Review Article

Therapeutic Advances in Endometriosis-Associated Infertility: From Conventional Hormonal Therapy To Linzagolix

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Abstract

Endometriosis is a chronic estrogen-dependent disorder characterized by endometrial-like tissue outside the uterine cavity and is strongly associated with pelvic pain, inflammation, adhesions, and impaired fertility. Endometriosis-associated infertility is multifactorial and may involve pelvic anatomical distortion, tubal dysfunction, impaired ovulation and fertilization, ovarian damage, reduced ovarian reserve, altered oocyte quality, and impaired embryo implantation. This review summarizes the clinical features, epidemiology, risk factors, pathogenesis, diagnostic methods, and therapeutic approaches associated with endometriosis-related infertility. Conventional management includes pain management, hormonal therapy, conservative surgery, lifestyle modification, and assisted reproductive technologies such as intrauterine insemination and in vitro fertilization. Combined ethinyl estradiol and levonorgestrel suppress ovulation and reduce estrogenic stimulation of endometriotic lesions, contributing to control of pain and menstrual symptoms. Linzagolix is an orally administered, non-peptide GnRH receptor antagonist that produces rapid and dose-dependent suppression of ovarian estrogen production. Clinical evidence described in the source document indicates reductions in dysmenorrhea, non-menstrual pelvic pain, and heavy menstrual bleeding, while add-back therapy may reduce hypoestrogenic effects during extended treatment. Management of endometriosis-associated infertility requires a patient-centered approach considering age, disease severity, ovarian function, and reproductive goals.

KEYWORDS: Endometriosis; Infertility; Endometriosis-associated infertility; Linzagolix; Ethinyl Estradiol + Levonorgestrel.

Introduction

1.1 Endometriosis

Endometriosis is a chronic gynecological condition in which endometrial-like tissue develops outside the uterine cavity, commonly involving reproductive organs and pelvic peritoneal surfaces. The ectopic tissue is associated with chronic inflammation and fibrosis and may produce dysmenorrhea, chronic pelvic pain and infertility. The disease affects reproductive-age women and can substantially affect reproductive health and quality of life [1].

Classification systems have been developed to describe disease extent and support clinical communication and research. The American Fertility Society and revised American Society for Reproductive Medicine systems are widely used, while the Enzian classification provides additional description of deep infiltrating disease [2,3]. Conventional staging is useful for anatomical description, but disease stage does not reliably predict pain severity or fertility outcomes [4-5].

1.2 Major Phenotypes

- Superficial peritoneal endometriosis: lesions mainly involving the peritoneal surface.
- Ovarian endometriosis (endometrioma): cystic ovarian disease associated with damage to ovarian tissue and possible reduction of ovarian reserve.
- Deep infiltrating endometriosis (DIE): lesions extending deeply beneath the peritoneal surface and often involving structures such as uterosacral ligaments, bowel, bladder or ureters.
- Extrapelvic endometriosis: uncommon disease outside the pelvic cavity, including sites such as diaphragm, lungs, **abdominal wall or surgical scars.**

1.3 Clinical Importance

Endometriotic lesions may undergo cyclic hormonal changes and repeated inflammatory activity. The resulting inflammation, fibrosis and adhesions can distort pelvic anatomy, affect ovarian and tubal function, and contribute to infertility. The degree of fertility impairment varies with disease type, extent, ovarian function, age and other reproductive factors [6,7].

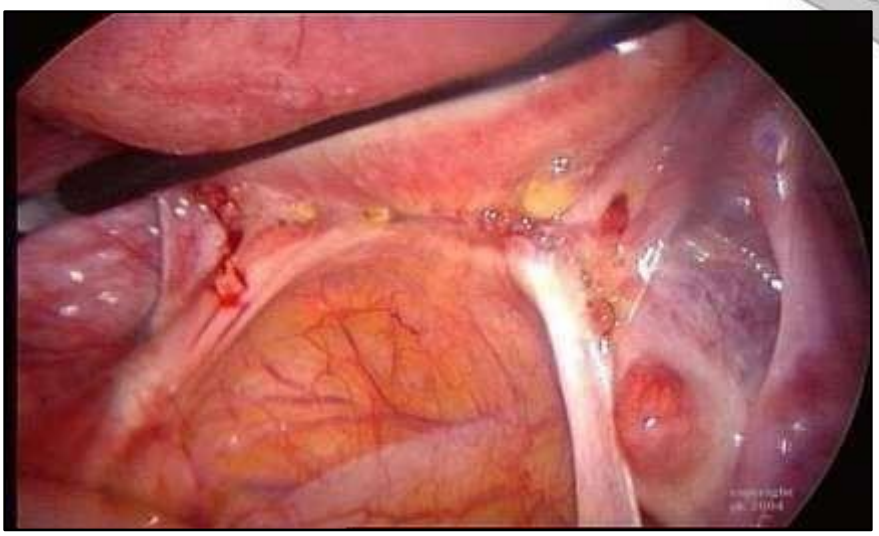


Figure 1. Laparoscopic appearance of endometriosis**.**

2. EPIDEMIOLOGY AND RISK FACTORS

2.1 Prevalence and Distribution

- Endometriosis affects approximately 10% of women and girls of reproductive age, corresponding to about 190 million people worldwide.
- Among women with chronic pelvic pain, reported prevalence is approximately 30–50%.
- Among women with infertility, reported prevalence is approximately 20–50%.
- Diagnosis is commonly delayed; the true prevalence may therefore be higher.
- It is most commonly diagnosed between 25 and 35 years, although it can occur during adolescence after menarche.
- The condition occurs worldwide; differences in reported prevalence are influenced by healthcare access, awareness and diagnostic methods.

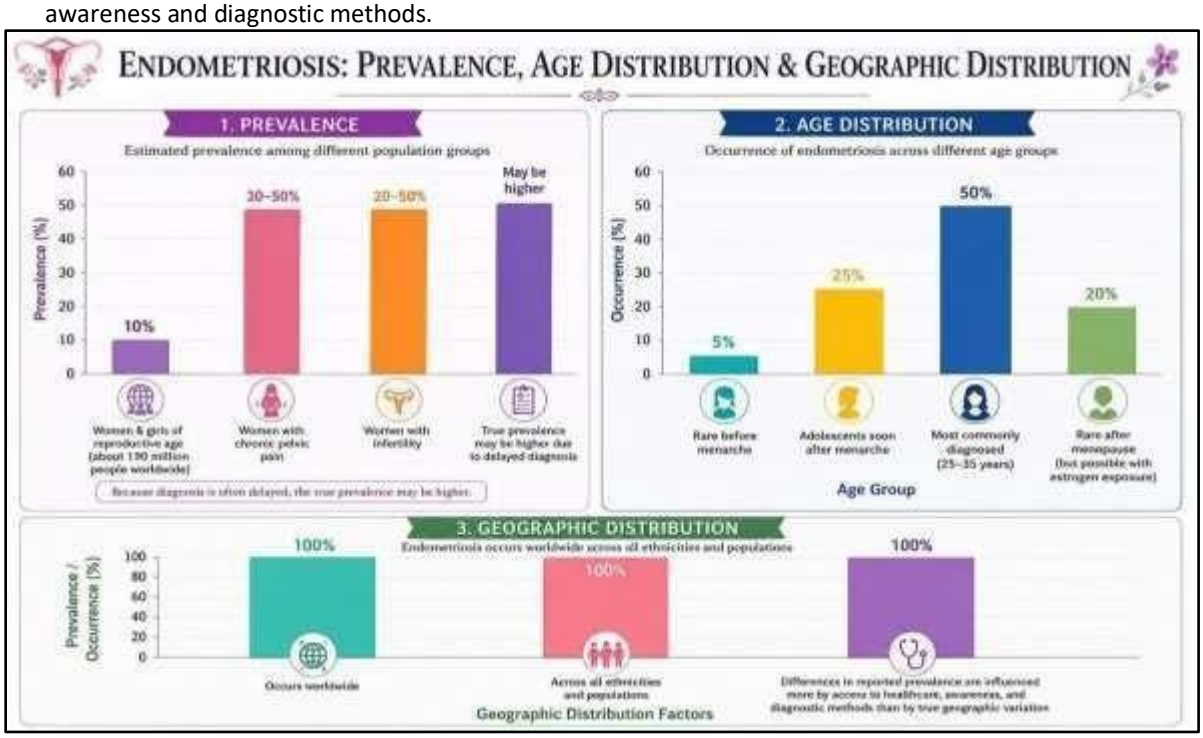


Figure 2. Prevalence, age distribution and geographic distribution of endometriosis.

2.2 Risk Factors

- Early menarche.
- Short menstrual cycles, particularly cycles shorter than 27 days.
- Heavy or prolonged menstrual bleeding.
- Nulliparity.
- Family history, particularly in first-degree relatives.
- Low body mass index.
- Congenital reproductive-tract anomalies causing menstrual outflow obstruction.

2.3 Protective and Burden-Related Factors

The source document lists multiparity, prolonged breastfeeding and use of combined hormonal contraceptives as factors that may reduce symptoms or disease progression. Endometriosis is also associated with chronic pelvic pain, infertility, reduced quality of life, lost productivity and increased healthcare costs.

Diagnostic delay is commonly described as about 6–10 years in many healthcare settings, with normalization of menstrual pain, limited awareness and need for specialist evaluation contributing to delay.

3. CLINICAL FEATURES AND DIAGNOSIS

3.1 Symptoms and Signs

- Progressive dysmenorrhea and chronic pelvic pain.
- Dyspareunia and infertility.
- Heavy or irregular menstrual bleeding.
- Dyschezia and dysuria, particularly during menstruation.
- Low back pain and fatigue.
- Pelvic tenderness, restricted uterine mobility and tenderness of uterosacral ligaments.
- Adnexal tenderness or an ovarian endometrioma.

3.2 Diagnostic Methods

Diagnosis is based on clinical assessment supported by imaging and, when indicated, surgical and histopathological evaluation. The document identifies medical history, pelvic examination, transvaginal ultrasonography (TVUS), magnetic resonance imaging (MRI), laparoscopy, histopathological examination, CA-125 testing and differential diagnosis as relevant approaches.

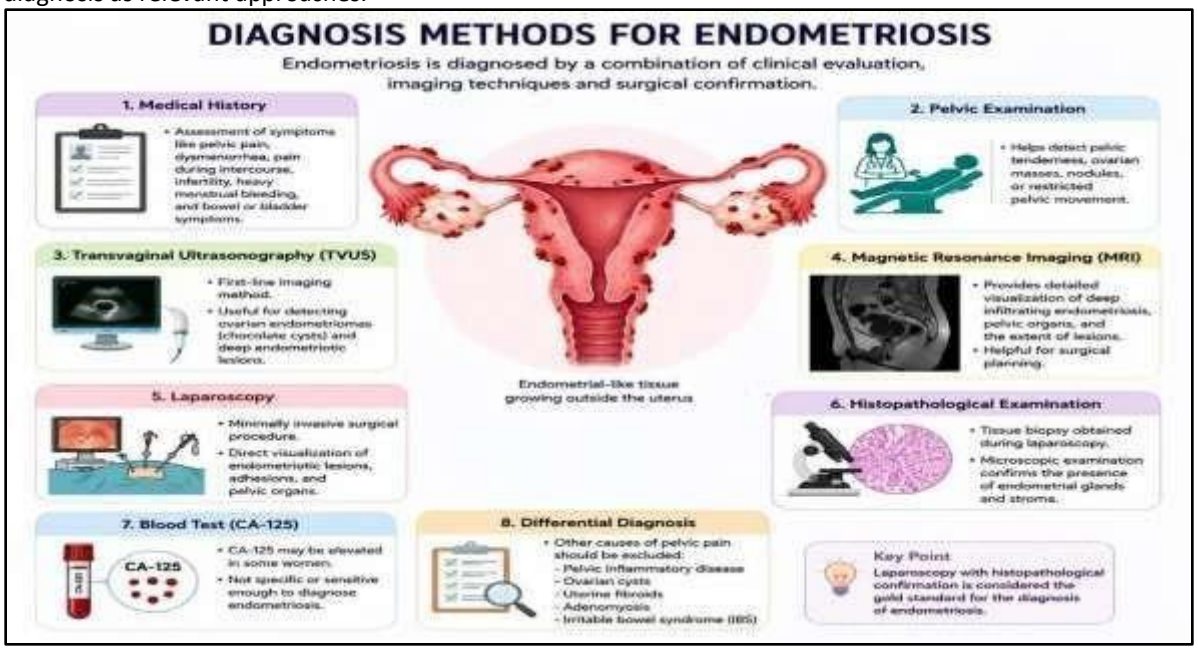


Figure 3. Diagnostic methods for endometriosis.

3.3 Clinical Significance of Diagnosis

Early recognition can reduce prolonged symptom burden and support individualized treatment. Imaging can assist in identifying ovarian and deep disease, while laparoscopy with histopathological examination can provide direct evaluation when clinically indicated. Because conventional staging does not fully predict pain or fertility outcomes, management should consider symptoms, anatomy, ovarian function and reproductive goals.

4. MANAGEMENT OF ENDOMETRIOSIS

4.1 Pharmacological and Surgical Management

1. Pain management – aims to reduce pelvic pain and improve daily functioning.
2. Hormonal therapy – suppresses the activity of endometrial-like tissue and controls symptoms.
3. Conservative surgery – laparoscopic removal or destruction of lesions while preserving the uterus and ovaries, particularly when fertility is desired.
4. Definitive surgery – hysterectomy, with or without ovarian removal, may be considered in severe disease when childbearing is complete.
5. Fertility treatment – IUI or IVF may be considered when infertility is present.
6. Lifestyle modification and regular follow-up – support overall health and monitor recurrence.

4.2 Complications

- Infertility or difficulty becoming pregnant.
- Chronic pelvic pain and severe dysmenorrhea.
- Dyspareunia, dyschezia and dysuria.
- Ovarian endometriomas, adhesions and pelvic anatomical distortion.
- Heavy or irregular bleeding and urinary or bowel involvement in severe disease.
- Fatigue, emotional distress and reduced quality of life.
- Recurrence after treatment; rarely, malignant transformation of an endometriotic lesion, particularly in longstanding ovarian disease.

4.3 Non-Pharmacological Management

The source document emphasizes a balanced diet, regular moderate physical activity, heat therapy, pelvic-floor physiotherapy, stress management, adequate sleep, psychological support, healthy weight maintenance, patient education and appropriate surgical management when indicated.

5. INFERTILITY: CONCEPT AND CLINICAL CONTEXT

5.1 Definition and Types

Infertility is described in the source document as failure to achieve pregnancy after 12 months or more of regular, unprotected sexual activity. Primary infertility refers to absence of a previous pregnancy, while secondary infertility occurs when pregnancy has occurred previously but conception is subsequently unsuccessful [8].

5.2 Female and Male Contributions

Female infertility may be associated with ovulatory disorders, increasing maternal age, reduced ovarian reserve, endometriosis, PCOS, tubal obstruction, uterine abnormalities and hormonal disorders. Male infertility may involve low sperm count, poor motility, abnormal morphology, reproductive-system abnormalities or sexual dysfunction [9,10].

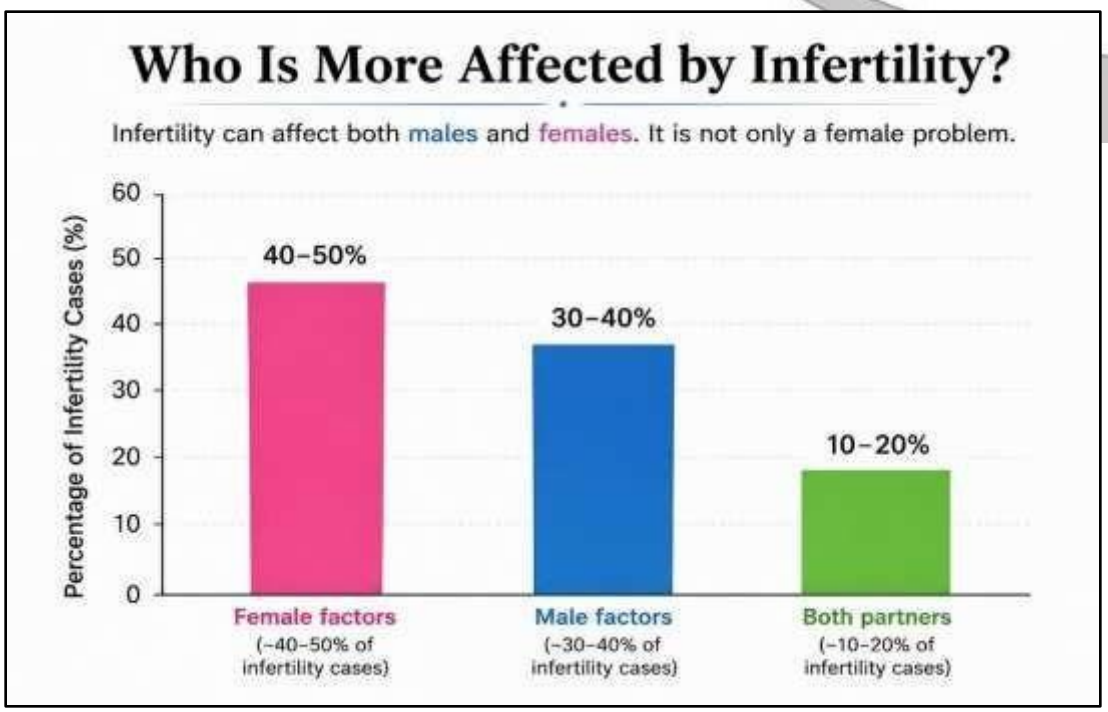


Figure 4. Distribution of infertility factors described in the source document.

5.3 Endometriosis-Associated Infertility

Endometriosis may interfere with ovulation, fertilization, embryo transport and implantation. Pelvic inflammation and adhesions can distort reproductive anatomy and affect ovarian and tubal function. Ovarian disease may damage healthy ovarian tissue and reduce ovarian reserve, while the inflammatory environment may affect oocyte quality, sperm function, fertilization and early embryo development [11-12].

5.4 Psychosocial Impact

Infertility can have emotional, psychological, social and financial consequences, including anxiety, depression, stress, frustration, social isolation and relationship difficulties. Counseling, education and psychological support are therefore important components of fertility care [13].

6. INFERTILITY: CAUSES AND DIAGNOSTIC EVALUATION

6.1 Major Causes

- Ovulation disorders, including those related to PCOS or hormonal imbalance.
- Blocked fallopian tubes associated with pelvic infection, pelvic inflammatory disease or endometriosis.
- Endometriosis with inflammation, adhesions or ovarian/tubal damage.
- Uterine fibroids, polyps or structural abnormalities affecting implantation.
- Reduced ovarian reserve and premature ovarian insufficiency.
- Thyroid, prolactin and other hormonal abnormalities.
- Male factors including low sperm production, poor motility, abnormal morphology, varicocele, hormonal disorders and testicular injury or infection.

6.2 Diagnostic Tests

The source document lists semen analysis, ovulation testing, hormone testing, AMH, FSH, LH, TSH and prolactin, TVUS, hysterosalpingography (HSG), sonohysterography, laparoscopy, ovarian reserve testing and genetic testing.

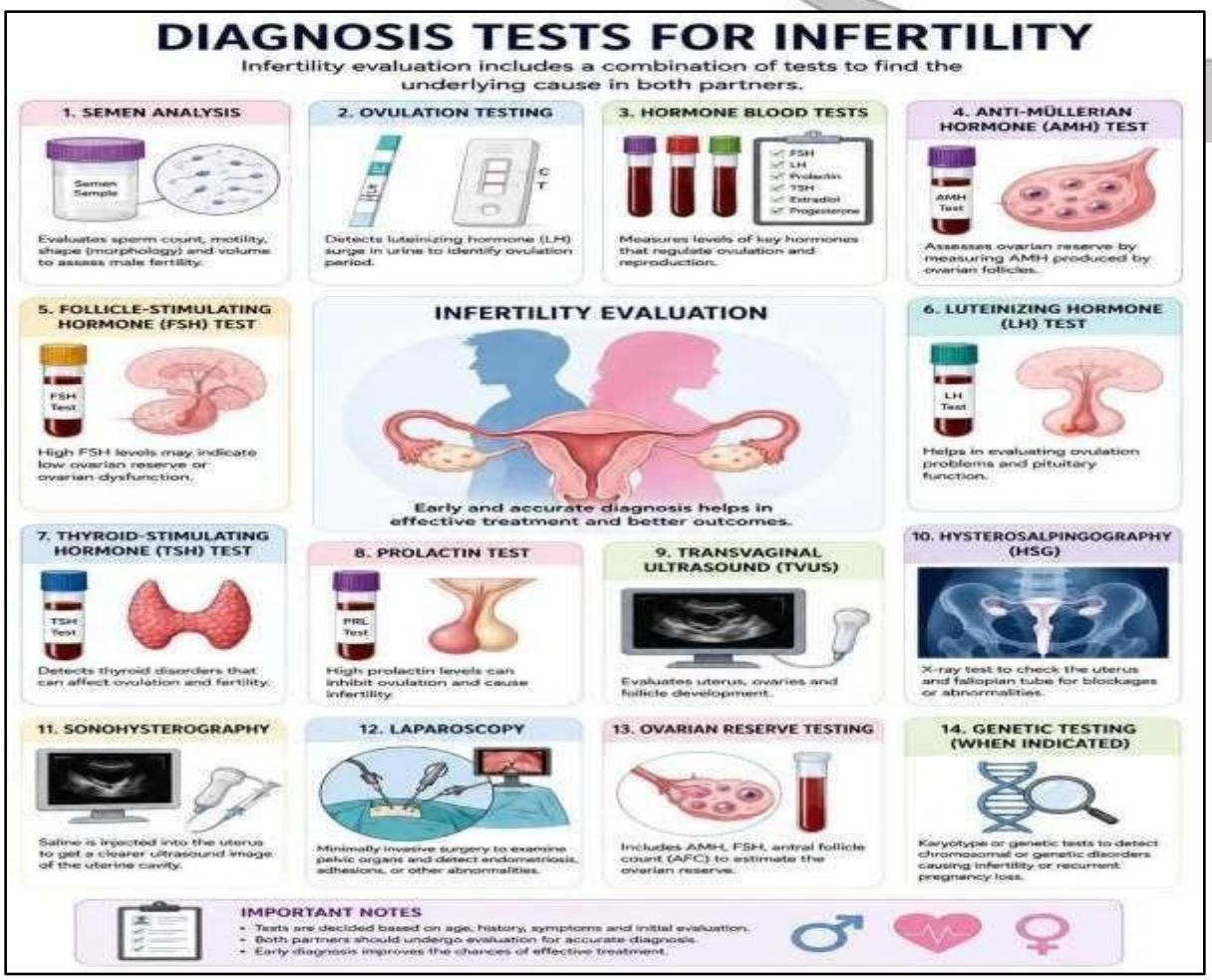


Figure 5. Diagnostic tests for infertility.

6.3 Risk Groups

Higher-risk groups described include people with increasing age, reproductive or hormonal disorders, endometriosis or PCOS, previous pelvic/reproductive infections, obesity or very low body weight, smoking or excessive alcohol exposure, certain medications/toxins/radiation, previous reproductive surgery and testicular problems.

6.4 Fertility Management

Management depends on cause, duration of infertility, age and reproductive goals. Options include lifestyle measures, ovulation-promoting drugs, hormonal treatment, surgery, IUI, IVF and other assisted reproductive technologies when indicated [14-15].

7. RELATIONSHIP BETWEEN ENDOMETRIOSIS AND INFERTILITY

Endometriosis is closely associated with infertility because it can disrupt several stages of reproduction. Ectopic endometrial-like tissue undergoes hormonal changes during menstruation and repeated local inflammation and bleeding. Persistent inflammation may produce adhesions and fibrous tissue that attach the ovaries and fallopian tubes to surrounding structures or alter their normal position [16].

Anatomical distortion can interfere with normal ovulation, oocyte pickup and movement through the fallopian tube. Adhesions around the tubes can hinder interaction between sperm and the oocyte. Ovarian endometriosis can damage normal ovarian tissue and reduce ovarian reserve. Recurrent inflammation may also influence oocyte quality [17].

The pelvic inflammatory environment is associated with oxidative stress and changes that may affect sperm function, fertilization and early embryo development. Alterations in the endometrial and immune environment may influence

implantation and early pregnancy development [18-19].

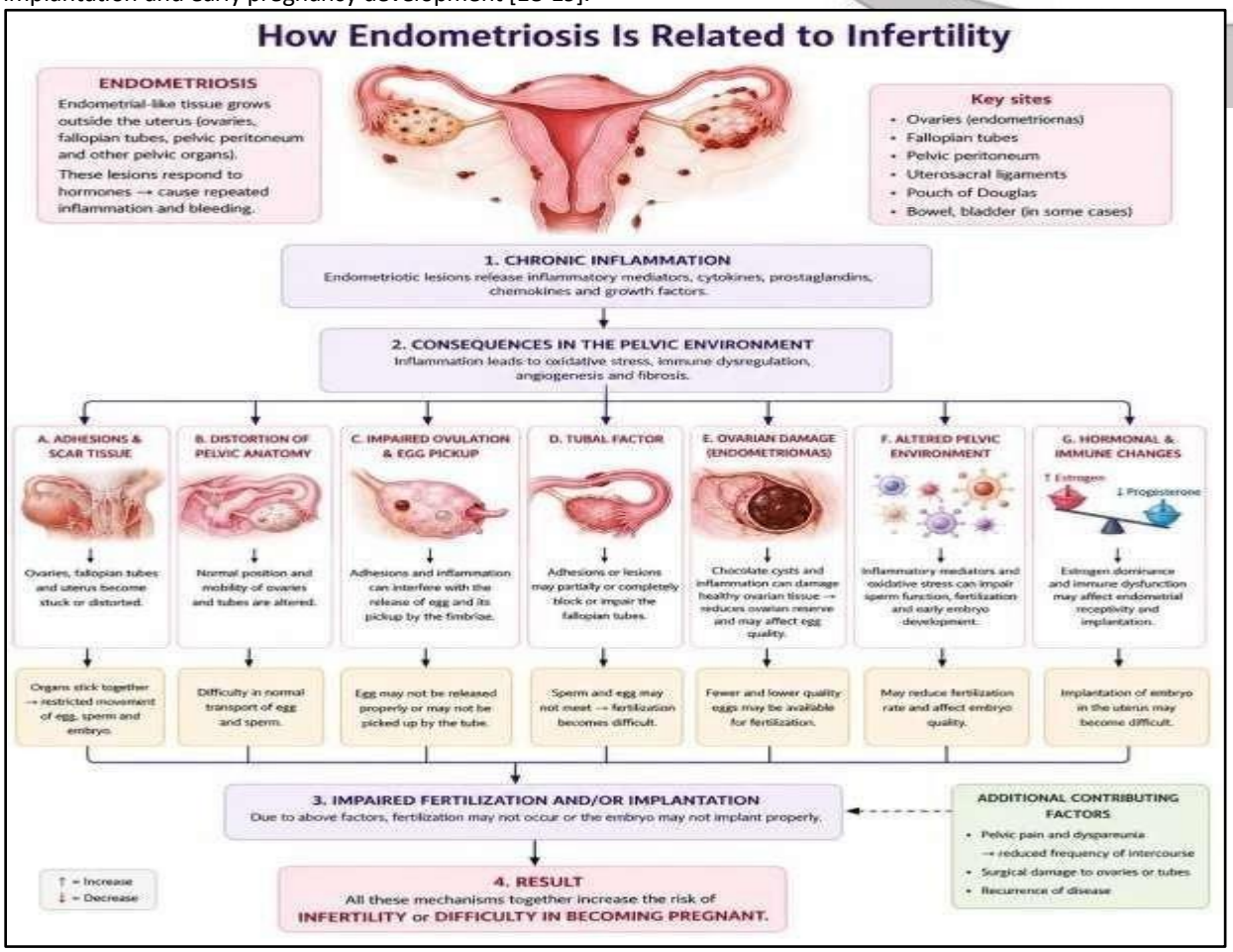


Figure 6. Relationship between endometriosis and infertility.

7.1 Main Mechanisms Linking the Two Conditions

- Pelvic inflammation and fibrosis.
- Adhesions and distortion of pelvic anatomy.
- Tubal dysfunction and impaired oocyte pickup.
- Ovarian damage and reduced ovarian reserve.
- Altered oocyte quality and fertilization environment.
- Changes in embryo development and endometrial receptivity.
- Pain and dyspareunia that may indirectly reduce opportunities for conception.

8. PATHOGENESIS OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY

Endometriosis is characterized by persistent inflammation associated with endometrial-like tissue outside the uterine cavity. Cyclic activity of ectopic lesions may produce repeated bleeding, inflammatory signaling, fibrosis and tissue damage. The inflammatory process described in the source includes increased cytokines, prostaglandins and reactive oxygen species (ROS) [20].

Chronic inflammation and adhesions can obstruct normal pelvic anatomy and disrupt ovulation, oocyte pickup and tubal transport. The inflammatory environment may reduce sperm function, impair fertilization, alter embryonic development and delay implantation. Hormonal and immune abnormalities can also reduce endometrial receptivity and contribute to impaired ovarian reserve and oocyte quality [21].

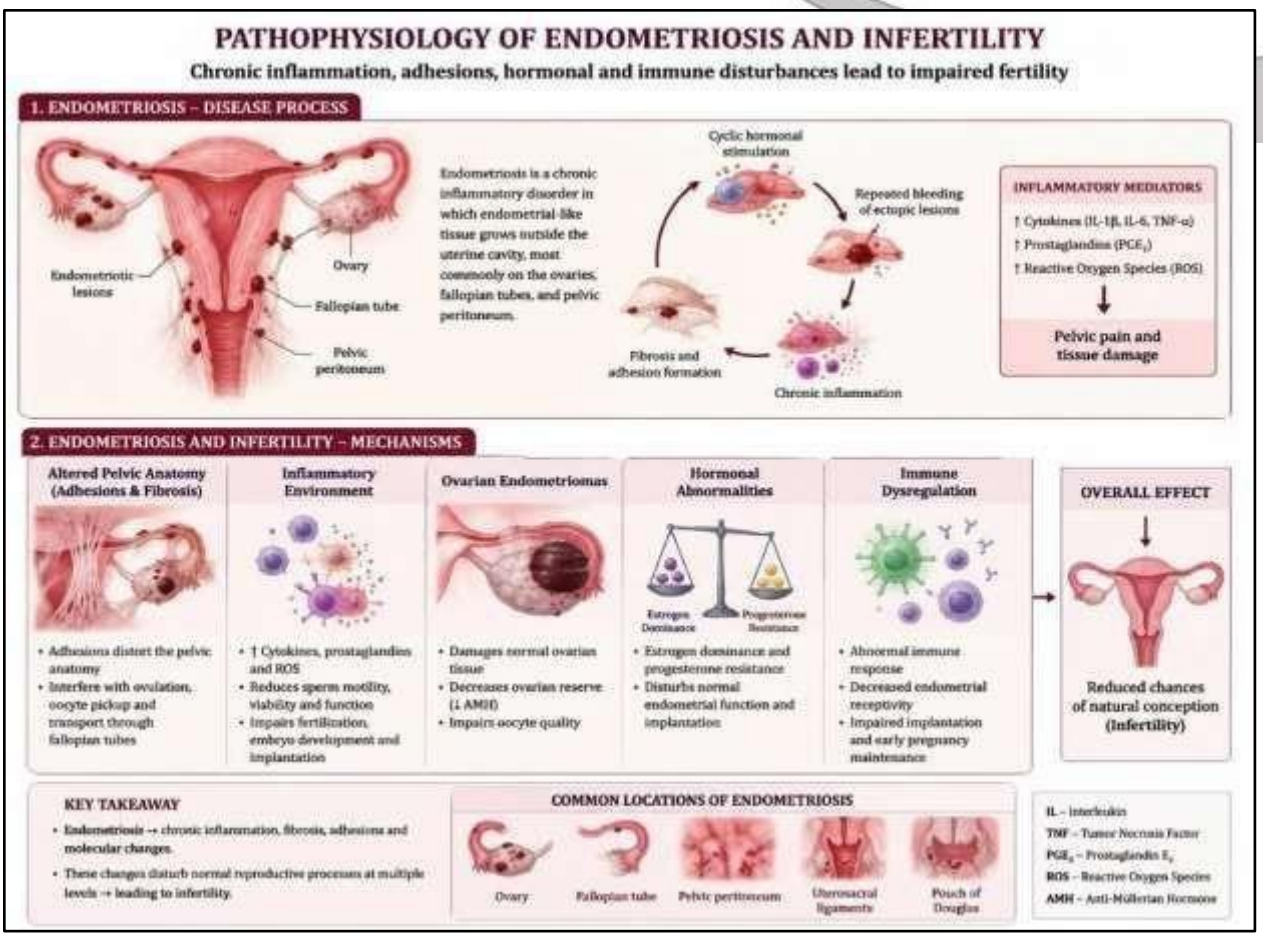


Figure 7. Pathophysiology of endometriosis and infertility.

8.1 Integrated Pathophysiological Sequence

Ectopic endometrial-like tissue → cyclic hormonal activity → repeated local bleeding and inflammation.
Inflammation → cytokines, prostaglandins and ROS → oxidative and tissue stress.
Persistent inflammation → fibrosis and adhesions → pelvic anatomical distortion.
Anatomical distortion → impaired ovulation, oocyte pickup and tubal transport.
Ovarian involvement → tissue damage and possible reduction of ovarian reserve.
Inflammatory and immune changes → impaired fertilization, embryo development and implantation.

8.2 Clinical Interpretation

The source emphasizes that infertility is multifactorial and that reproductive impairment does not necessarily correspond directly to the severity of pain or anatomical stage. Assessment should therefore integrate symptoms, disease extent, ovarian function and reproductive goals.

9. ETIOLOGY AND TYPES OF ENDOMETRIOSES

9.1 Etiology

The exact cause of endometriosis remains unclear. The source describes genetic, hormonal, immunological and environmental contributions. Sampson's theory of retrograde menstruation is presented as a widely accepted explanation, in which viable endometrial cells pass through the fallopian tubes into the pelvic cavity and establish lesions [22].

Other proposed mechanisms include coelomic metaplasia, in which peritoneal cells may transform into endometrial-like cells, and lymphatic or hematogenous spread, which may help explain lesions at distant sites. Family history

indicates a genetic contribution, while estrogen-dependent growth, impaired immune surveillance, chronic inflammation and environmental exposures may influence development and progression [23-24].

9.2 Types

- Superficial peritoneal endometriosis – the most common form described; superficial lesions on pelvic peritoneum may cause inflammation, pain and infertility.
- Ovarian endometriosis (endometrioma) – cystic ovarian lesions containing thick, dark blood; may damage healthy ovarian tissue, affect ovarian reserve and influence oocyte quality.
- Deep infiltrating endometriosis – lesions extending more than 5 mm beneath the peritoneal surface, often involving uterosacral ligaments, rectovaginal septum, bowel, bladder or ureters; fibrosis and adhesions can cause substantial pelvic distortion.
- Extrapelvic endometriosis – uncommon disease outside the pelvis, including diaphragm, lungs, abdominal wall, surgical scars and urinary tract; symptoms may be cyclic and site-specific [25].

9.3 Relevance to Infertility

The phenotype and anatomical location can influence the mechanism of reproductive impairment. Ovarian disease may affect ovarian reserve, while deep disease and adhesions may cause anatomical distortion. Superficial disease can still alter the inflammatory pelvic environment.

10. CONVENTIONAL HORMONAL THERAPY: ETHINYL ESTRADIOL + LEVONORGESTREL

10.1 Drug Profile

- Ethinyl estradiol: synthetic estrogen; chemical formula C18H24O2; molecular weight 272.38 g/mol.
- Levonorgestrel: progestogenic agent that prevents or delays ovulation; chemical formula C21H28O2; molecular weight 312.45 g/mol.

The combination forms a combined oral contraceptive. The source document describes it as a treatment used to control endometriosis-associated pain and dysmenorrhea and to reduce estrogenic stimulation of ectopic endometrial tissue [26].

10.2 Mechanism of Action

Administration of ethinyl estradiol + levonorgestrel.
Suppression of FSH and LH secretion.
Suppression of ovulation and reduction of ovarian estrogenic stimulation.
Reduced estrogen stimulation of endometriotic lesions and induction of endometrial atrophy.
Reduced menstrual bleeding and pelvic inflammation.
Reduced pelvic pain and risk of recurrence after conservative surgery.

10.3 Therapeutic Uses

- Management of endometriosis-associated pain.
- Management of dysmenorrhea and chronic pelvic pain.
- Prevention of recurrence after conservative surgery.
- Contraception in women with endometriosis.

10.4 Important Adverse Effects and Contraindications

Adverse effects listed include venous thromboembolism, hypertension, stroke, myocardial infarction, liver dysfunction and gallbladder disease. Common side effects include nausea, vomiting, headache, breast tenderness, breakthrough or irregular bleeding, bloating, weight gain, mood changes, dizziness and skin changes.

The source lists pregnancy, current or previous DVT/PE, thrombophilia or high clot risk, stroke or myocardial infarction, migraine with aura, severe/uncontrolled hypertension, severe liver disease, estrogen/progestin-sensitive cancer, unexplained abnormal vaginal bleeding, major vascular diabetic complications, prolonged immobilization, heavy smoking in women aged 35 years or older, and hypersensitivity as contraindications.

11. EMERGING THERAPY: LINZAGOLIX

11.1 Introduction and Drug Class

Linzagolix is an orally administered, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist. It reversibly and dose-dependently suppresses the hypothalamic–pituitary–ovarian axis by competitively inhibiting GnRH receptors in the pituitary, reducing FSH and LH release and subsequently lowering ovarian estrogen production [26].

11.2 Mechanism of Action

Linzagolix binds directly to GnRH receptors in the anterior pituitary.
GnRH receptor signaling is blocked.
LH and FSH release decreases.
Ovarian estradiol production decreases in a dose-dependent manner.
Reduced estrogen stimulation decreases activity of endometriotic lesions.
Endometriosis-associated pain and bleeding symptoms are reduced.

11.3 Pharmacological and Clinical Effects

- Reduces endometriosis-associated pelvic pain and dysmenorrhea.
- Reduces non-menstrual pelvic pain and heavy menstrual bleeding.
- Reduces menstrual blood loss and may improve hemoglobin levels when heavy bleeding contributes to anemia.
- Suppresses estrogen-dependent stimulation of endometriotic lesions.
- May improve quality of life and daily functioning.
- Produces rapid, reversible and dose-dependent hormonal suppression.

11.4 Add-Back Therapy

Long-term estrogen suppression can produce hypoestrogenic effects such as hot flushes and reduction in bone mineral density. The source document describes add-back therapy as an approach that may reduce these effects while maintaining therapeutic benefits [27,28].

11.5 Advantages

- Once-daily oral administration.
- Rapid estrogen suppression.
- Dose-dependent effect.
- No injection or surgical procedure required.
- Can be used with or without add-back therapy depending on treatment context.

12. LINZAGOLIX: SAFETY, USES AND THERAPEUTIC PERSPECTIVE

12.1 Therapeutic Uses

- Treatment of endometriosis-associated pain.
- Reduction of moderate-to-severe pelvic pain and dysmenorrhea.
- Reduction of non-menstrual pelvic pain.
- Improvement of dyspareunia and endometriosis-related symptoms.
- Management of uterine fibroid-associated heavy menstrual bleeding.
- Long-term oral treatment with appropriate add-back therapy when indicated.

12.2 Adverse Effects

- Decreased bone mineral density with long-term use.
- Hypoestrogenic symptoms, including hot flushes.
- Mood or depressive symptoms.
- Elevated liver enzymes.
- Ovarian cysts, hypersensitivity reactions and other adverse effects listed in the source.

12.3 Contraindications

- Pregnancy and breastfeeding.
- Undiagnosed abnormal uterine bleeding.
- Severe hepatic impairment.
- Osteoporosis or significant loss of bone mineral density.
- Hypersensitivity to linzagolix.
- Known or suspected hormone-dependent malignancy.

• Severe renal impairment, depending on formulation and clinical guidance.

12.4 Place in a Patient-Centered Strategy

Endometriosis-associated infertility requires treatment decisions based on age, disease severity, ovarian function and reproductive goals. Hormonal therapy is primarily directed toward symptom and disease control rather than immediate conception. When pregnancy is desired, fertility-preserving strategies, surgery when indicated, and assisted reproductive technologies such as IUI or IVF may be considered. Linzagolix represents an important emerging pharmacological option for symptom control, while fertility planning remains a separate and essential component of care.

12.5 Key Evidence Highlight

The source document highlights the EDELWEISS phase III program as evidence supporting clinically meaningful improvements in dysmenorrhea and pelvic pain, with add-back therapy helping address hypoestrogenic effects during extended treatment.

13. SUMMARY

Endometriosis is a chronic estrogen-dependent condition characterized by endometrial-like tissue outside the uterine cavity. It is associated with inflammation, fibrosis, adhesions, pelvic pain and impaired fertility. Approximately 10% of reproductive-age females are affected according to the source document, with higher prevalence reported among women with chronic pelvic pain and infertility.

Infertility associated with endometriosis is multifactorial. Pelvic anatomical distortion, tubal dysfunction, ovarian damage, reduced ovarian reserve, altered oocyte quality, inflammatory changes, impaired fertilization and disturbed implantation can all contribute. Diagnosis combines history and examination with TVUS, MRI, laparoscopy and histopathology when appropriate. Fertility evaluation also includes ovulation, hormonal, ovarian-reserve, tubal and male-factor assessment.

Management includes pain control, hormonal therapy, conservative surgery, lifestyle measures, psychological support and fertility treatment. Ethinyl estradiol plus levonorgestrel suppresses ovulation and estrogenic stimulation and is described in the source as a conventional option for symptom control and recurrence prevention. Linzagolix is an oral GnRH receptor antagonist that provides rapid, reversible and dose-dependent suppression of ovarian estrogen production and has demonstrated reductions in pain and bleeding symptoms in the clinical evidence summarized in the source.

14. CONCLUSION

Endometriosis and infertility are closely linked through interacting anatomical, inflammatory, ovarian, hormonal and implantation-related mechanisms. The effect on fertility is not uniform, and disease severity or pain intensity alone does not determine reproductive outcome. Early recognition, appropriate classification and individualized management are therefore important.

A comprehensive strategy should consider symptom control, fertility preservation, ovarian reserve, disease extent, age and reproductive goals. Conventional hormonal treatment remains useful for symptom management, while surgery may be appropriate in selected patients and IUI or IVF can support conception when indicated. Linzagolix adds an emerging oral pharmacological approach for endometriosis-associated symptoms, with dose-dependent estrogen suppression and the potential use of add-back therapy to reduce hypoestrogenic effects.

Overall, effective care requires coordinated medical or surgical treatment, fertility planning, lifestyle support, psychological care and regular follow-up. Continued clinical research into newer therapies may further improve long-term symptom control, reproductive care and quality of life.

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