Integrative Perspectives on Endometriosis: Etiology, Genetic Insights , Diagnosis and Therapeutic Interventions

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- ***Abstract*** - Endometriosis is a chronic, estrogen-dependent gynecologic disease marked by the presence of endometrial-like tissue located outside the uterine cavity, which causes pain, infertility, and reduced quality of life. After significant research, its multifactorial etiology and complicated pathophysiology remain to impinge on early diagnosis as well as appropriate management. This review discusses the shifting paradigm of understanding endometriosis from its early etiologic theories—such as endometrial stem cell recruitment—to molecular and genetic changes driving disease development and malignant transformation into endometriosis-related ovarian cancer. Diagnostic modalities, such as imaging and biomarker strategies, are addressed, in addition to current pharmacological treatments like hormone therapies, anti-inflammatory drugs, and emerging targeted therapies. Dietary factors affecting symptom modification and therapy response are also assessed. In the pharmacovigilance context, the review emphasizes the need to monitor drug safety profiles, adverse drug reactions, and long-term therapeutic effects in order to maximize patient care. The results underscore the need to incorporate pharmacovigilance systems in the management of endometriosis to facilitate early recognition of treatment-related risks and maximize overall therapeutic efficacy.
- ***Key Words:*** Ovarian cancer , stem cell , genetic alterations , chronic inflammation , Immune dysregulation , Endocrine infertility.

Categories: Obstetrics/Gynecology

- ***Introduction :***

Endometriosis is a reproductive disorder in which endometrial tissue is aberrantly located outside the uterus. Endometriosis affects nearly 10% of women of reproductive age, and 30% to 50% of those with the condition suffer from chronic pelvic pain and/or infertility, the two major clinical symptoms (1,2).It is the most perplexing gynecological condition. The most widely recognized explanation endometriosis is that endometrial tissue is implanted in the peritoneal cavity by retrograde menstruation. The first theory describing the origin of endometriosis is the retrograde menstruation theory. According to this idea, endometriosis develops when sloughed endometrial cells and debris after menstruation travel retrogradely down the fallopian tubes and enter the pelvic cavity. 76%-90% of women having patent fallopian tubes experience retrograde

Menstruation , albeit not all of these women have endometriosis(3).

Endometriosis can be classified into three subtypes based on its histopathology and anatomical locations: superficial endometriosis, deep infiltrating endometriosis (DIE), and ovarian endometriotic cysts (known as endometriomas , or so-called chocolate cysts Superficial endometriosis usually appears on the surface or in the sub serosal soft tissue of the peritoneum or visceral organs, whereas DIE involves lesions that extend deep into the muscular layer of the intestine, bladder wall, diaphragm, or other organs.

THE ORIGIN OF ENDOMETRIOSIS

The normal-appearing ectopic endometrium that establishes and survives outside the uterus is one of the most interesting aspects of endometriosis. Over time, multicellular organisms have formed basic rules for how cells differentiate as they develop tissues: (a) repair DNA when damaged by internal or external factors, (b) wait for signals from neighboring cells to divide, (c) stay where they are supposed to be. Endometriosis seems to break the third rule. Whether driven by internal or external factors, endometriosis cells appear to have lost their connection to their origin, forming a cellular diaspora.

Several theories attempt to explain the origin of endometriosis and how tissue can spread throughout the abdominal cavity. Two of the most studied theories are retrograde menstruation and the involvement of stem cells from outside the uterus. Other proposed theories include the spread through blood or lymph, coelomic metaplasia, and Müllerian rest induction. However, no single theory fully explains all clinical presentations and pathological features of endometriosis, including rare cases where it appears in the thoracic cavity in women with Mayer-Rokitansky-Küster-Hauser syndrome and in men. It is also possible that superficial endometriosis, deep infiltrating endometriosis, and ovarian endometriotic cysts arise through different mechanisms, which align with different theories.

Unlike cancer, where the focus is usually on epithelial cells, studies on the evolutionary paths and clonal development of endometriosis face challenges because endometrium-specific stromal cells are a natural part of endometriosis along with glandular epithelium. The relationship between epithelial cells and endometrium-like stromal components needs clarification in various models to better understand the origin of endometriosis. In the next sections, we will discuss retrograde menstruation and stem cell theories in detail and assess their validity across different types of endometriosis, especially focusing on the relationship between epithelium and stroma in the same endometriotic lesions.

ENDOMETRIAL STEM CELL RECRUITMENT THEORY

The stem cell origin theory of endometriosis has gained attention in recent years. The two main versions of this theory focus on where the stem cells come from, either the uterine endometrium or bone marrow. Regardless of where they originate, hormones and other factors in the tissue environment help with adhesion, invasion, inflammation, angiogenesis, and avoiding immune detection, all of which are necessary for endometriosis to develop. In a normal endometrium, there are several groups of multipotent endometrial stem cells, including those derived from the epithelium, mesenchyme, and a mixed side population. This theory is strong because it not only aligns with the retrograde menstruation model but also explains the development of deep infiltrating endometriosis (DIE) and endometriosis outside the abdominal cavity. Endometrial stem cells may move into the angiolymphatic space during menstruation and enter the bloodstream to find suitable areas for growth(5).

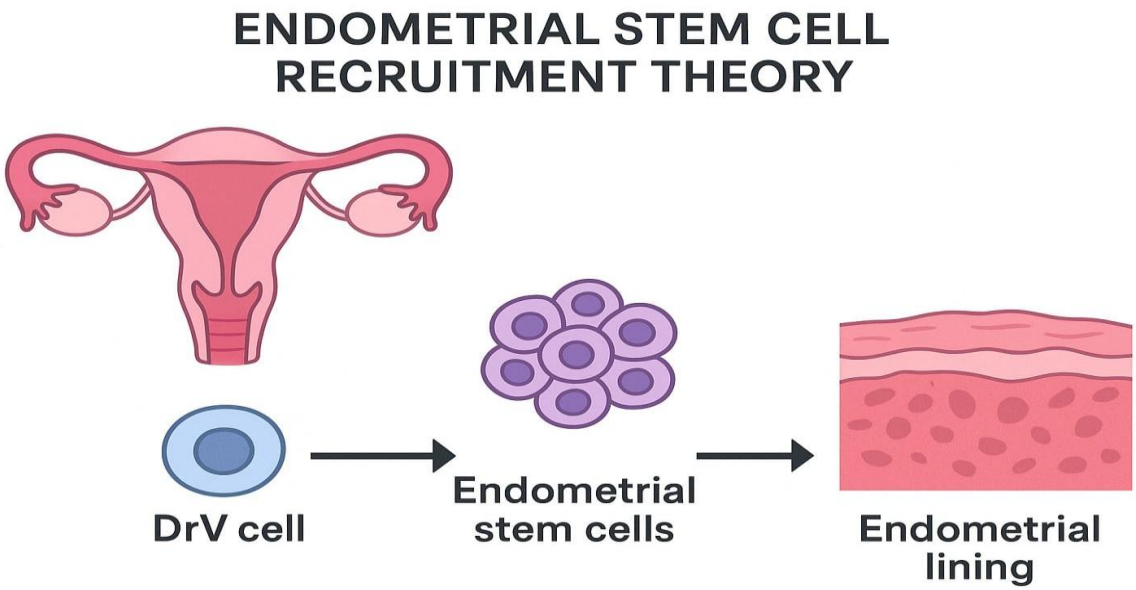


Fig . 1 (Endometrial stem cell recruitment theory)

Epithelial stem cells are believed to be located in the basalis layer of the endometrium, near the functionalis layer, where they are shielded from regular menstruation. These stem cells likely regenerate the epithelium of the functionalis layer during the proliferative phase in response to estrogen. Currently, there are no specific markers available to isolate endometrial epithelial stem cells. Markers that need further study include stage specific embryonic antigen 1 (SSEA-1), which is highly present in the endometrium basalis; leucine repeat–containing G protein–coupled receptor 5 (LGR5), which is expressed in the functionalis epithelium nearest the basalis layer; and N-cadherin, a potential marker for epithelial progenitor cells. N-cadherin is highly expressed in the glandular epithelium of the basalis and diminishes as the gland extends into the functionalis.

N-cadherin-positive basalis epithelial cells in human endometrium have strong clonogenicity, proliferative potential, and self-renewing ability, traits that decrease with the loss of N-cadherin. These cells can develop into cytokeratin-positive gland-like structures in three-dimensional cultures, reinforcing their stem cell-like qualities. One previous study found very small embryonic stem cell–like cells in adult mouse endometrium. It was suggested that these cells could be a source of the endometrial stem cell population. Another study supported this idea by showing that these cells expressed human endometrium glandular and stromal markers in mice. The study later identified CD146+PDGFR-B+ mesenchymal stem cells in culture(6). This specific cell population warrants further characterization and investigation. Despite significant research in this area, there is no direct evidence that endometrial stem cells contribute to the development of endometriosis(6,7).

MOLECULAR GENETIC CHANGES IN ENDOMETRIOSIS :

Recent studies have revealed a significant finding: somatic mutations of cancer-related genes are commonly found in various types of endometriosis, including deep infiltrating endometriosis (DIE), endometriotic cysts, and iatrogenic endometriosis. This is surprising since endometriotic tissue usually appears normal and looks the same as the lining of the uterus under a microscope. Additionally, unlike cancer cells, endometriotic cells generally have limited ability to grow. However, a study by Anglesio et al. in 2017 found that 83% of benign DIE lesions had somatic mutations, and 26% contained cancer driver mutations, including mutations in KRAS, PIK3CA, ARID1A, and PPP2R1A. All these mutations were found only in the epithelial tissue (see Table 1).

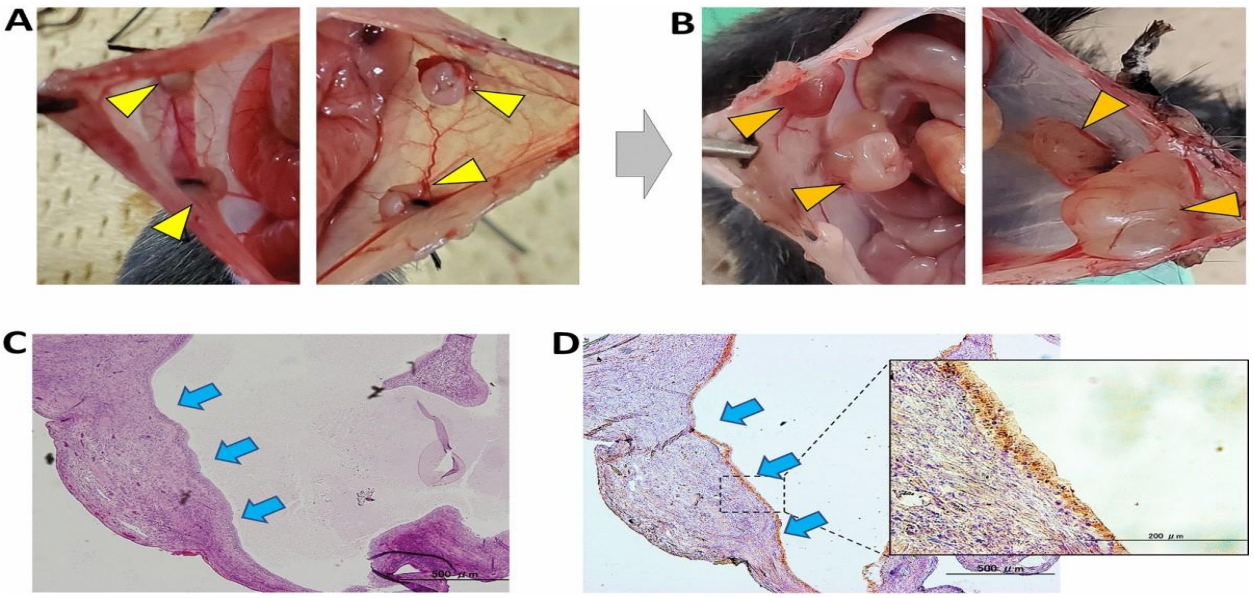
Table No. 1

Gene symbol	Gene name	Localization	Function	Role in cancer
KRAS	Kirsten rat sarcoma viral oncogene homolog	Chromosome 12: p12.1; plasma membrane	GTPase activity, positive control of cell growth and division, cell response to stimuli, cellular metabolism, regulator of signal transduction	Oncogene
ARID1A	AT-rich interaction domain 1A (SWI-like)	Chromosome 1: p35.3; nucleus	ATP-dependent chromatin remodeling factor, DNA binding, transcription regulator, DNA damage response	Tumor suppressor
PIK3CA	Phosphatidylinositol- 4,5-bisphosphate 3-kinase, catalytic subunit alpha	Chromosome 3: q26.3; cytosol	AKT pathway activator; serine/threonine protein kinase; cell growth, proliferation, differentiation, motility, survival; intracellular trafficking	Oncogene
PPP2R1A	Protein phosphatase 2, regulatory subunit Aalpha	Chromosome 19: q13.41; cytosol, mitochondria, nucleus	Serine/threonine protein phosphatase, negative control of cell growth and division, regulation of gene transcription	Oncogene or tumor suppressor, depending on mutation type

These genes are also commonly mutated in uterine endometrioid carcinomas and endometriosis-related ovarian cancers(12). This unexpected finding opens new paths for research into the causes of endometriosis and might help develop a classification system that improves prognosis and personalized treatment. It is also crucial to find out if these cancer-related mutations are important for the development of endometriosis. Recent sequencing data complicate this question. Some normal endometrial glands have shown somatic mutations in cancer-related genes, such as KRAS. So, while some mutations occur in cancer driver genes, they may only indicate clonal variations that relate endometriosis to mutated stem cells in the uterus but may not hold significant biological importance. Generally, cancer development requires multiple (at least three) cancer driver mutations. To date, no more than one mutation of a cancer driver gene has been found in endometriosis cases. Where do these epithelial stem or progenitor cells come from? They likely originate from the endometrium. This idea is supported by findings that glands in normal endometrium have been shown to carry cancer-related mutations in genes associated with endometriosis. Epithelial stem or progenitor cells may enter the bloodstream, return to the endometrium during the proliferative phase, and mistakenly form DIE. It's also possible that bone marrow-derived stem cells (BMDSCs) are the source of these epithelial stem or progenitor cells. However, this is less likely since mesenchymal stem cells from the bone marrow must decide to become epithelial cells, and this has never been confirmed. More importantly, there is no evidence that BMDSCs carry the somatic mutations in the cancer-related genes that are often found in endometriosis.

ENDOMETRIOSIS-ASSOCIATED OVARIAN CANCERS:

Although overall regarded as a benign condition, endometriotic tissue has been shown by histopathological and epidemiological research to be the source of ovarian clear cell carcinomas and ovarian endometrioid carcinomas, collectively endometriosis-associated cancers. These are type I ovarian cancers with distinctive molecular genetic changes that differ from type II ovarian cancers (high-grade serous carcinomas) (21). The risk of future ovarian cancer diagnosis in women with long-term endometriosis is two to three-fold increased compared to women without endometriosis, but those series primarily evaluate risk in ovarian endometriotic cysts and not DIE or superficial endometriosis. The strongest evidence for an endometriotic etiology for some type I ovarian cancers is derived from characteristics observed upon inspection of resected endometriotic cysts.

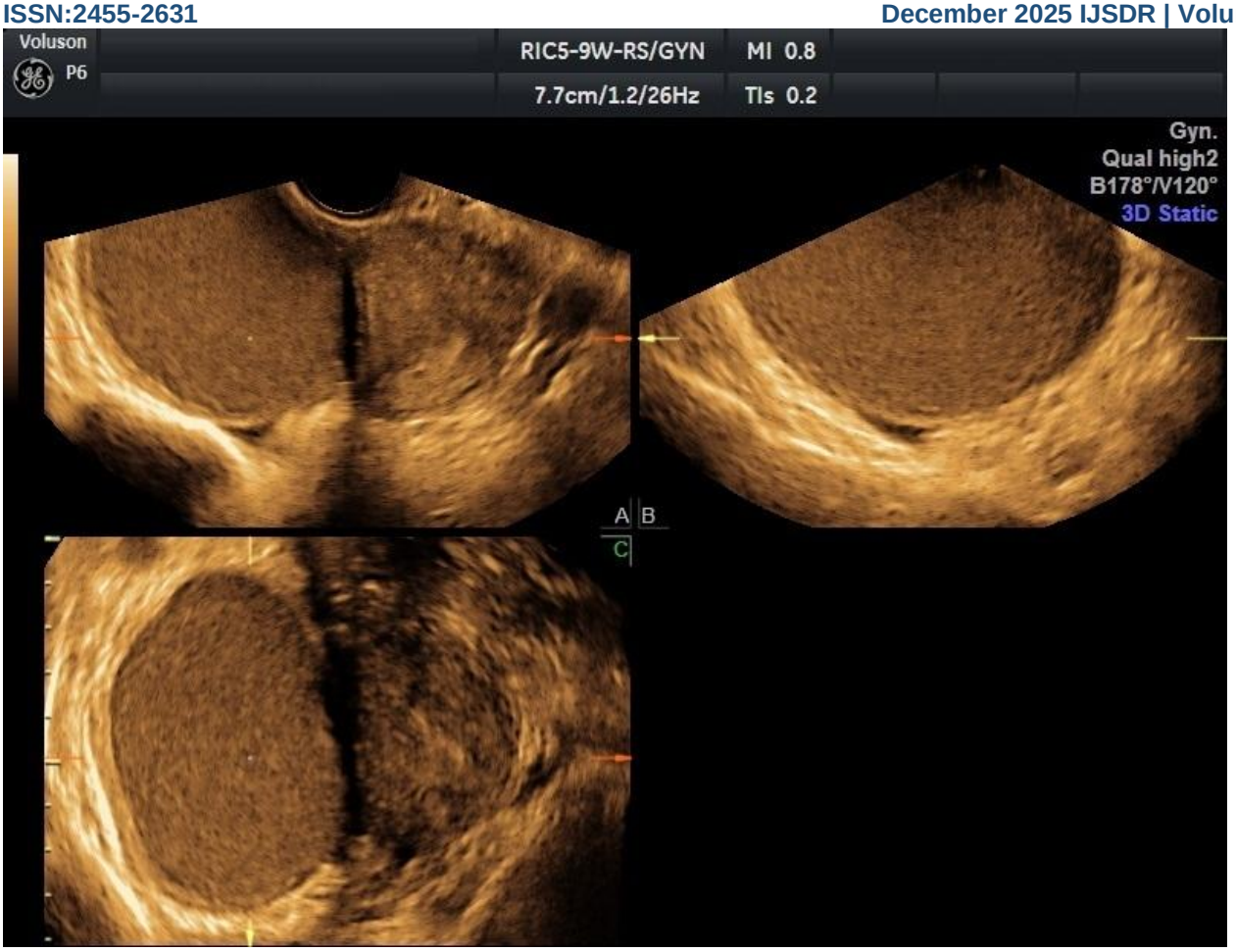


Various phases of tumor development—varying from normal-looking epithelium lining the endometriotic cyst to atypical endometriosis to borderline tumor to in situ carcinoma to invasive carcinoma—have been noted in resected endometriotic cysts, which provide irrefutable proof that endometriotic cysts give rise to endometriosis-linked cancers . Multifocal endometriotic lesions may be clonally associated, and endometriosis-related ovarian

neoplasms may arise from endometriotic lesions harboring an adequate number of mutations related to cancer, a situation encountered in large ovarian endometriotic cysts (21). It is probable that the somatic mutations are acquired during the growth of endometriotic cysts. The initial cells that form the cyst need to go through numerous divisions while forming the cyst, and there could be a much larger number of epithelial cells compared to superficial or deep infiltrating lesions. Apart from sporadic case reports , small discrete endometriotic lesions like superficial endometrioses and DIE do not have an increased risk of progression into endometriosis-associated cancer because they have an extremely low mutation burden.

Pathophysiology:

The development of endometriosis involves interactions among endocrine, immune, proinflammatory, and pro-angiogenic processes. Despite various theories and hypotheses that aim to clarify the mechanisms, the exact pathophysiology of endometriosis remains unclear. This variety of theories adds confusion to understanding the disease and complicates the determination of medical and surgical treatment options (13). One of the most accepted theories is related to ectopic endometrial cells, known as Sampson's Theory of Retrograde Menstruation. This hypothesis suggests that endometrial cells flow in the opposite direction through the fallopian tubes into the peritoneal cavity during the shedding of the uterine lining during menstruation. The problem with this theory is that it can explain some locations where endometriosis is found, like ovarian and superficial peritoneal lesions. However, it does not account for other areas, such as extraperitoneal lesions or deep infiltrating endometriosis (14). Additionally, researchers have identified cases of endometriosis in girls who have not yet begun menstruating, which challenges this theory. Clinical reports also indicate that some men have endometriosis, though this is rare. Finally, while researchers estimate that up to 90% of women experience retrograde menstruation, not all develop endometriosis, suggesting that other factors are involved (15). The theory that has gained more recognition is the Homeobox (HOX) genes theory. These genes are highly preserved DNA sequences that control the positioning of embryonic structures. HOX genes play a role in developing the female reproductive system by encoding transcription factors that attach to DNA regulatory regions of target genes involved in organizing segments during embryogenesis (16). Symptoms from endometriosis, along with treatments and the potential need for surgery, negatively affect quality of life. Patients with symptomatic endometriosis show higher levels of stress, somatization, and fatigue in their daily lives. Previous studies have also shown that these women often experience depression and anxiety disorders. Fertility issues appear to be an independent risk factor for mental health problems. Couples dealing with infertility report lower self-assessment, a higher occurrence of depressive symptoms, and sexual dysfunctions (17). The ability to have children is a fundamental need in human life. The World Health Organization defines infertility as the inability to achieve pregnancy after 12 months of regular unprotected sexual intercourse. The prevalence of infertility varies by geographic region and patient age or other health conditions, ranging from 3.5% to 16.7% in developed countries. This issue affects about 9% of Poles of reproductive age who want to conceive (18). Furthermore, global trends show that the number of people with infertility gradually increased from 42.0 million in 1990 to 48.5 million in 2010.



- **Pharmacological management of Endometriosis -**

Why Endometriosis is So Painful:

When researchers look for new ways to treat endometriosis, they focus on three key problems that make the disease tick:

1. Too Much Inflammation: The body has a big, out-of-control inflammatory response. Inflammation is at the very core of the pain.
2. Estrogen Overload: There is an excessive amount of the hormone estrogen being produced.
3. Hormone Misfire (Progesterone Resistance): The cells become resistant to progesterone, the hormone that should naturally help keep the estrogen in check.

This creates a kind of vicious cycle, causing the painful symptoms and disrupting the normal way cells and the immune system work.

The Estrogen Factory: Fueling the Growth

The very key to the endometriosis implants surviving and growing is having a constant, local supply of estrogen. The implants are clever; they build their own estrogen! They use an enzyme called aromatase that allows them to turn simple compounds like cholesterol into estradiol (a powerful type of estrogen). This is like having a private estrogen factory right in the painful tissue.

This locally-made estrogen, combined with the estrogen coming from the ovaries and body fat, acts like a powerful fertilizer, constantly promoting the survival and growth of the endometriotic tissue wherever it is in the body. The resulting high levels of inflammatory chemicals like prostaglandins and cytokines are what cause the intense pain and make the inflammation so hard to clear.

- **NON STEROIDAL ANTI-INFLAMMATORY DRUGS:**
  NSAIDs are the most commonly used first-line treatments for managing pain from endometriosis and menstrual cramps. The pain associated with endometriosis often comes from high levels of prostaglandins,

interleukins, and cytokines. NSAIDs block the COX enzyme, which is vital for producing these inflammatory substances. Though both COX1 and COX2 receptors are present, studies indicate that ectopic endometrial tissue has more COX2 receptors. Both selective and non-selective COX inhibitors are commonly used for pain relief. Recent studies have suggested that selective COX2 inhibitors, like rofecoxib, may also help slow the growth of endometrial tissue. However, there is still unclear evidence about the effectiveness of NSAIDs in controlling endometriosis..

Hormone Therapies for Endometriosis:

When it comes to managing the pain of endometriosis, hormone therapies are often a key part of the treatment plan. They work by regulating the hormones that fuel the growth of endometrial tissue outside the uterus. Here's a breakdown of the common types and what you can expect:Combination Hormonal Contraceptives-This group includes birth control pills, patches, and vaginal rings. They are called "combination" because they contain both estrogen and progestin.

How they help: By providing a steady dose of hormones, they often suppress the body's natural cycle. This can significantly reduce pain, and for many women, it means they stop having a monthly period while on the treatment, or have much lighter and less frequent bleeding.These contraceptives contain just one hormone: progestin. This category includes pills (the mini-pill), injections (shots), and hormonal IUDs (intrauterine devices). Progestin works by thinning the uterine lining and suppressing ovulation. These options are effective at cutting down on endometriosis-related pain. Similar to the combination therapies, most women taking these either don't get a period or have fewer periods overall.

Important Considerations and Side Effects .While these therapies are very helpful, it's important to be aware of potential downsides. Hormone therapy can cause side effects, including:

- Weight gain
- Depression or mood changes
- Acne
- Increased body hair
- Irregular bleeding

Irregular bleeding (especially when first starting a new method).Before starting any hormonal treatment, you should have a detailed conversation with your doctor about the potential risks and the benefits for your specific situation. A crucial point to remember: If you decide to stop taking this type of medicine, be prepared for the possibility that your original endometriosis symptoms may return. If this happens, make sure to let your doctor know right away so you can discuss the next steps in your treatment plan.

Beyond Contraceptives: GnRH Analogues .Another type of hormone therapy your doctor might discuss is Gonadotropin-releasing Hormone (GnRH) Analogues.(The article you provided cuts off here, but generally, GnRH analogues work by temporarily putting the body into a state similar to menopause to significantly suppress hormone production and endometrial growth).

- ***Diagnosis***

Conservative surgery cuts out endometriosis tissue. Conservative surgery tries to leave the uterus and the ovaries intact. If you have endometriosis and you're trying to get pregnant, this kind of surgery can improve your chances. It also might help if the condition brings on awful pain — but endometriosis and pain can return later after surgery.

During laparoscopic surgery, your surgeon places a slender viewing instrument called a laparoscope through a small cut near your navel. Surgical tools are inserted to remove endometriosis tissue through another small cut.

Some surgeons do laparoscopy with help from robotic devices that they control. After surgery, your health care team may recommend taking hormone medicine to help improve pain.

Fertility treatment

Endometriosis can lead to trouble getting pregnant. If it is difficult for you to get pregnant, your health care group might advise you to undergo fertility treatment. You could be sent to a physician who specializes in treating infertility, known as a reproductive endocrinologist. Fertility treatment can consist of medication that causes ovaries to produce more eggs. It also consists of a series of procedures that combine eggs and sperm outside of the body, known as in vitro fertilization. Your personal circumstances determine the treatment that's best for you.

Hysterectomy with removal of the ovaries:

Hysterectomy is the removal of the uterus. Removing the uterus and ovaries was previously considered to be the best treatment for endometriosis. Now, some believe that it is an option as a last resort to alleviate pain after other treatments have failed. Other experts prefer surgery that involves removing the endometriosis tissue carefully and completely. Oophorectomy, or the removal of the ovaries, induces premature menopause. The absence of hormones produced by the ovaries might alleviate endometriosis symptoms for some. However, for others, remaining endometriosis after surgery persists with symptoms. Early menopause also poses a risk of cardiovascular and blood vessel diseases, particular metabolic disorders and premature death. In individuals who don't wish to become pregnant, hysterectomy occasionally is used to treat symptoms associated with endometriosis. These are heavy bleeding and crampy menses from uterine cramping. Even if the ovaries are retained, a hysterectomy can indirectly impact your health many years later. That is particularly the case if you have the procedure before age 35(20).

When choosing the appropriate therapy to treat endometriosis, a health care provider must consider each common symptom and its desires, the potential collateral effects, age, extent, disease location, previous treatments, and economical points. In certain situations involving bladder, bowel, ureters, or extrapelvic structures, and those with concomitant pain conditions, there is a need to give the patient a multidisciplinary treatment so that there is proper and integral care [37,38]. Treatments available now are hormonal treatment and the elimination of injuries, yet they are only of limited efficiency. For trauma, surgical removal with hormonal therapy is the primary treatment approach; however, these procedures frequently have side effects in addition to variable efficacy [5]. Surgery typically plays a significant role in the treatment of infertility as observed in endometriosis. Stage of the condition and outcome should be taken into consideration when assessing the success of the surgical treatment compared with approaches to alternative management [39].

Medical therapy options include non-steroidal analgesics, hormonal contraceptives, gonadotropin-releasing hormone analogs (GnRH), and aromatase inhibitors. However, the advantage of pre- or postoperative medical therapy remains indefinite. The deprivation of endometriosis prior to surgery can minimize inflammation and aid in injury eradication. Although post-operative hormonal removal is capable of preventing recurrence, it should be noted that in the various systematic reviews, neither medical treatment pre-operatively nor post-operatively has any overall clinical effect (22,23). It should be noted that surgical treatment is not included in this review.

Non-Pharmacological Treatment:

Treatment of endometriosis depends on symptoms, size, and location of lesions. The primary method involves surgery, pharmacotherapy, and thorough individual treatment. But even with the pharmacological treatment employed and the efficacy of current therapies, other non-pharmacological or natural alternatives have been sought at present to obtain a reduction in the adverse effects or complications potentially produced by pharmacological treatments, thereby creating an ongoing pursuit of safe and effective treatments that can be

sustained in the long term due to their natural origin (22). Endometriosis pathogenesis encompasses the dysregulation of several physiological processes. Natural or herbal therapies are geared towards inhibiting, interacting with, and regulating cellular functions to enhance proliferation, inflammation, and angiogenesis, which define the growth of endometrial tissue outside the uterine environment. In addition, since it is an estrogen-dependent disorder, described alternative therapies are directed mostly towards regulating and inhibiting the production of estrogens (21).

One of the most frequently detailed options in literature is application of Resveratrol as an antioxidant, anti-inflammatory, and antiangiogenic agent. Experimental research on murine models by Ricci AG et al. proposes that Resveratrol treatment profoundly curbs cell growth and vascular density of lesions formed by endometriosis as well as endometrial endothelial cell growth. Resveratrol is a phytoalexin polyphenol produced by plants. It has been demonstrated to inhibit cell invasion and induce apoptosis with low estrogenic activity. In the same research, the activity of epigallocatechin-3-gallate (EGCG) in combination with Resveratrol-induced therapy has been elaborated as utilizing both therapies together, resulting in lesion size reduction with statistically significant outcomes. Yet, the EGCG alone has been found to be useful in the treatment of benign feminine reproductive illness due to its ability to function as an antioxidant and target numerous pathways, inducing apoptosis, lipid peroxidation, cholesterol abduction, and free radical scavenging, rendering it clinically potential as an alternative therapy (25).

Conversely, herbal extraction with anti-inflammatory properties exists among the outlined therapies. Together, the Pueraria extract, which is also referred to as the kudzu flower, suppresses the aromatase activity found in endothelial cells and eliminates the adhesion and migration. Similarly, hexane extract of black garlic is employed due to its proapoptotic, antioxidant, and anticarcinogenic activity, induced by suppressing certain signaling pathways, and is a potential substitute in endometriosis prevention and treatment. Likewise, Uncaria tomentosa extract has been employed as a remedy treatment in other inflammatory pathologies, such as endometriosis, since it modulates the cell cycle by inducing apoptosis and inhibiting prostaglandin 2 (PGE2) activity (26).

In the case of curcumin, Arablou and Kolahdouz-Mohammadi have commented on the therapeutic effects of this phenolic compound on endometriosis. They reported that it hinders the advancement and invasion of endometrial cells and inflammation. Additionally, Chowdhary et al., in their protocol, came to the conclusion that curcumin imparts positive effects on stromal cells from patients with endometriosis, in which downregulation of cytokines and chemokines and inhibition of STAT3 and JNK phosphorylation dose-dependently were noted, rendering it a suitable choice for symptoms caused by endometriosis [47].

Recent studies on the impact of curcumin on gynecological diseases have provided impressive findings. For example, it has been proven that curcumin brings about notable relief of symptoms caused in urinary infection owing to its anti-inflammatory, antitumor, and antioxidant properties, along with its antiangiogenic features which infer that curcumin may represent a promising second-line treatment in endometriosis working on inflammation, oxidative stress, invasion, apoptosis, and adhesion (22).

Another fundamental study in animal models has shown the melatonin ability to decrease the size of endometrial mass. In these experiments, it was noted that cellular proliferation caused by estradiol was blocked after 48 h of melatonin treatment. Moreover, it was noted how melatonin suppressed estradiol-induced epithelial–mesenchymal transition and endometrial epithelial cell migration (21).

At the same time, application of Calligonum comosum extract, in certain studies, has been shown to be linked with the inhibition of endometrial wounds' growth during development through triggering lower vascularization, proliferation, and immune infiltration. Other alternative treatments such as the application of acai extract,

viburnum opulus, and silimarina have been reported by their antioxidants, anti-inflammatory, antiproliferative, and proapoptotic actions that significantly lowered the size and proliferation of endometrial wounds (26).

Pharmacological Interventions:

Progestins are the pharmacological first-line therapy of endometriosis. Progestins are synthetic substances with progestogenic action. In binding to progesterone receptors, it induces a reduction in the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to anovulation and amenorrhea. They also induce a hypoestrogenic effect inhibiting the inflammation process and angiogenesis and inducing apoptosis of the endometrial cells, thereby inhibiting endometriosis and dysmenorrhea. The main application relies on the removal or minimization of the attached pain (27).

The flexibility in the mode of administration of these medications renders them truly useful as they are able to be administered orally, intramuscularly, subcutaneously, and intrauterinely. The side effects are most frequently seen as bleeding or uterine spotting irregularities, weight gain, humor swings, and bone loss (only prolonged medroxyprogesterone acetate treatments) (28).

- ***Treatment of endometriosis*** **:**

In the treatment of endometriosis, the most frequently used progestins are the following.

The aim of medical treatment for endometriosis has been to alter the menstrual cycle hormonally to produce a pseudo pregnancy, pseudo-menopause, or chronic anovulatory condition. The usual daily dose of danazol for the treatment of endometriosis is 600-800 mg; despite this, the dose is associated with marked steroid side effects, such as hirsutism, mood change, an irreversible deepening of the voice, bad effects on serum lipids, and, in exceptional instances, irreversible and life-threatening liver damage (29). Endometriosis is generally treated with progesterone medications. They cause endometrial cells to decidualize, which leads to atrophy. Abnormal uterine bleeding, vomiting, breast discomfort, and depression are all potential side effects The side effects of hypoestrogenism consist of vaginal heavy bleeding, vaginal dryness, decreased libido, breast discomfort, insomnia, and depression . Endometriosis has been treated with diverse hormones and medications. Hormone therapy frequently stops ovulation by inhibiting the ovaries from secreting hormones, such as estrogen. This may help lower the rate of local development and activity of the endometrium and endometrial lesions. Due to their adverse side effects, various hormones like methyl testosterone and estrogen have been withdrawn. Other drugs have been insufficiently studied, such as clomiphene, tamoxifen, and the antiprogestational drug mifepristone. Laparoscopy is utilized to diagnosis endometriosis surgically. A laparoscope, a thin viewing tube, is introduced into the belly with a small cut during laparoscopy. To have a second opening for the surgical instruments, a second cut might be made in the lower abdomen. Your physician can examine the surface of the ovaries, uterus, fallopian tubes, and other structures closely with a laparoscope. Surgical devices for cutting scar tissue or taking tissue biopsies may also be attached to the laparoscope. Laparoscopic removal of endometriomas is recommended for ovarian cysts larger than 4 to 5 cm in diameter. Endometriosis has been treated with everything from monopolar cautery and scissors to a wide variety of lasers and ultrasonic scalpels. Endometriosis pain is treated surgically by interrupting brain circuits that transmit pain signals. Different considerations should be taken, such as the optimum way to access the pelvis and abdomen, which can be achieved through laparoscopy or laparotomy. Laparoscopy is time-saving and less costly and less recovery time.

Medroxyprogesterone Acetate (MPA)-
Progesterone 17-OH derivatives are given intramuscularly or subcutaneously every three months with a depot formulation or orally. The MPA decreases pain from endometriosis and enhances quality of life and productivity. However, it is associated with a serious side effect: loss of mineral bone density and increased fracture risk. That is why the FDA only recommends its use in the event of other therapies being insufficient and for up to 2 years at most.

Analgesics-

Although they are not a treatment for endometriosis on their own, pain relievers are utilized as first-line treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and some opioids are used to relieve pain associated with endometriosis. NSAIDs are considered the first-line symptomatic treatment due to their ability to inhibit prostaglandin production and inflammation. However, it is recommended to limit their long-term use due to their side effects, such as gastric ulcers and acute kidney injury (30). Likewise, they also decrease the stimulation of afferent nerves and directly affect nociceptive receptors to prevent the production and release of substances that generate pain.

New Therapies-

Most research that is still under assessment for the treatment of endometriosis medically has characterized the primary treatment option as GnRH antagonists because of their effectiveness and safety.

A study presented by Volpini et al. refers to the application of nanotechnology through novel theranostic applications of nano products and integration of phototherapy and other nanotechnologies as novel treatment modalities for endometriosis (31). Among the principal techniques that have been researched in the area of nanotechnology is the application of magnetic hyperthermia, which involves the injection of nanoparticles for the destruction of endometrial tissue; but up to now, it has been tried only in murine models, although it is not excluded that in the future it may be an excellent second-line treatment.

- **Nutrition Related to Endometriosis**

In view of the chronic nature of endometriosis and its variability in response to different treatments, various strategies are necessary for managing these patients. One of these alternative practices is dietary control; approximately half of the women with dietary support have reported great improvement in their condition.

High Fiber, Low in Trans Fatty Acids Diet, and Its Response in Endometriosis**.**Estrogens play a relevant role in the pathogenesis of endometriosis, so any factor in the diet that modulates estrogen activity will be important. Increasing dietary fiber and decreasing saturated fat have been found to help reduce circulating estrogen concentrations by 10 to 25% .A high consumption of trans fatty acids has been shown to increase proinflammatory markers such as Interleukin 6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α), involved in the pathogenesis of endometriosis (32).Some fatty acids, such as Omega-6, are precursors of proinflammatory prostaglandins associated with increased pelvic pain in endometriosis. However, some dietary fats have protective roles against the condition. A study conducted by Missmer et al. on premenopausal women reported fewer diagnoses of endometriosis in women with high Omega-3 consumption.

Association of Meat Consumption with the Onset of Endometriosis:Meat consumption may be linked with elevated levels of estradiol, estrone sulfate, and proinflammatory biomarkers that result in a heightened state of inflammation and the onset of endometriosis. In a study by Yamamoto et al., women with a high red meat intake (more than two servings daily) developed a 56% higher risk of endometriosis.

Vitamin Supplementation D, C, and E and Their Assistance with Symptoms of Endometriosis:

Vitamin D (VD) deficiency has been found to relate to an increased risk for endometriosis and exacerbation of symptoms. VD treatment in a clinical trial by Mehdizadehkashi et al. on endometriotic women alleviated the symptoms by decreasing pelvic pain . This could be due to the anti-inflammatory action of VD by reducing C-reactive protein (CRP) . Vitamin C (VC) and Vitamin E (VE), being anti-oxidants, have the potential to reduce the role of inflammation in endometriosis. VC and VE supplementation has been found to alleviate pelvic pain, dyspareunia, dysmenorrhea, and risk of endometriosis.

Caffeine and Endometriosis:

Caffeine intake has been reported to elevate estrogen and estrone in the follicular phase, potentially raising the risk of estrogen-related pathologies like endometriosis (33). In a meta-analysis by Kechagias et al., no correlation between caffeine intake and higher risk of endometriosis was established. Nonetheless, they did report a correlation between the quantity of caffeine intake and endometriosis. Large doses of caffeine (>300 mg/day) are potentially linked to increased risk for endometriosis (Table 2)

Table no . 2

Treatments for Endometriosis :

Category	Treatment	How It Works
Pharmacological (Medications)	Dienogest (DNG)	Lowers estrogen levels, reduces inflammation and new blood vessel growth, and helps endometriotic cells die off.
Pharmacological (Medications)	Norethindrone acetate (NETA)	Relieves menstrual pain, pain during sex, and pain during bowel movements.
Pharmacological (Medications)	Medroxyprogesterone acetate (MPA)	Helps reduce overall pelvic pain caused by endometriosis.
Pharmacological (Medications)	Elagolix (GnRH-a)	Reduces moderate to severe menstrual pain by lowering hormone levels.
Non-Pharmacological (Natural or Alternative)	Resveratrol	Slows down cell growth and blood vessel formation in endometrial tissue.
Non-Pharmacological (Natural or Alternative)	Black garlic extract	Has antioxidant and cell-protective effects that help reduce endometriosis growth.
Non-Pharmacological (Natural or Alternative)	Curcumin (from turmeric)	Reduces inflammation and prevents endometrial cells from spreading.
Non-Pharmacological (Natural or Alternative)	Melatonin	Lowers the size of endometrial growths and prevents hormone-driven cell changes.

Non-Pharmacological (Natural or Alternative)	Calligonum comosum extract	Helps stop endometrial lesions from growing.
New Treatments	Nanotechnology	Uses tiny particles and techniques like magnetic heat and light therapy to target endometrial tissue.

Endometriosis is strongly associated with a variety of psychiatric symptoms, mainly the occurrence of depression, anxiety, psychosocial distress, and reduction of quality of life. In evaluating the relationship between endometriosis and psychiatric disorders, it is important to take into account whether chronic pelvic pain (CPP) is present; CPP is characterized by non-neoplastic pain felt within the pelvic regions that is persistent or recurring for at least 6 months []. Specifically, women with CPP report high levels of depression and anxiety, loss of work ability, restriction in social activities, and poor quality of life.

Sachedina and Todd studied the interaction between CPP and endometriosis among adolescents. This research indicates that endometriosis is among the main causes of CPP in this population and touches on the issue of how endometriosis, which is sometimes not diagnosed in a timely manner, can affect the patient's quality of life and mental health (34) .

It should be remembered that the severity of pain is not related to the stage of endometriosis. So, women with minimal endometriosis can be severely affected by pelvic pain, and those with advanced endometriosis can have less severe or chronic pain. The above descriptions imply the potential role of psychological factors in the pain experience of women with endometriosis

In Gambadauro et al.'s meta-analysis, those studies comparing women with and without endometriosis or women with endometriosis with and without pain in the pelvis were compared. The findings of this study showed that patients with endometriosis suffering from pelvic pain reported significantly more depression than those pain-free . In another research by Lorençatto et al., depression prevalence was assessed in a group of women with endometriosis and CPP compared to a group of women with endometriosis but without CPP. The findings of the study indicated that 86% of the women with CPP were depressed, compared to 38% of women without pain being depressed. Moreover, those symptoms of depression, like somatic distress, inhibition on work, dissatisfaction, and unhappiness, were more prominently found among women with pain (35).

-Infertility

Endometriosis is a female reproductive-aged disease with the potential to lower fertility .Evidence has demonstrated diminished pregnancy rates and live births and a higher miscarriage rate among women suffering from endometriosis and adenomyosis (37). Infertility in endometriosis patients could be the result of a range of conditions from anatomical distortion caused by adhesions and fibrosis to endocrine disturbances and immunopathies . Up to the present day, no medication or operation notably enhances fertility.

-Sexual Dysfunction

As endometriosis is due to inflammatory reactions and invasion of anatomical structures, this condition may lead to dysmenorrhea, dyspareunia, dyschezia, dysuria, and CPP (36). Dyspareunia affects sexual life and social relationships in a negative way. Surgical excision of endometriotic lesions causes a decrease in dyspareunia and an increase in sexual activity and satisfaction. In contrast, women with endometriosis report a significantly lower

frequency of sexual intercourse than healthy women, and symptoms lower the quality of intercourse, hindering sexual activity. Sexual dysfunction is associated with impairment in quality of life .

-Pregnancy

During pregnancy, endometriosis is particularly challenging. While symptoms may be anticipated to diminish and endometriotic lesions to diminish during pregnancy, the situation is more complex than this. In some instances, malignant change in ovarian endometriotic lesions has occurred. This process is compounded by the involvement of chronic inflammation, adhesions, resistance to progesterone, and dysregulation of genes involved in embryo implantation. As a result, pregnancy in women with endometriosis may be marked by disease-related complications such as spontaneous hemoperitoneum and intestinal complications, as well as adverse pregnancy outcomes. These include preterm birth, fetal growth restriction, hypertensive disorders, obstetric hemorrhages (such as placenta previa and placental abruption), miscarriage, or the need for cesarean section. While recent evidence is conflicting and does not indicate significant association of endometriosis with such complications, with the exception of miscarriage and cesarean delivery, it is clear that endometriosis can significantly affect pregnancy (36).

- Reproductive Age

Endometriosis is a major condition experienced by as many as 5–15% of women of reproductive age around the world, further emphasizing its importance in this particular age range. This period in a woman's life, which is marked by the possibility of conception, is especially impacted by endometriosis. This illness undermines fertility and has an impact on many components of health and wellbeing as a whole .

Result:

The review highlights endometriosis is a multi-factorial condition with hormonal, genetic, immunological, and environmental components. The theory of recruitment of endometrial stem cells gives fresh insight into disease inception, including how aberrant stem cells are responsible for the formation of ectopic endometrial tissue. Genetic and molecular research further identifies changes in estrogen regulation, inflammation, and cell proliferation pathways that maintain the disease process.

Pharmacological and hormonal treatments—oral contraceptives, progestins, and GnRH agonists—continue to be the focus of therapy, although long-term use necessitates vigilant pharmacovigilance because of side effects such as bone loss and mood alterations. Described data also suggest a potential association between endometriosis and ovarian cancer, especially clear cell and endometrioid subtypes, which highlights the importance of regular surveillance[39]

In general, results emphasize the critical role of pharmacovigilance in maintaining drug safety, maximizing therapy, and facilitating personalized care in the management of endometriosis.

Conclusion :

Endometriosis continues to be a multifaceted, chronic disorder with important impact on women's health and quality of life. While evolving knowledge of its stem cell basis, molecular pathways, and hormonal regulation has provided useful information, efficient long-term control remains problematic. Pharmacovigilance is crucial in the promotion of safe and effective therapy use, tracking adverse effects, and steering clinicians towards personalized treatment strategies.

Combining pharmacovigilance with clinical and molecular studies is capable of producing better therapeutic approaches, complication diagnosis at an early stage, and improved patient safety. Continual research, awareness, and robust surveillance systems are necessary to create safer, more specific treatments and eventually enhance the lives of patients suffering from endometriosis.

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References:

1. Dyson MT, Roqueiro D, Monsivais D, Ercan CM, Pavone ME, et al. 2014. Genome-wide DNA methylation analysis predicts an epigenetic switch for GATA factor expression in endometriosis. PLOS Genet 10:e1004158 [PubMed: 24603652]
2. Burney RO, Giudice LC. 2012. Pathogenesis and pathophysiology of endometriosis. Fertil. Steril 98:511–19 [PubMed: 22819144]
3. Eisenberg VH, Weil C, Chodick G, Shalev V: Epidemiology of endometriosis: a large population-based database study from a healthcare provider with 2 million members. BJOG. 2018, 125:55-62. 10.1111/1471-0528.14711.
4. Tampaki EC, Tampakis A, Kontzoglou K, Kouraklis G. 2017. Commentary: somatic stem cells and their dysfunction in endometriosis. Front. Surg 4:37 [PubMed: 28770208]
5 Valentijn AJ, Palial K, Al-Lamee H, Tempest N, Drury J, et al. 2013. SSEA-1 isolates human endometrial basal glandular epithelial cells: phenotypic and functional characterization and implications in the pathogenesis of endometriosis. Hum. Reprod 28:2695–708 [PubMed: 23847113]
6 Nguyen HPT, Xiao L, Deane JA, Tan KS, Cousins FL, et al. 2017. N-cadherin identifies human endometrial epithelial progenitor cells by in vitro stem cell assays. Hum. Reprod 32:2254–68 [PubMed: 29040564]
7 Parasar P, Sacha CR, Ng N, McGuirk ER, Chinthala S, et al. 2017. Differentiating mouse embryonic stem cells express markers of human endometrium. Reprod. Biol. Endocrinol 15:52 [PubMed: 28716123]
8 Sakr S, Naqvi H, Komm B, Taylor HS. 2014. Endometriosis impairs bone marrow–derived stem cell recruitment to the uterus whereas bazedoxifene treatment leads to endometriosis regression and improved uterine stem cell engraftment. Endocrinology 155:1489–97 [PubMed: 24484171]
9 Kulak J Jr., Fischer C, Komm B, Taylor HS. 2011. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology 152:3226–32 [PubMed: 21586552]
10 Figueira PG, Abrao MS, Krikun G, Taylor HS. 2011. Stem cells in endometrium and their role in the pathogenesis of endometriosis. Ann. N. Y. Acad. Sci 1221:10–17 [PubMed: 21401624]
11 43. Nezhat C, King LP, Paka C, Odegaard J, Beygui R. 2012. Bilateral thoracic endometriosis affecting the lung and diaphragm. JSLS 16:140–42 [PubMed: 22906342
12 Anglesio MS, Papadopoulos N, Ayhan A, Nazeran TM, Noë M, et al. 2017. Cancer-associated mutations in endometriosis without cancer. N. Engl. J. Med 376:1835–48 [PubMed: 28489996]
13 .Wang P.H., Yang S.T., Chang W.H., Liu C.H., Lee F.K., Lee W.L. Endometriosis: Part I. Basic concept. Taiwan. J. Obstet. Gynecol. 2022;61:927–934. doi: 10.1016/j.tjog.2022.08.002.
14 Wang Y., Nicholes K., Shih I.M. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 2020;15:71–95. doi: 10.1146/annurev-pathmechdis-012419-032654.
15 Cousins F.L., McKinnon B.D., Mortlock S., Fitzgerald H.C., Zhang C., Montgomery G.W., Gargett C.E. New concepts on the etiology of endometriosis. J. Obstet. Gynaecol. Res. 2023;49:1090–1105. doi: 10.1111/jog.15549.
16 Lazim N., Elias M.H., Sutaji Z., Abdul Karim A.K., Abu M.A., Ugusman A., Syafruddin S.E., Mokhtar M.H., Ahmad M.F. Expression of HOXA10 Gene in Women with Endometriosis: A Systematic Review. Int. J. Mol. Sci. 2023;24:12869. doi: 10.3390/ijms241612869.
17 Shahraki Z., Davari-Tanha F., Ghajarzadeh M. Depression, sexual dysfunction and sexual quality of life in women with infertility. BMC Women's Health. 2018;18:92. doi: 10.1186/s12905-018-0584-2. [DOI] [PMC free article] [PubMed] [Google Scholar

18 Mascarenhas M.N., Flaxman S.R., Boerma T., Vanderpoel S., Stevens G.A. National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys. PLoS Med. 2012;9:e1001356. doi: 10.1371/journal.pmed.1001356.
19 Dogan E, Saygili U, Posaci C, et al. Regression of endometrial explants in rats treated with the cyclooxygenase-2 inhibitor rofecoxib. Fertil Steril. 2004;82(Suppl 3):1115–1120. doi: 10.1016/j.fertnstert.2004.06.033.
20 https://www.mayoclinic.org/diseases-conditions/endometriosis/diagnosis-treatment/drc-20354661.
21 Anglesio MS, Bashashati A, Wang YK, Senz J, Ha G, et al. 2015. Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. J. Pathol 236:201–9 [PubMed: 25692284]
22 ohnson N.P., Hummelshoj L., Adamson G.D., Keckstein J., Taylor H.S., Abrao M.S., Bush D., Kiesel L., Tamimi R., Sharpe-Timms K.L., et al. World Endometriosis Society consensus on the classification of endometriosis. Hum. Reprod. 2017;32:315–324. doi: 10.1093/humrep/dew293.
23 anbo 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.
24 Chowdhury I., Banerjee S., Driss A., Xu W., Mehrabi S., Nezhat C., Sidell N., Taylor R.N., Thompson W.E. Curcumin attenuates proangiogenic and proinflammatory factors in human eutopic endometrial stromal cells through theNF-κB signaling pathway. J. Cell. Physiol. 2019;234:6298–6312. doi: 10.1002/jcp.27360.
25 Hazimeh D., Massoud G., Parish M., Singh B., Segars J., Islam M.S. Green Tea and Benign Gynecologic Disorders: A New Trick for An Old Beverage? Nutrients. 2023;15:1439. doi: 10.3390/nu15061439
26 Meresman G.F., Götte M., Laschke M.W. Plants as source of new therapies for endometriosis: A review of preclinical and clinical studies. Hum. Reprod. Update. 2021;27:367–392. doi: 10.1093/humupd/dmaa039.
27 Capezzuoli T., Rossi M., La Torre F., Vannuccini S., Petraglia F. Hormonal drugs for the treatment of endometriosis. Curr. Opin. Pharmacol. 2022;6:102311. doi: 10.1016/j.coph.2022.102311
28 Vannuccini S., Clemenza S., Rossi M., Petraglia F. Hormonal treatments for endometriosis: The endocrine background. Rev. Endocr. Metab. Disord. 2022;23:333–355. doi: 10.1007/s11154-021-09666-w.
29 Buttram VC, Belue JB, Reiter R: Interim report of a study of danazol for the treatment of endometriosis . Fertil Steril. 1982, 37:478-83. 10.1016/S0015-0282(16)46151-0
30 Kalaitzopoulos D.R., Samartzis N., Kolovos G.N., Mareti E., Samartzis E.P., Eberhard M., Dinas K., Daniilidis A. Treatment of endometriosis: A review with comparison of 8 guidelines. BMC Women's Health. 2021;21:397. doi: 10.1186/s12905-021-01545-5.
31 Park Y., Demessie A.A., Luo A., Taratula O.R., Moses A.S., Do P., Campos L., Jahangiri Y., Wyatt C.R., Albarqi H.A., et al. Targeted Nanoparticles with High Heating Efficiency for the Treatment of Endometriosis with Systemically Delivered Magnetic Hyperthermia. Small. 2022;18:e2107808. doi: 10.1002/smll.202107808.
32 Arab A., Karimi E., Vingrys K., Kelishadi M.R., Mehrabani S., Askari G. Food groups and nutrients consumption and risk of endometriosis: A systematic review and meta-analysis of observational studies. Nutr. J. 2022;2:58. doi: 10.1186/s12937-022-00812-x.
33 Helbig M., Vesper A.S., Beyer I., Fehm T. Does nutrition affect endometriosis? Geburtshilfe Frauenheilkd. 2021;81:191–199. doi: 10.1055/a-1207-0557
34 Fall M., Baranowski A.P., Fowler C.J., Lepinard V., Malone-Lee J.G., Messelink E.J., Oberpenning F., Osborne J.L., Schumacher S. European Association of Urology EAU Guidelines on Chronic Pelvic Pain. Eur. Urol. 2004;46:681–689. doi: 10.1016/j.eururo.2004.07.030.
35 Lorençatto C., Petta C.A., Navarro M.J., Bahamondes L., Matos A. Depression in Women with Endometriosis with and without Chronic Pelvic Pain. Acta Obstet. Gynecol. Scand. 2006;85:88–92. doi: 10.1080/00016340500456118.

36 Della Corte L., Di Filippo C., Gabrielli O., Reppuccia S., La Rosa V.L., Ragusa R., Fichera M., Commodari E., Bifulco G., Giampaolino P. The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. Int. J. Environ. Res. Public. Health. 2020;17:4683. doi: 10.3390/ijerph17134683

37 Vercellini P., Viganò P., Bandini V., Buggio L., Berlanda N., Somigliana E. Association of Endometriosis and Adenomyosis with Pregnancy and Infertility. Fertil. Steril. 2023;119:727–740. doi: 10.1016/j.fertnstert.2023.03.018.
38 Giudice, L. C. (2020). Clinical practice: Endometriosis. The New England Journal of Medicine, 382(13), 1244–1256.
39 Burney, R. O., & Giudice, L. C. (2012). Pathogenesis and pathophysiology of endometriosis. Fertility and Sterility, 98(3), 511–519.
40 Zondervan, K. T., Becker, C. M., & Missmer, S. A. (2020). Endometriosis. The Lancet, 395(10226), 730–743.