi:10.1111/aji.13296.
24. **Malvezzi H, Hernandes C, Piccinato CA, Podgaec S.** Interleukin in endometriosis-associated infertility-pelvic pain: systematic review and meta-analysis. *Reproduction* 2019;158:1-12. doi:10.1530/REP-18-0618.
25. **Tanbo T, Fedorcsak P.** Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. *Acta Obstet Gynecol Scand* 2017;96:659-667. doi:10.1111/aogs.13082.