

# Discerning Endometriosis as a Multifaceted Entity: A Comprehensive Review

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**Keywords:** Cancer; Endometriosis; Infertility; Management; Pathogenesis

## ABSTRACT

**Background:** Endometriosis is a hormone-dependent benign inflammatory disease of the female reproductive system characterized by the presence of endometrium in an abnormal or ectopic location causing pain & infertility and affects approximately 10% of reproductive-age women. A more in-depth insight into the complex mechanisms involved in the commencement, development, and advancement is required to accomplish the desired objectives of therapy effective against the symptomatic disease, associated infertility, and malignancies.

**Methods:** We searched the PubMed database using the following search terms in various combinations "Endometriosis and Pathogenesis, Infertility, Pregnancy, Cancer, Biomarkers, Risk factors, Management" and identify relevant English language studies published up to June of 2020. Furthermore, articles were included within the citing references.

**Results:** This review has been structured from a historical perspective that facilitates an up-to-date comprehension of the disease, illustrated by relatively recent molecular and genetic signs of progress.

**Conclusion:** This article will furnish the readers with up-to-date knowledge regarding the biomarkers, infertility, pregnancy, and carcinoma with the ailment and also shed light on the management of the disease.

**Abbreviations:** ASRM: American Society for Reproductive Medicine; EFI: Endometriosis Fertility Index; QoL: Quality of Life; MRI: Magnetic Resonance Image; TVUS: Transvaginal Ultrasonography; DIE: Deep Infiltrating Endometriosis; CT: Computerized Tomography; MDCT-e: Multidetector CT Enema; MRI-e: MRI Enema; BMI: Body Mass Index; EAOC: Endometriosis-Associated Ovarian Cancer; RTKs: Receptor Tyrosine Kinase; ART: Assisted Reproductive Technology; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; COX: Cyclooxygenase; ASA: Acetylsalicylic Acid; GnRH: Gonadotropin-Releasing Hormone; ADR: Adverse Drug Reaction; OCP: Oral Contraceptive Pill; COC: Combined Oral Contraceptives; CI: Confidence Interval; FDA: Food Drug Administration; CHC: Combined Hormonal Contraceptive; Ais: Aromatase Inhibitor; VEGF: Vascular Endothelial Growth Factor; CPI: Cell Proliferation Index

## Introduction

Endometriosis is defined as a hormone-dependent benign inflammatory disease of the female reproductive system

characterized by the implantation and growth of lesions formed by endometrial stromal and epithelial cells present outside the

uterine cavity, mainly in the peritoneum associated with abdominal viscera [1-3]. However, it is stated by some studies that glandular and stromal cells can be present outside the uterus such as on the surfaces of ovaries and the pelvic [4]. Various kinds of literature have suggested that endometriotic lesions are not restricted within the boundaries of the abdominopelvic cavity. Still, it is also found in other parts of the body, such as gastrointestinal tract, lungs, diaphragm, abdomen, and pericardium [5,6]. The urinary tract, the thorax, and the nasal mucosa [7], liver [8]. Also, endometriotic foci have been found on the uterine ligaments, cervix, labia, and vagina [9] peripheral and axial skeleton, as well as the central nervous system [10]. Although it is benign, it happens spontaneously in women and non-human primates that menstruate, causing pain and infertility [11].

### Prevalence

Endometriosis affects approximately 6% to 10% that covers 176 million women of childbearing age, as high as 35-50% women with pain or unexplained infertility [12] and becoming a substantial socioeconomic burden globally [5,6]. However, an actual incidence of endometriosis is quite difficult to rule out due to expensive diagnosis and surgical based procedures, so the estimated range varies from 10%-15% [13]. The general assessment indicates about 25% of all women may have endometriosis in their thirties to forties and after diagnoses for hospitalizations for genito-urinary issues result in 6.9% disease involvement [14]. The pelvic region comprises three significant forms of endometriosis such as ovarian, peritoneal, and infiltrating endometriotic lesions. Morphologically, lesions are divided into three groups viz; white, red, and black lesions. The red lesion interprets with a high level of vascularization, later followed by whitish lesion due to inflammation and fibrosis and classical black lesions are characterized by cyclic tissue decomposition and healing with the subsequent formation of scar tissue [6].

### Classification (The Revised ASRM Criteria for Endometriosis Staging)

The American Fertility Society score which is presently better known as American Society for Reproductive Medicine (ASRM) named based on data obtained from the operating room and comparative study of therapeutic interventions which is widely accepted classification among clinicians [15]. ASRM classifies the severeness of endometriosis based on location, number, morphology, and size of the lesions found during the surgical procedures into point score from Stage I (minimal) to Stage IV (severe) [16] (Table 1). The ASRM classification system's major limitation remained unclear for many years, whether it has any prognostic significance regarding the prediction of a woman's fertility potential after surgery, which is paramount for patients trying to conceive. Endometriosis Fertility Index (EFI) is being more recent classification because it includes point scores from the ASRM system combined with additional anamnestic, and post-

surgical information [17]. EFI is a simple, robust, and validated clinical tool employed for setting the management plan of endometriotic infertile women that predicts pregnancy rate after the surgical staging of endometriosis. It furnishes reassurance to those women with good predictions and avoids wastage of both time and treatment for those with poor prognoses [18].

**Table 1:** The staging system of endometriosis.

Stage	Class	Point score	Remarks
STAGE I	MINIMAL	BETWEEN 1-5	Higher Score, Greater Severity of Endometriosis
STAGE II	MILD	BETWEEN 6-15	
STAGE III	MODERATE	BETWEEN 16-40	
STAGE IV	SEVERE	> 40	

Note: This table explains about the staging system of endometriosis. ASRM classifies the severeness of endometriosis based on location, number, morphology, and size of the lesions found during the surgical procedures into point score from Stage I (minimal) to Stage IV (severe).

### Clinical Features

Despite being a common gynecological disease, endometriosis can be either asymptomatic or symptomatic, and most commonly it is characterized by cyclic menstrual pain, chronic pelvic pain, dyspareunia, menorrhagia, and dyschezia [19] as well as dysuria, back pain and bladder or bowel problems (for instance, painful urination or bowel movements) [20]. The pelvic pain in women with endometriosis is described as pain before the onset of menses and deep dyspareunia that worsens upon menstrual flow. Sacral and lower backaches during menses also can be present [21].

### Societal and Financial Impacts of Endometriosis

Endometriosis has a great impinge not only physically but also on mental health, social life, and daily activities of living, productivity and ultimately become a significant economic and social burden on patients, their families & relatives, and society as a whole. Notwithstanding its increasing prevalence and expensive diagnosis & management, the present understanding of the disease is limited due to lack of fund and advanced research causes a slowdown of the needed innovation in the field of diagnosis and treatment [22]. The prospective study assesses the estimated running cost of endometriosis in 10 countries stated \$12 419 per woman (approximately €9579) annually, comprising one-third of the direct health care costs with two-thirds attributed to a loss of productivity. This total spending seems to be a significant factor for decreased quality of life (QoL).

This study showed that the gradual expensive diagnosis economic burden associated with endometriosis espied in the referral centers is high and is similar to other chronic diseases (diabetes, Crohn's disease, Rheumatoid arthritis) [23]. Endometriosis is estimated to have the societal burden of more than \$49 billion in the USA alone with a decline in productivity per

women accounting twice high as expenses of healthcare [24]. In defiance of advancements in the diagnosis and understanding of endometriosis, many women with endometriosis often associated with multiple side effects, and high recurrence rates are struggling due to inefficient non-invasive diagnostic methods and treatments [25,26]. The QoL of the patients is broadly affected with a negative impact on social and family life, and high health care costs due to endometriosis [27,28].

### Risk Factors

There are several existing evidence of risk factors that may play a role in the etiopathogenesis of endometriosis including age, genetic factors, menstrual parameters, anthropometric measures, body habitus, lifestyle factors, and environmental exposures. Endometriosis is one of the salient diseases seen in the reproductive age of women which may be explained by estrogenic atmosphere strongly implicated in its pathogenesis and considered an average age of diagnosis being 28 years [29]. The risk of endometriosis has been linked to ethnicity, and several studies have reported a nine-fold increase in Asian women's risk when compared to the European-American white female population. A manifold of education has been said the link with ethnicity as Asian women have nine times greater risk than the European- American white female [30]. Nonetheless, black women appear less likely to be diagnosed with endometriosis compared with white women [31].

Some reproductive problems such as early menarche ( $\leq 11$  years of age), short menstrual cycles ( $\leq 27$  days), heavy and long-lasting bleeding, reduced parity and reduced lifetime duration of lactation collaborate with the increased risk of endometriosis [2,15,32]. Endometriosis is inversely correlated with body weight, body mass index, and waist-to-hip ratio. Besides, it is more common in taller and thinner women due to consistently elevated levels of estradiol in follicular phase [33]. The altered endangerment of endometriosis has been reported in association with certain lifestyle factors such as smoking, exercise, and consumption of alcohol and caffeine [34]. The risk of endometriosis appears to be increased in women who are associated with the following pictures [2,30,35,36] (Table 2).

**Table 2:** Risk factors in association with endometriosis.

SN	Risk factors of endometriosis
1	Asian women than American and European white women
2	Early menarche ( $\leq 11$ years of age)
3	Taller and thinner women
4	Advancing age up to menopause
5	Short menstrual cycles ( $\leq 27$ days)
6	Longer duration of menstrual flow ( $> 7$ days)
7	Heavy menstrual bleeding
8	Delayed childbirth
9	Reduced or no parity
10	First-degree relatives (mother, sister, daughter) with endometriosis

Note: Table 2 explains the relationship between endometriosis and several risk factors. The risk of endometriosis has been linked to ethnicity, race, age, body mass index, height and other diseases.

### Role of Animal Model in Diagnosis

The conventional discovery and development of diagnostic markers & new therapeutic drugs have been handicapped due to the unavailability of suitable animal models for *in vitro* testing and their limited use [37]. Thus, the researcher believes that an appropriate model's evolution may occupy a strong position to reduce the prevalence rate and provide quality life to many females of the younger generation. They stated that humans and non-human primates are the only mammal option that spontaneously develops endometriosis. Still, the limitations of humans and expenses of primate studies have made a boundary to the researcher to make use of small animal models. Non-primates could be another possible option for medical research. However, unfortunately, they neither menstruate nor are capable of developing endometriosis. Even so, several researchers decided to use rabbits, rats, and mice to investigate multiple aspects of the disease. Although several studies have proven valuable for studying some aspects of the disease, surgical induction of endometriosis lacks the potential to address the underlying cellular mechanisms of endometrial attachment and invasion that are critical for the initial establishment of ectopic lesions in women.

Therefore, researchers moved forward to establish the best animal model with similar pathophysiology of human disease [38]. Among various animal models of endometriosis, rodent models have a plethora of benefits such as; cheaper due to their small size, large litters, and short gestation. Additionally, these animal models play a significant role in the study of endometriosis because of the wide availability of genetic knock-out mice, antibodies against murine and rat proteins as well as knowledge of the murine genome. Many different model systems have been generated in mice and rats, each with specific characteristics that are consequential for the interest of study [39]. Females with very early stages of the endometriosis are rarely diagnosed, making it difficult to scrutinize the elaboration and progression of ectopic lesions in a large population. Numerous experimental models of endometriosis have been developed to fulfil these crucial gaps, which can explain the pathophysiology and the consequences of this [38]. More significantly, rodent models of endometriosis are often utilized for preclinical testing to identify new therapeutic agents. The usage of experimental endometriosis models for therapeutic testing has recently been reviewed.

### Pathogenesis

Even after decades of research the exact cause of endometriosis is not yet fully comprehended. However, existing documents suggest that combinations of hormonal, immunologic, genetic, and environmental factors are contributing to the origin and development of endometriosis [3]. There are several leading

mechanisms like retrograde menstruation, altered immunity, coelomic metaplasia, and metastatic spread. Moreover, the other possible pathogenic elements like hormonal imbalance, immunological, environmental toxin, genetic, and epigenetic mechanisms may occur to allow the disease establishment and progression [40]. Eventually, stem cell and genetic emergence of the disease are also being suggested for undergoing novel research. In 1940, Sampson proposed a distinctive theory in connection with the pathogenesis of endometriosis called retrograde menstruation, which is a widely accepted theory. Normally, endometrium sheds sloughs off through the cervix and vagina during the menstrual phase of the cycle, but sometimes it moves upward and backward through the fallopian tube into the peritoneal cavity known as retrograde menstruation.

It was found that approximately 90% of the subjects were estimated to experience a certain amount of endometrial sheds into their peritoneal cavity. Still, only a small proportion of them have developed endometriosis [41]. However, some authors explained that retrograde menstruation in association with other abnormalities like eutopic anomalies of the endometrium (such as; the altered synthesis and secretion of proteins and gene expression) and immune system abnormalities might be involved in the pathophysiology of endometriosis [42]. Whereas other researchers have hypothesized that pathogenesis of endometriosis for the development of ectopic lesions is enhanced by a replicate capacity due to a surge in telomerase synthesis in the sloughed endometrium during retrograde [43]. Meanwhile, induction theory was hypothesized by another researcher which includes: the sloughing endometrium gives off “factors” during menstruation, and that causes changes in the surface epithelium of the ovary leading the differentiation of endometrium-like tissue and migration to the peritoneal cavity.

According to *in situ* theory, the totipotent cells endure homogenous from the fetus surviving into adulthood and during the reproductive age, get stimulated and thus differentiating into endometriotic lesions [44]. There might be a certain contribution of endometrial stem cells in the etiology of the disease which describes certain rare and extreme cases of endometriosis. Pathogenesis of endometriosis most likely involved various factors, and extensive investigation has explored the role of genetics, environmental factors, and the immune system in predisposing patients. A new insight into normal physiology of uterus and pathogenesis of endometriosis is found to be sought by the identification of endometrial as well as extra uterine stem/progenitor cells that aim the uterus and endometriotic implants [45].

### Epigenetics of Endometriosis

Epigenetics describes changes to the cytosine base pairs and histones remodeling that affect gene expression, however, they are not mutations of the DNA itself. Several mechanisms might

change the epigenetics of endometriosis; they are heritable changes in gene expression that occur without alterations to the underlying DNA sequencing [46]. As they are stable and heritable, they facilitate the propagation of the transformed cell line and can be preserved in cell divisions. Besides, they are reversible due to which, remodeling to any future cells in that line could alter the epigenetic profile further or remove it together [47]. The refashioning includes DNA methylation, histone methylation, acetylation, sumoylation, ubiquitylation, and phosphorylation, as well as chromatin remodeling and RNA transcriptional alterations [46]. There are specific genes that are known to be overexpressed in decidualization, having been seen down-regulated in endometriosis and vice versa. These comprise various elements like transcription factors, hormones, growth factors, cytokine/chemokine’s signaling, cell cycle regulation, adhesion, the immune system, and proteases, including genes associated with steroidogenesis, implantation, and placental development could also be affected [48].

### Endometriosis in Association with Fertility

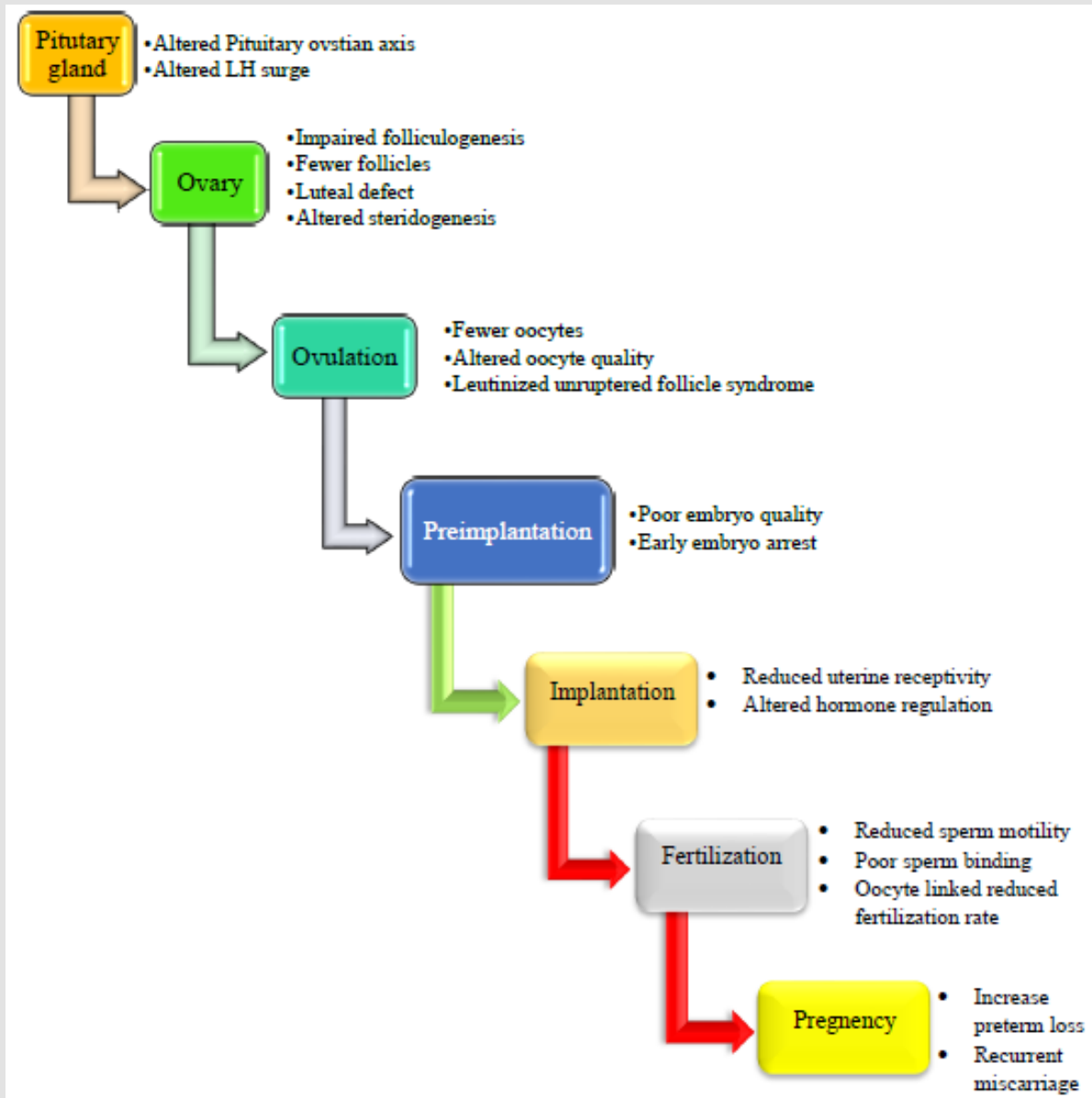
Fertility is affected by many pathways in the case of endometriosis such as peritoneal inflammation and endocrine imbalance, which interfere with ovarian function and ultimately reduce oocyte’s competence, but minimal and mild endometriosis has been shown to improve fertility modestly after removal of superficial foci. The chance of fertility after resection of endometriomas and deep infiltrating lesions has remained undocumented [17]. As inferred by women’s accounts, it may be salutary for drawing out relevant clinical guidelines for the clarification of evidence depicting association among endometriosis and Fertility and treatment of conditions and dissipating the shared beliefs, along with the notion that pregnancy is an appropriate alternative for a cure. Besides, it may be employed for developing the protocols for understanding and addressing the fertility concerns specific to women those who do not reveal themselves as heterosexual [49].

### Endometriosis in Association with Infertility

The routine intricacy that is seen in women with moderate to severe endometriosis is infertility [5]. A large cohort study revealed an increased risk of subsequent infertility by 2-fold in women age of fewer than 35 years with a prior history of laparoscopically confirmed endometriosis [15]. During endometriosis, the inflammatory environment of Pelvic anatomy becomes distorted and results in the reduced monthly fecundity rate *via* mechanical interruption like pelvic adhesions. These disruption imbalances the process of oocyte release or pickup alters sperm motility, interferes with the myometrium contraction ability, impairs fertilization, and embryo transport. Also, gamete transport and embryo implantation are affected due to escalation in cytokine production, which reduces the tubal function and decline in the tubal motility and contractility. The current evidence proposed the mechanisms of endometriosis-associated with infertility [50].

Impairment of the hypothalamo-pituitary-ovarian axis may kick into infertility in women carrying with a prolonged follicular phase, decreased serum estradiol levels, and reduced peak luteinizing hormone concentration [51]. The principal reason for morbidity in women with endometriosis is infertility. In people who have endometriosis, 30 to 50 percent face infertility, and consequently,

fecundity decreases from 15 to 20 percent each month in healthy women up to 2 to 5 percent in those with endometriosis [34,52,53]. According to history, women having endometriosis-associated infertility are prone to minute, exact or multidimensional abnormalities [51,54-57] (Figure 1).



**Figure 1:** Endometriosis in association with infertility.

Note: Endometriosis has been associated with infertility. However, this figure tries to explain the mechanisms by which endometriosis affects gametes and embryos, the fallopian tubes and embryo transport, implantation and the eutopic endometrium; these abnormalities begins from altered pituitary ovarian axis leading to infertility.

### Endometriosis in Association with Sub-Fertility

Endometriotic lesions may vary from just a few implants to extensive adhesions and organ infiltration and even outside the pelvic cavity, validated by ASRM classification into four classes:

minimal, mild, moderate, and severe endometriosis [58]. There were several pieces of evidence to support the hypothesis that the presence of endometriosis causes subfertility. This evidence includes an increased prevalence of endometriosis in sub fertile

women compared with women of proven Fertility, a reduced monthly fecundity rate (MFR) in baboons with mild to severe endometriosis in comparison to those with minimal endometriosis or a normal pelvis, a trend toward a reduced MFR in infertile women with minimal to mild endometriosis when compared to women with unexplained infertility, a reduced MFR and cumulative pregnancy rate after donor sperm insemination in women with minimal-mild endometriosis compared with those with a normal pelvis, a reduced implantation rate per embryo after IVF in women with moderate to severe endometriosis in comparison to women with a normal pelvis, and an increased MFR and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis [59].

### Endometriosis and Pregnancy

Endometriosis is a disease of women's reproductive period. The individual with a previous diagnosis of the disease had adverse consequences such as an increased risk of pregnancy and neonatal complications, and this risk remained significant after adjusting for maternal age. The risk of multiple pregnancies, breech presentation, and placenta previa was more than two-fold higher in women with endometriosis than in the control group. Besides, the estimated risk of stillbirth was more than 1.5-fold higher in the affected group. Endometriosis does not influence fetal well-being because the pregnant mothers with endometriosis are at higher risk of obstetric complications like miscarriages, threatened miscarriages, preterm labor, preterm birth, and a higher cesarean section rate [60]. Women with endometriosis are more vulnerable to serious and important adverse maternal, fetal and neonatal outcomes [61]. As revealed by a large study, people with endometriosis had greater odds of pre-eclampsia (OR 1.13, 95% CI 1.02-1.26), antepartum bleeding/placental complications (OR 1.76, 95% CI 1.56-1.99), and cesarean delivery (OR 1.47, 95% CI 1.40-1.54) [62].

### Diagnosis

Primarily, those suspected patients are screened by physical examinations and pelvic ultrasound. Secondly, further investigations are performed such as target pelvic examination, transvaginal ultrasound, and pelvic magnetic resonance image (MRI) by an expert [63]. The gold standard of diagnosing the endometriosis clinically is a histopathological examination that is many times undergone by a laparoscopy. If a woman has a thorough history of following clinical features such as; recurring or persistent pelvic pain, dysmenorrhoea, dyspareunia, and infertility along with physical symptoms like; pain during pelvic examinations, nodules in the uterosacral ligament, retrocervix and vaginal fornix, as well as vagina and rectum is advised for a diagnostic laparoscopy to confirm the endometriosis [64].

Imaging technology occupies a significant position in the diagnosis of the disease. However, in the case of endometriosis, it is imperative not only for assessing the extent of disease; but also sets a guideline for surgical excision of the targeted area. The

advancements in radiological techniques namely; transvaginal ultrasonography (TVUS) or Magnetic Resonance Imaging (MRI) are very useful clinically in symptomatic patients [65]. Pelvic endometriosis comprises three major separate commodities such as peritoneal, ovarian, and deep infiltrating endometriosis (DIE) with different pathogenesis [66]. Also, the multislice computerized tomography (CT) enteroclysis and multidetector CT enema (MDCT-e) and MRI enema (MRI-e) are useful in the evaluation of bowel endometriosis and their sensitivity and specificity are 98.7% and 100%, respectively [67,68].

### Biomarkers of Endometriosis

Researchers are exploring the utility of biomarkers for early diagnosis as a noninvasive approach, but more investment in this area is required for it to be fruitful. Current blood-based biomarkers under investigation include; regulators of gene expression (micro-RNAs), inflammatory markers, tumor markers, growth factors, and hormonal markers, proteomics, metabolomics, oxidative stress, autoantibodies as well as endometrial and menstrual effluent biomarkers. Despite extensive research in the field of biomarkers for endometriosis including blood, urine, body fluids and endometrial biopsy, neither a single biomarker nor a panel of biomarkers has been proven for a noninvasive diagnostic test which can provide sufficient sensitivity and specificity [69]. The invention of new and validated putative biomarkers are crucial for the advancement of the field and are top research priorities for endometriosis proposed in 2009 and 2013 by highly ranked researchers [23,70].

### Endometriosis- Associated Cancer

The association between endometriosis and gynecological cancer on a molecular basis is obscure. Formation of endometrial-like tissue and lesion on the surface of the uterus and fallopian tubes cause pelvic inflammation, severe pain, and infertility [71,72]. The relationship between endometriosis and ovarian cancer was first published in 1927 [73]. No epidemiological evidence was published until the end of the 20th century. After that, the first large epidemiological study popped in from Sweden along with two big studies (20,686 and 64,492 participants respectively). The studies revealed that there was an increased risk of ovarian cancer for those women who were suffering from endometriosis [74,75]. Also, there are many pathological factors involved to cause endometriosis, which includes; early menarche, abnormal uterine bleeding, abnormal estrogen level, low body mass index (BMI), cell adhesion factors, angiogenic factors, elevated gonadotropins, and chronic inflammation. According to the previous pieces of evidence of endometriosis, the parents, siblings, children as well as twins of those who have the disease, the likelihood of cancer may be up to ten folds higher than the healthy population.

Moreover, single nucleotide polymorphism may increase the risk of endometriosis and its associated cancer [76]. The overall risk of Endometriosis-associated carcinoma remains low despite

it is a common medical issue. According to a huge epidemiological study, the all-inclusive prevalence of ovarian cancer in a patient diagnosed with endometriosis was 0.3-0.8 percent, which was 2-3 times perilous than the controls [77]. Endometriosis is somatically taught genetic change similar to those found in cancer, leading to clonal expansion and genetically abnormal cells. Endometriotic cysts are monoclonal characterized by loss of heterozygosity in 75 percent of them, and mostly affecting 9p, 11q, and 22q chromosomes [78]. Jiang, X et al. investigated the possibility of endometriosis - associated ovarian cancer. In this study, 40 cases of endometriosis were examined for clonal status, the functional alteration in TP53, RAS and, all losses is the candidate of ovarian tumor suppressor on chromosome arm 6q, 9p, 11q, 17p, 17q and 22q genes were investigated [79]. The permanent and irreversible changes of a nucleotide sequence in endometriotic lesions called a somatic mutation, and many genetic mutations have been identified in endometriosis-associated ovarian cancer (EAOC).

39 genes were identified in the association between endometriosis and cancer. Several studies focused on the loss of heterozygosity of 10q gene, chromosomal aneuploidy, genomic alteration PGR and, ESR1 gene were common in women cancer [71,80,81]. Sato, et al. investigated that the functional alteration of tumor suppressor gene (PTEN/MMAC) which is located on chromosome arm 10q, in this study 54 cases of endometrioid carcinoma and endometrial cyst were included. The result was suggested that LOH at this site occurs 8 of 19 endometriosis - associated ovarian carcinomas (42.1%), 6 of 22 clear cell carcinoma (27.3%), and 13 of 23 endometriosis cyst (56.5%). Similarly, 4 out of 20 endometriosis - associated carcinomas having a somatic mutation in PTEN were identified [82]. Specific protein markers for ovarian carcinoma have been evaluated in atypical endometriosis. Hepatocyte nuclear factor - 1 $\beta$  (HNF-1 $\beta$ ) is a transcription factor that has significantly been expressed in ovarian cancer and seldom expressed in non-clear cell carcinoma [83]. The data collected antecedent research suggested that endometriosis is a monoclonal neoplastic disease and also a precursor of EAOC notwithstanding menopause. On one hand various types of molecular events like alteration of p53 gene, PTEN silencing, K-ras mutations have been discovered in EAOC. While activation of HNF-1 on the other hand, appears to be distinctive to clear cell carcinoma in becoming apparent in Endometriosis [84].

According to contemporary studies of whole - genome or targeted sequencing ARID1A and PIK3CA genes were identified as having frequent mutations while PPP2RIA and KRAS having moderate mutations in ovarian cell carcinomas [85-87], mutations of PTEN, CTNNB1, and KRAS in endometrioid carcinoma [83,88,89]. Activation of oncogenic KRAS and PI3K survival pathways and inactivation of tumor suppressor genes PTEN and ARID1A in combination with the results of gene expression profiling of these two tumor types are suggested for clear cell and endometrioid

ovarian carcinomas respectively [90-92]. Besides, IP3k/AKT/mTOR is the most investigating signaling mechanism for many cellular activities like cell growth, cell survival, proliferation, protein synthesis, transcription, and angiogenesis. Dysregulation of the signaling pathway causes activation of other downstream signaling mechanisms leading oncogenesis in humans. IP3K is a lipid kinase of G-protein coupled receptor and receptor tyrosine kinase (RTKs) family protein according to their structure; it is categorized in three classes I, II, and III. Again, Class, I of IP3K is sub-classified into two categories (IA and IB).

It is a group of heterodimer proteins consisting of p85 and p110 regulatory subunit encoded in 3 distinct genes viz; PIK3CA, PIK3CB, and PIK3CD. Catalytic activation of p110 leads to phosphorylation of 3<sup>rd</sup> carbon of the inositol that had of phosphatidylinositol 4-5 biphosphate (PIP2) lead to produce phosphatidylinositol [3-5] triphosphate (PIP3), for the activation of 2<sup>nd</sup> messenger PIP3, thus triggering AKT in the plasma membrane. The blockade of this pathway leads to independent cell growth due to a lack of a negative regulator of PIP3K/AKT/ [93,94]. Endometriosis is a benign inflammatory disease however, the molecular and cellular features work in a similar manner like; malignancy occurs, including increased cell proliferation, re-expression of the pluripotent transcription factor OCT4 [95], epithelial-to-mesenchymal transition [96] acquisition of migratory phenotype [95,97] development of distant foci, cell adhesion, invasion [98] angiogenesis, and at times, treatment resistance [99]. It is not fully declined but there is a strong association between endometriosis and ovarian cancer. Genetic mutation is the major factor of ovarian cancer thus many protein markers are used for advanced diagnosis, prognosis, and treatment. All genomic and proteomic markers facilitate the development of the best diagnostic tool for endometriosis - associated ovarian cancer.

## Management

Endometriosis is a chronic inflammatory disease that requires long term or lifelong treatment. Three major therapeutic management types exist for endometriosis, including Medical treatment, surgery, and assisted reproductive technology (ART) [100]. Accurate diagnosis is imperative because it provides outright information regarding severity of the disease. Many societies such as American College of Obstetricians and Gynecologists and American Societies of Reproductive Medicine approved medical treatment before definitive diagnosis [101,102]. The medical treatment provides only short term pain relief but when combined with surgical intervention, divulges long term relief. The main concern is how endometriosis-associated pain can be managed. Physicians believe in optimal management for this condition. All these treatments are suppressive and do not possess curative effect.

- 1) Egg preservation in young patients affected by endometriosis.

- 2) Preoperative surgical management to inhibit evolution and to avoid removal of cyst that might look like endometriosis.
- 3) Postoperative hormonal suppression to decrease recurrence of endometriosis [103].

### Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to reduce pain associated with dysmenorrhea in 80% of women. It inhibits cyclooxygenase (COX), a key enzyme in the biosynthesis of prostaglandin in endometriosis-associated pain and inflammation. Cyclooxygenase is two types viz; COX-1 and COX-2. NSAIDs and acetylsalicylic acid (ASA) inhibit both COX-1 and COX-2 but have a selective effect to primarily inhibit COX-2. However, management with NSAIDs is not significant, because endometrial pain appears by involving other factors in addition to prostaglandin. Ibuprofen, Naproxen, Mefenamic acid, Diclofenac, Meclofenamate, Ketoprofen are commonly seen effective in dysmenorrhea. It acts quickly within 30 to 60 minutes and can be taken on a regular basis according to the score of pain. Oral contraceptives can be used as second-line treatment if NSAIDs fail or decrease the pain incompletely. Individual NSAIDs have different types of actions depending upon their selective and non-selective receptor binding capacity. Besides, there might be specific side effects of NSAIDs, such as gastrointestinal (nausea, vomiting, peptic ulcer), hypersensitivity, rashes syndrome, intestinal nephritis, etc. [104-106].

### Hormonal Therapy

Gonadotropin-releasing hormone (GnRH) agonists are useful to deplete further synthesis of endogenous gonadotropins from the pituitary gland, interrupting the menstrual cycle, eventually resulting to cause endometrial atrophy and amenorrhea [107]. Progestin is an acceptable alternative drug for first-line therapy of endometriosis and has been used for over 30 years. Endometrial carcinoma has been treated with a more diverse method than the other malignant tumors that affect intra pelvic organs in untreatable cases. Radiotherapy, chemotherapy, and hormonal therapy are used in cases of endometrial malignancy. Here in hormonal treatment is better for those who wish to remain fertile after the early development of pre-menopausal endometrial cancer [108,109]. Progestin is effective in suppressing endometrial tumor growth in comparison to GnRH and Danazol. The cost-effectiveness and lower incidence of estrogen deficiency associated with adverse drug reaction (ADR) are lower than GnRH and danazol in the treatment of endometriosis. Thus, investigators have considered progestin as more effective and useful than GnRH and Danazol. Progestin with hormonal contraceptives can be provided either alone or in combination with estrogen to prevent development endometriosis hyperplasia. It decreases glandular cellularity by including apoptosis and inhibits angiogenesis in the myometrium [109-111].

### Medroxyprogesterone Acetate (MPA)

MPA is a synthetic and one of the most studied progestin that is typically used to cure irregular menstruation and abnormal uterine bleeding. It has been a greater effect on pain and improving quality life in placebo therapy, but the MPA and GnRH agonist dose 15-50 mg daily administration the efficacy has been found equivalent [110,112]. Ushijima K et al. conducted the Multicenter phase II clinical trial study. They found an 82% complete rate response in endometrial hyperplasia, where all the patients received 600 mg MPA with low dose Aspirin for 8 to 16 weeks and were monitored in following after 3 years. During the observation period, 12 pregnancies and 7 normal deliveries were achieved, which proved that MPA is effective in fertility-sparing treatment with a high dose and least toxicities for endometrial cancer and endometrial hyperplasia [113].

### Danazol

It is a synthetic steroid with strong anti-gonadotropins and weak androgenic properties, which inhibit estrogen and progesterone receptors' results in preventing endometriotic atrophy and reduced menstrual cycles [114]. Selak V, et al. 2001 in a Cochrane systematic review, evaluated the effectiveness of Danazol to placebo in the treatment of endometriosis along with infertility in women of reproductive age. The data represented that treatment with Danazol was effective in endometriosis-associated pain, and Laparoscopic scores were improved as compared to with or without placebo treatment [115]. Luisi S, et al. 2009 evaluated the efficacy of Danazol in young women with menorrhagia. Total 55 (30 had one or two miscarriages & 25 were nullipara) women were selected for this study after biopsies (hysteroscopy-directed biopsy) to exclude endometriosis hyperplasia, polyps. Also, they were prescribed 200 mg danazol daily at night by vaginal route for 6 months.

The result was useful as there was a significant reduction in the severity of blood loss in all women after 2 months of treatment [116]. Furthermore, another investigation by Szubert M, et al. 2014 depicted the efficacy of danazol treatment in endometriosis and pain management. 103 cases were selected and laparoscopy was performed during follow up. Only 71 women were diagnosed with having endometriosis and other women were suffering from minor pain in the pelvis. Treated with 2X200 mg danazol daily for 6 months, only 35 participants completed the study (two follow up visits at third and sixth months). After treatment, the pain score and concentration of CA-125 in plasma was significantly decreased [117].

### Hormonal Contraceptives

Limited studies said that oral contraceptives are useful in the treatment of endometriosis-associated with chronic pain. GnRH is the principal regulatory hormone of FSH) and LH. All these



hormones are involved in the synthesis and regulation of estrogen for ovulation and follicular development. Oral Contraceptive Pill (OCP) inhibits the synthesis of LH and FSH to prevent estrogen and progesterone synthesis by suppressing the activation of GnRH, resulting in the prevention of endometrial proliferation and produces scanty cervical mucus [109]. Estrogen - progestin combination or alone progestin is one of the most common contraceptives used as the first-hand treatment for chronic pain in the case of endometriosis and ovarian function. These can be prescribed through oral contraceptive pills, transdermal patches, vaginal rings. Estrogen - progestin combination or alone progestin is one of the most common contraceptives used as the first-line treatment of endometriosis-associated with chronic pain and ovarian function. These can be prescribed through oral contraceptive pills, transdermal patches, vaginal rings [118]. According to the degree of success in women who were affected by endometriosis or its associated pain, the cost, ease of administration, and tolerance effect are the key factor of these drugs to make them common.

Continuous therapy of combined oral contraceptives (COC) is better to control chronic pain as compared to cyclic administration [111]. A systemic review by Vercellini P, et al. 2011 revealed that the common relative risk of 0.63 [95% confidence interval (CI), 0.47-0.85] for current OC users, 1.21 (95% CI, 0.94-1.56) for past users and 1.19 (95% CI, 0.89-1.60) for ever users. This study indicated that OC is effective in reducing endometriosis and its symptoms [119]. A study undergone by Sullivan H, et al. 1999 to rule out whether the dose of COC was effective in endometriosis or ovarian activities revealed that COC had positive impacts on endometriosis. A total of 30 healthy women were included, who were administered 60 mcg of Gestodene and 15 mcg of Ethinyl Estradiol on 21<sup>st</sup> and 24<sup>th</sup> day in every 28 days menstrual cycle and were monitored over 5 months. The outcome was that such a regimen is an active treatment for endometriosis as compared to an alone ultra-low dose of estrogen treatment [120]. Medroxyprogesterone acetate 10-100 mg of norethindrone acetate 5 mg daily is commonly prescribed to treat endometriosis; this progesterone is completely suppressing hypothalamic-pituitary axis for preventing ovulation [121].

### Gonadotropin Releasing Hormone (GnRH) Agonist

GnRH agonists are one of the most common drugs used for the treatment of endometriosis. These drugs are down-regulating GnRH receptors from the hypothalamic-pituitary gland, which decreases gonadotropin secretion to inhibit ovulation and reduce serum estrogen level [122]. It is prescribed only after consultation with a physician. Leuprolide is a GnRH agonist that is effective in endometriosis as approved by the Food Drug Administration (FDA) [123]. Initially, the administration of Leuprolide stimulates LH and FSH which leads to increment in steroidogenesis thus, it elevates estrogen level in females and testosterone along with dihydrotestosterone (DHT) in males. Moreover, long term administration of Leuprolide can decrease the hormonal level,

which may ultimately inhibit gonadotropin release by inhibiting the secretion of LH and FSH in both males and females [124]. In comparison with combined hormonal contraceptive (CHC) treatment, GnRH agonists have better efficacy in endometriosis and its associated chronic pain [125]. Various research have been conducted to improve novel treatment with GnRH agonists for endometriosis and its associated symptoms, to conclude how currently existing therapies work, which type of biochemical abnormalities are seen and how can they be minimized. All these studies concluded a similar effect of GnRH agonists found effective in preventing endometriosis and chronic pain [126-130].

### Gonadotropin Releasing Hormone Antagonist (GnRH-Anta.)

GnRH antagonists have an advantage over the agonists about initial flare and hypoestrogenism through a direct mechanism that completely inhibits the GnRH receptors resulting in immediate suppression of LH and FSH secretion [131]. With the aid of cloning and high throughput peptide screening of oral human GnRH receptors, antagonist Elagolix was developed. It has a high affinity to bind GnRH receptors and reduces the interaction with CYP450 in inhibiting LH and FSH [132,133]. Clinical research was conducted in two different doses; 150 and 200 mg. First was 150mg daily for 24 months and second, 200 mg twice a day for 6 months. In 2018, USFDA approved 150 - 200 mg Elagolix for the management of endometriosis [134,135]. At the moment, various formulations are available but oral, and injectable preparations are widely used that competitively inhibit the GnRH secretion. The other two types of GnRH antagonists called Relugolix and Linzagolix are introduced, which work to prevent the advanced stage of endometriosis-associated pain. Both the drugs are under clinical trials phase III. In the clinical trial, 40 mg Linzagolix is used in combination with Ethyl estradiol 0.1 mg or 0.5 mg NETA (clinical trial registration No. NCT03204318, NCT03204331, and NCT02778919) [135].

### Aromatase Inhibitor

The Aromatase enzyme comprised two types of polypeptides. The first one belongs to the superfamily of the cytochrome P450 (CYP450arom), which is the product of single gene CYP19, and second is flavoprotein (flavoprotein NADPH-CYP450 reductase). It is expressed on different body sites like ovarian granulosa cells, adipose tissue, placental syncytiotrophoblast, osteoblasts, and brain. Aromatase's main source is ovarian cells in premenopausal women, while adipose tissues in postmenopausal women [136,137]. Aromatase converts approximately 2% of Androstenedione to E1. Further, it turned to E2 in postmenopausal women by 17 $\beta$ -Hydroxysteroid dehydrogenase type 1 in peripheral tissue resulting to high level of E2 circulating in the blood to cause endometrial hyperplasia and carcinoma [138]. The agent Aromatase inhibitor (AIs) was first employed to manage estrogen receptor activating breast carcinoma.

AIs represent the new promising treatment of endometriosis. It has the capability to reduce estrogen production by inhibiting the enzyme cytochrome P450 [139]. AIs are classified into three generations. The first generation is Glutethimide, which has many adverse effects like lethargy, hypersensitivity, nausea, etc. The second generation is, Fadrozole and Formestancel have more selective and higher efficacy over the first generation and have less adverse effects. The third generation Aromatase inhibitors, namely; Letrozole, Anastrozole, and Examestande, are triazole derivatives that are selective, reversible as well as more potent, making them ideal for using clinically. These agents are prescribed in premenopausal women to decrease the estrogen level and increase FSH secretion from pituitary glands. Treatment with Aromatase inhibitors must be combined with other potent drugs to down-regulate [137].

### Letrozole

Letrozole is a non-steroidal aromatase inhibitor that has been commonly used for the management of endometriosis-associated pelvic pain and breast carcinoma. It was first reported in 2004 for the management of endometriosis. Letrozole has been used alone or in combination with other steroidal or non-steroidal analogs for the treatment of [140]. In the preclinical study, the animals were selected and made develop endometriosis by Vernon and Wilson's method. After the 14th day of model development, the animals underwent laparoscopy to measure heterotrophic. After that, they were provided 0.5 mg/kg AIs (Letrozole) daily for 3 weeks. Upon completion of treatment, the animals were re-examined, and the size of heterotrophy was determined. Besides, the histopathology study was carried out in both groups (control and AIs treated group). The result suggested that 0.5 mg/kg for 21 days of treatment with Letrozole decreases the size of heterotopies. The total percentage of reduction of  $79.92\% \pm 7.89\%$  was observed [141]. A Prospective non-randomized study was carried out, including 20 patients with endometriosis and its associated chronic pelvic pain. Both Letrozole and norethindrone were prescribed in combined form as 2.5mg/kg for 6 months starting from the 3<sup>rd</sup> day of the menstrual cycle. Besides, the pain score was recorded 30 days before starting the treatment. The result showed that following the procedure, and all the patients showed significant improvement in pain and [142].

### Role of Micro-RNAs in Endometriosis Treatment

Micro-RNAs (miRNAs) are the highly conserved 9-22 nucleotide long non-coding RNAs that play a crucial role in cellular functions such as; cell proliferation, angiogenesis, apoptosis, and gene expression. miRNAs are directly bound to the 3 untranslated regions of messenger RNA (mRNA) [143]. miRNAs have been found in most body fluids and the expression of miRNAs differs between healthy and diseased people however its physiological roles are obscure [144]. Endometriosis is a multifactorial disease characterized by the presence of endometrial tissue surrounding the womb. miRNAs are

expressed in different gynecological disorders like; malignancies, leiomyoma, endometriosis, etc. Ovarian carcinoma is a rampant lethal malignancy in developed countries [145]. As angiogenesis is a key factor in endometriosis, several studies have reported that increment in VEGF level causes endometriosis [146-148]. miRNAs are involved in apoptosis disease progression as a result of which, in endometriosis, they are used as a diagnosing tool for detecting the progress of the disease and cell proliferation. Also, miRNAs are potential and efficient in the early detection of [143].

### Anti-Angiogenesis Factor

Presently available medical treatment is effective to suppress hormonal synthesis. Oral contraceptives, androgenic agents, progestin analogs, GnRH agonists and GnRH antagonists have been successfully used for the treatment of endometriosis. However, these agents are not effective in eradicating the disease in some cases. Long term use of these agents exhibits major adverse effects. Interleukins-8, vascular endothelial growth factor (VEGF) receptor-2, Endoglin, Urokinase-type plasminogen activator, matrix metalloproteinase-2, and 9, as well as a placental growth factor, is found in an activated endometrial cell in tumors [111,149-151]. Previous studies showed that soluble truncated fms like tyrosine kinase-1 receptor and affinity-purified VEGF antibody are significantly useful to inhibit the angiogenesis factor in endometriosis. The blockade of VEGF signaling prevents endometrial lesions and associated carcinoma. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody that prevents vascular density and also leads increment in apoptotic cell demise in case of surgically induced endometriosis.

Bevacizumab is in phase II clinical trial 15 mg/kg intravenous route of administration every 3 weeks until the disease progression is effective in endometrial carcinoma [152,153]. Thalidomide is also used as an anti-angiogenic agent in endometriosis. The mechanism of action of thalidomide is suppression of phosphoinositide 3 kinases (P13K)/protein kinase B (AKT) signaling to inhibit the formation of angiogenesis-related effect [154]. Antônio LG, et al. investigated the effect of thalidomide in the progression of endometrial lesions. 1 and 10 mg/kg thalidomide was administered in Wistar rats daily for 10 days. After 10 days of treatment, the tissue was isolated, and the cell proliferation index (CPI) was identified. The result proved that thalidomide had significantly reduced the lesion area and CPI [155]. Women who had relapsing endometriosis after surgical treatment of ovarian and peritoneal endometriosis were made discontinue GnRH agonist treatment, meanwhile, 300 mg/kg of thalidomide was prescribed for 6 months. Eventually, following the anti-angiogenic treatment with thalidomide, the relapse of endometriosis was completely suppressed [156].

### Surgical Treatment

Surgical management of endometriosis requires extensive knowledge of the disease that should be managed by a

multidisciplinary team to lead professional gynecologists. Laparoscopy is a useful tool for the diagnosis of disease and determining the severity of disease before starting the surgical treatment [157]. It is effective in suppressing symptoms and chronic pain and can increase the fertility of women. Approximately, 50% of cases will re-develop symptoms within a few years of surgery. The severity of the disease determines the successful surgical treatment of Endometriosis [122]. Patients who have chronic pelvic pain or ovarian endometrium and do not respond to medical management need surgical treatment. There are some approaches for considering surgical management viz;

- 1) Egg preservation in young patients affected by endometriosis.
- 2) Preoperative surgical management to inhibit evolution and to avoid removal of cyst that might look like endometriosis.
- 3) Postoperative hormonal suppression to decrease recurrence of endometriosis [103].

## Conclusion

It is mandatory to understand that endometriosis is a complex, debilitating disease comprising multiple factors in its origin and development. Researchers are comprehending the distinct clinical features, including chronic pelvic pain and infertility, to discover the significant markers or therapeutic strategies to battle the mysterious disease. It is significant to gain cognizance into the complex etiology of endometriosis due to different causes viz; the unavailability of non-invasive diagnostic markers, delay in diagnosis, high risk of recurrence of the disease following surgical removal of the tissue, and lack of a definitive cure for the disease. This article will furnish the readers with up-to-date knowledge regarding the pathogenesis, biomarkers, association of infertility, pregnancy, and carcinoma with the ailment and also shed light on the management of the disease.

## Future Prospective

Still, endometriosis research is lacking the exact mechanism for etiology, biomarkers, and effective treatment modalities to generate convincing data with high sensitivity and specificity. Besides, limitations derive from small sample size and suboptimal characterization of specimens.

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## Ethical Consideration

Conflict of interest: Authors declare that they have no conflict of interest.

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