Diagnosis & Management of Endometriosis: Pathophysiology to Practice
APGO Educational Series on Women’s Health Issues
Diagnosis & Management of Endometriosis: Pathophysiology to Practice

INFORMATION

Diagnosis & Management of Endometriosis: Pathophysiology to Practice, a module fully funded by an unrestricted educational grant from Abbott Laboratories, reviews the current evidence and practical clinical experience for the evaluation and treatment of endometriosis. The module also looks at recent data that may one day lead to improved outcomes for patients who currently suffer from pain, infertility, and other symptoms often associated with endometriosis.

The complete module includes three components:

1. Online monograph for (a) medical school faculty to use to supplement training of residents and students and (b) practicing healthcare providers to use to enhance their knowledge of endometriosis-related care. The monograph is a 30-page resource with text, figures, tables, and a full reference list. The aim is to distill this evidence-based yet practice-oriented text into a primer on the full spectrum of endometriosis management focused on key teaching points and principles for clinical practice. The monograph is downloadable as a PDF for offline reference as well.
2. Set of PowerPoint teaching slides on endometriosis-related care derived from the monograph for use as a teaching tool in medical schools, residency and fellowship programs, and continuing education presentations. The slides include speaker notes for use by educators.
3. Series of four interactive case studies. The self-directed interactive case studies use a combination of illustrations and 2D or 3D models, each focusing on a different aspect of endometriosis-related care. Each case study demonstrates concepts and principles across the scope of the monograph and slide set, and each includes interactive questions for the learner to answer at various points throughout the case narrative.

TARGET AUDIENCE

Endometriosis is an enigmatic disease commonly associated with significant morbidity and reduction in quality of life among reproductive-age females. Timely diagnosis and effective management of the disease represent a significant challenge for both clinicians and patients. Efficacious treatment requires a multidisciplinary approach to effectively manage the wide-ranging symptoms commonly associated with endometriosis, including dyspareunia, infertility, and reduced quality of life. This educational activity is intended for obstetricians/gynecologists and other healthcare professionals involved in the diagnosis and treatment of endometriosis, with emphasis on the fundamental skills essential for timely intervention and adequate treatment(s). By applying key concepts and employing fundamental techniques, healthcare professionals will be able to effectually diagnose, reduce morbidity, and optimize outcome in their affected patients.

PURPOSE & CONTENT

- Understand the history and pathophysiology of endometriosis.
- Understand the critical need for timely diagnosis and effective intervention.
- Understand the considerable effects of chronic disease and employ best-practice techniques to mitigate them.
Educational Objectives
At the conclusion of this activity, the participant should be able to:
• Understand the pathophysiology, varied presentation, and symptoms of endometriosis.
• Identify factors that can inform a timely and accurate diagnosis.
• Demonstrate an ability to recommend appropriate medical and surgical management.

Discussion of Off-Label Use
Because this course is meant to educate physicians with what is currently in use as well as what may be available in the future, there may be “off-label” use discussed in the presentation. The audience will be informed if and when off-label use is being discussed.

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INTRODUCTION

Endometriosis Defined
Endometriosis is an inflammatory, estrogen-dependent disease that often results in substantial morbidity, pelvic pain, multiple surgeries, and infertility. Characterized by the existence of endometrial glands and stroma outside the uterine cavity, the disease represents a significant clinical challenge, commonly associated with significant morbidity and reduction in quality of life among reproductive-age females.

Early symptoms may be underappreciated by caregivers, healthcare consumers, and clinicians alike, and timely diagnosis combined with effective management cannot be undervalued. The lack of reliable noninvasive detection methods may likely contribute to lengthy delays in diagnosis. Practitioners from all disciplines, particularly obstetricians and gynecologists, must understand not only the medical aspects of this disease but the tremendous psychosocial and cost burdens as well.

Endometriosis is clinically defined as the presence of endometrial-like tissue found outside the uterus, resulting in a chronic, inflammatory reaction. This aberrant process leads to microscopic internal bleeding, development of painful endometriomas, inflammation, fibrotic scarring, and formation of adhesions (Figure 1). There may also be marked distortion of pelvic anatomy. Symptoms are wide-ranging and often start early in life, but they may go unrecognized by both

Figure 1. Burst Ovary
the medical and lay communities. Indeed, symptoms may present even as early as 8 years of age, and high rates of disease and symptoms indicative of possible future endometriosis have been noted in adolescents and young women based on prevalence data.\(^2\)

Classic signs include severe dysmenorrhea, deep dyspareunia, chronic pelvic pain, Middleschmertz, associated cyclical or perimenstrual symptoms (eg, of bowel or bladder) with or without abnormal bleeding, infertility, and chronic fatigue.\(^1\) Women with endometriosis may also suffer from autoimmune or inflammatory diseases, allergies, and asthma.\(^3\) As well, endometriosis shares similarities with several autoimmune disorders, including elevated levels of cytokines, decreased apoptosis, and cell-mediated abnormalities.\(^4\) Severely compromised quality of life and sexual health are common.

Endometriosis typically develops on pelvic structures including the rectovaginal septum, bladder, bowels, intestines, ovaries, and fallopian tubes, but it may also be found in distant regions including the diaphragm; the lungs, where it can induce catamenial pneumothorax; and very rarely, areas as far outside the abdominopelvic region as the brain (Figure 2). The ovaries are among the most frequent of sites, with gastrointestinal and the urinary tracts, soft tissues, and diaphragm following. Depending on location, the disease may present with varied symptoms ranging from bowel obstruction, melena, hematuria, dysuria, dyspnea, and swelling of soft tissues, respectively.\(^5\)

Endometriosis is an enigmatic disease that can present as a diagnostic and therapeutic challenge; ectopic pregnancy, pelvic infection, and ovarian torsion may mimic the symptoms and should be ruled out in the emergent setting.

Often called a “disease of theories,” the definitive cause or causes of endometriosis remain under debate, though demonstrated association with a number of hereditary, environmental, epigenetic, and menstrual characteristics exists. The chronic inflammatory reaction, infertility, and pelvic pain associated with endometriosis may also correspond to a variety of

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**Figure 2. Pelvic Structures Where Endometriosis Typically Develops**

- Fallopian tube
- Ovary
- Uterus
- Rectovaginal septum
- Cervix
- Rectum
- Bladder
- Uterovesical fold
- Vagina
- Perineum

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co-morbid conditions, ranging from autoimmune disease to food and environmental allergies and intolerances. The disorder remains a leading cause of gynecologic hospitalization and hysterectomy, and efficacious treatment requires a multidisciplinary approach to improve the wide-ranging sequela ranging from dyspareunia and chronic pain to infertility and subjective well-being.

**Symptomology**

Symptoms vary considerably, often mimicking those of other conditions including pelvic inflammatory disease, adenomyosis, fibroids, and ovarian cancer. Few laboratory tests are valuable in the diagnosis of endometriosis; for example, CA-125, CCR1mRNA, and MCP1 have low accuracy. A CBC with differential may help to eliminate other causes of pain, such as infection, but is of little use in confirming presence or absence of the disease. Likewise, urinalysis and urine culture can rule out infection, and cervical Gram stain with cultures can confirm or deny sexually transmitted diseases, which may lend to pelvic pain and infertility. Beta HCG can rule out complications of possible pregnancy. Subsequently, anything other than surgical confirmation is considered uncertain.

While laparoscopic intervention is the primary means of definitive diagnosis, a third of patients with pelvic pain have completely normal pelvic anatomy at the time of surgical evaluation. To some extent, the clinically visualized findings may represent a “tip of the iceberg” phenomenon, in that deep, infiltrating lesions may appear on the surface as minute fibrotic implants. In these cases, the extent of the disease cannot be determined by visual inspection. However, minimally invasive laparoscopic surgery remains the gold standard for diagnosis and treatment.

The degree or stage at which endometriosis is present has no correlation with pain or symptomatic impairment. Symptoms are variable but typically reflect area of involvement and may include:

- Dysmenorrhea
- Heavy or irregular bleeding
- Pelvic pain
- Lower abdominal or back pain
- Dyspareunia
- Dyschezia, often with cycles of diarrhea/constipation
- Bloating, nausea, and vomiting
- Inguinal pain
- Dysuria

Women with endometriosis are more likely to report their pain as “throbbing” and experience dyschezia when compared to women with an apparently normal pelvis, and specific menstrual symptoms have been reported to occur more frequently in women with the disease versus a control group. Endometriosis is more commonly found on the left side, with at least one study indicating 56% of women having left-sided disease versus 50% having right-sided disease.

Women may also report hematochezia in association with menses when endometriosis involves the rectosigmoid colon. Similarly, flank pain and/or hematuria may be present if the bladder or ureters are involved. Sexually active women may report dyspareunia, which may be due to scarring of the uterosacral ligaments, nodularity of the rectovaginal septum, cul-de-sac obliteration, and/or uterine retroversion, all of which may also lead to chronic backache. These symptoms are often exaggerated during menses. Women with deep infiltration of the uterosacral ligaments may have the most severe impairment of sexual function.

Acute exacerbations may be caused by chemical peritonitis due to leakage of old blood from an endometrioma. With conscious laparoscopic pain mapping, painful lesions were found to involve peripheral spinal nerves rather than autonomic nerves. Partial or complete bowel obstruction may occur due to adhesion formation or a circumferential endometriosis lesion. Ureteral obstruction and hydronephrosis can result from endometrial implants on the ureter or mass effect from an endometrioma.

Early symptom recognition, particularly in adolescence, will lead to timely intervention, accuracy of diagnosis, effective treatment, and adequate referral as needed, which will ultimately assist in reducing the associated morbidity of endometriosis.

**Historical Background**

Although characteristics of endometriosis have been described as far back as 1600 BCE in the Egyptian Ebers Papyrus, Benagiano and Brosens note that over the years a number of investigators have attempted...
to reconstruct the pathway leading to the discovery of what we call today adenomyosis and endometriosis.

Medical historian Vincent Knapp, PhD, contends that endometriosis was described well over three centuries ago, attributing credit to German physician Daniel Schrön. In his dissertations, Schrön described a “female disorder in which ulcers appear[ed] in the abdominal, the bladder, intestines and outside the uterus and cervix, causing adhesions.” Critics of Knapp’s assertions, however, believe that Schrön’s lectures referred instead to infections rather than endometriosis.

Noted Montpelier physician Jean Astruc may have been referencing endometriosis in his 1740 medical tome, wherein he wrote, “All in general know, that it is as natural as happy for women to have their menses without any preternatural Accidents. On the contrary, vicious…Menstruation…denotes some Permanent Vice in that Organ…Difficult Menstruation is that wherein Women commonly suffer before or at the Time of their Evacuation, and painful Colicks, sensible Pains of the Matrix (uterus)…are the most constant accidents; though vomiting, diarrhea, constipation, and the like are also rarely wanting.”

In years following, other physicians would begin describing ectopic endometrial tissue in various cases, with the first histological description credited to Von Rokitansky in 1860. Researcher Thomas Cullen later suggested that endometriomas, or as he called them, adenomyomas, strongly resembled the mucous membrane of the uterus.

It is Albany, New York, physician John Sampson, MD, however, who is generally considered forefather of the disease, with his work on peritoneal and ovarian endomeiromas providing the first theory on pathogenesis—though his postulation on retrograde menses and endometriosis is not without critique. Emil Novak and other pioneering researchers in years to come would identify, refine, classify, and postulate on the sequela and pathogenesis of the enigmatic disease known today as endometriosis.

Three basic concepts have evolved during the late 20th century: (1) localized inflammatory process is supported by elevated cytokines and growth factor concentrations in the peritoneal fluid of the affected, (2) angiogenesis is favored in the establishment of implants, and (3) there exist biochemical differences in the eutopic and ectopic endometrium of women with the disease. These factors contribute to pathogenesis and related symptomatology; today, endometriosis has become a major clinical issue.

Pathogenesis

Since Dr. Sampson first coined the term “endometriosis” in 1921, extensive research on pathogenesis has been carried out. Despite progress, however, no single theory has proven sufficient to explain pathogenesis satisfactorily; current concepts hold that multifactorial immune, hormonal, genetic, environmental, and anatomic factors may be responsible. The most notable theories are described herein.

It is proposed that there are, in fact, three distinct entities, each with different pathogenesis: peritoneal, ovarian, and deeply fibrotic disease (formerly referred to as deeply infiltrating endometriosis, or DIE). Deep endometriosis, together with cystic ovarian endometriosis, represents the most severe form of disease.

Researchers agree endometriosis is likely to be polygenic and multifactorial, but the exact pathogenic mechanisms are still unclear. Each theory singularly fails to account for all forms of endometriosis, thereby indicating multifactorial mechanisms.

Development can be divided into five basic processes: adhesion, invasion, recruiting, angiogenesis, and proliferation. Genetics, biomolecular aberrations in the eutopic endometrium, dysfunctional immune response, anatomical distortions, and a proinflammatory peritoneal environment may all ultimately be involved.

The oldest concept assumes that endometriosis arises in situ from wolfian or mullerian duct remnants, or from metaplasia of peritoneal or ovarian tissue. Proposed as early as 1870 by anatomist Heinrich von Waldeyer as germinal epithelium of the ovary, this theory continues to be popular today and has the support of pathologists, who often refer to it as the metaplastic theory.

Endometriosis found in the cul-de-sac, on the uterosacral and broad ligaments, beneath the ovarian surface, on the peritoneum, on the omentum, and within the retroperitoneal lymph nodes is often referred to as mullerianosis. Disease diagnosed in adolescents either prior to or shortly after menarche
supports the notion of embryonic mullerian rest pathogenesis.19

Often seen as an extension of the coelemic metaplasia theory, which holds that germinal epithelium of the peritoneal serosa and ovary can be transformed by metaplasia, the induction theory proposes that one or several endogenous, biochemical, or immunological factors could induce endometrial differentiation in undifferentiated cells.19 This asserts that substances released by the endometrium are transported by blood and lymph systems to induce endometriosis in various areas of the body. Transplantation further utilizes the theory that these substances can induce endometriosis through iatrogenic, lymphogenic, and hematogenic spread, which would account for the uncommon, extrapelvic sites of endometriosis invasion.

“Sampson’s theory,” dating back to 1921, is perhaps the most popular—if not flawed—of theories. Initially, Dr. Sampson assumed that lesions are the result of “seedlings” from the ovaries.19 Later, in 1927, he proposed the disease actually results from reflux menstruation, wherein endometrium is showered backwards onto the peritoneum and ovaries, thus taking hold and implanting. However, as retrograde menstruation is a very common phenomenon among women of reproductive age, there are undoubtedly other factors that contribute to the pathophysiology and pathogenesis of the disease.20 Sampson’s theory fails also to explain why progression occurs in some women only. Essentially, this theory considers endometriosis as normal endometrial cells that behave abnormally because of abnormal peritoneal milieu; however, this is not supported or borne out universally.17

The key event in the process is implantation or metaplasia, which thus has been the subject of many investigations, and the early subtle lesions become very important.21 The roles of molecular alteration, that is, genomic instability, and cell survival are emerging debates in disease pathogenesis. Iron-induced oxidative stress has been purported to play a fundamental role, secondary to influx of iron, during retrograde menstruation with recent studies demonstrating HNF-1β overexpression in endometriotic foci. HNF-1β increases the survival of endometriotic cells under iron-induced oxidative stress conditions possibly through the activation of forkhead box (FOX) transcription factors and/or endometriosis-specific expression of microRNAs. Endometriotic cells expressing HNF-1β also display cell cycle checkpoint pathways required to survive DNA-damaging events.22

More recent research also links a K-RAS variant allele (found in 31% of women with endometriosis as opposed to 5% of a large diverse control population) to the development of the disease. In a murine model, endometrial xenografts containing the K-RAS variant demonstrated increased proliferation and decreased progesterone receptor levels. These findings suggest that an inherited polymorphism of a let-7 miRNA binding site in K-RAS leads to abnormal endometrial growth and endometriosis. The LCS6 polymorphism is the first described genetic marker of endometriosis risk.23

Promising research on stem cells in the possible etiology of endometriosis is also flourishing. Scientists have identified adult stem cells in several tissues, including the endometrium, with evidence to suggest a role of stem/progenitor cells in development of the disease.24 Human endometrium undergoes cycles of growth and regression with each cycle; adult progenitor stem cells are likely responsible for the regenerative capacity. These same cells may have an enhanced capacity to generate endometriosis if shed in retrograde fashion as well. Mesenchymal stem cells are also involved in the pathogenesis of endometriosis and may be the principal source of endometriosis outside of the peritoneal cavity when they differentiate into endometriosis in ectopic locations. Finally, in addition to progenitor stem cells, recent publications have identified multipotent stem cells in the endometrium.25

With many studies now providing credible evidence to define endometriosis as an epigenetic disorder, future research will transform further understanding of pathogenesis and pathophysiology, as well as provide novel targets for noninvasive diagnostics and drug therapies to treat this unrelenting disease.19

**Epidemiology & Pathophysiology**
Prevalence corresponds to, and increases with, awareness and training of the surgeon, but endometriosis is estimated to affect nearly 176 million women globally; 775,000 in Canada and 8.5 million in North America overall.26 Mistakenly once believed to be a disease of older women, nearly 70% of teens with pelvic pain are later diagnosed with endometriosis.27 Early intervention and increased awareness is requisite to reduce morbidity, infertility,
and progressive symptomatology in patients of all ages.

Parity and infertility have long been associated with endometriosis, with infertility among the chief clinical findings. As well, associated pain, anatomic distortion, development of adhesions, altered inflammatory response characterized by neovascularization and fibrosis formation, abnormal T- and B-cell functionality, abnormal complement deposition, and altered interleukin-6 are among clinical consequences.\(^\text{10}\) Endometriosis is also clearly associated with dysmenorrhea, but it is unknown whether this is a cause or a consequence.\(^\text{21}\)

There is no known disease prevention. Related to a number of hereditary, environmental, epigenetic, and menstrual characteristics and alterations, some sharing certain common processes with cancer,\(^\text{28}\) endometriosis remains the third leading cause of gynecologic hospitalization in United States\(^\text{29}\) and is considered a leading cause of female primary and secondary infertility, prevalent in 0.5% to 5.0% in fertile and 25% to 40% of infertile women.\(^\text{30}\) The disease is also a leading cause of hysterectomy in the United States, with significant associated morbidity.\(^\text{31}\)

Though no particular demographic, personality trait, or ethnic predilection has been defined, certain characteristics have been associated with diagnosis, including decreased risk with late age at menarche\(^\text{32}\) and shorter menstrual cycles with longer duration of flow.\(^\text{33}\)

Likewise, family history cannot be undervalued, with consistent findings illustrating a near 10-fold increased risk in those women with first-degree relatives who have endometriosis.\(^\text{34}\) Further genetic analyses will clarify the role of family in disease risk.

Dioxin pollution has been suggested to be causally related to endometriosis based on the observation of increased incidence and severity of disease in primates treated previously with dioxins.\(^\text{35}\) Related data suggest plausibility that dioxin exposure of specific timing and dosage may precipitate endometriosis through interaction with estrogen receptors or suppression of progesterone receptors.\(^\text{19}\) Conversely, at least one more recent study concluded that dioxin may not contribute to the etiology of endometriosis at all.\(^\text{36}\)

No clear association has been defined between endometriosis prevalence and chronic immunosuppression, for example, in transplant patients, nor with smoking affecting NK activity, nor with caffeine or alcohol, nor with any lifestyle variable.\(^\text{21}\) Studies have found that higher body mass index decreases risk of both deep as well as ovarian and pelvic endometriosis, as does parity,\(^\text{37}\) though pregnancy is not a cure.

Frequency of endometriosis in women of higher social class has been reported, but this is likely the result of bias. The same diagnostic bias may explain the higher frequency in white women versus women of color, and in fact, data on prevalence in different races often do not consider the reason for admission for surgical procedure, which may be selectively associated with a higher or lower likelihood of an endometriosis diagnosis. Few studies have evaluated comparable population and socioeconomic conditions; those that did revealed no substantial differences among women of different races.\(^\text{19}\) Less understood are the factors, if any, of nutrition and exercise, lifestyle, personality traits, and other variables, with little evidence regarding these as more than simply modulating roles.

Data on specific phenotypic traits of women with the disease are also sparse. However, in a recent provocative study by Vercellini and colleagues\(^\text{38}\) determined that women with the most severe form of endometriosis appeared more attractive to external observers than those with peritoneal and/or ovarian endometriosis, as well as those without endometriosis. Women with severe rectovaginal disease were judged to have a leaner silhouette, larger breasts, and a history of earlier coitarche. Whilst phenotyping may have future use in conjunction with genetic and environmental data to elucidate the pathogenesis of endometriosis, the authors did caution that further studies are warranted to “exclude a spurious relationship between attractiveness and rectovaginal endometriosis and to rule out the potentially confounding effect of deep dyspareunia on some aspects of sexual behavior.”

**Economic Impact**

The literature concerning economic evaluations on endometriosis is likewise spare, with few studies systematically addressing fiscal impact. Much of the existing data refer to generalized costs associated with pelvic pain and infertility, with few targeting endometriosis-specific cost data. Similarly, no studies quantify the economic impact among
adolescents. Nonetheless, while the true burden may be underestimated, the economic burden from both a sufferer’s and societal perspective is profound.

One database analysis found that direct endometriosis-related costs were considerable and appeared driven by hospitalizations; as endometriosis-related hospital length of stay steadily declined from 1993 to 2002, per-patient cost increased 61%; approximately 50% of >600,000 endometriosis-related ambulatory patient visits involved specialist care; and females 23 years old or younger constituted >20% of endometriosis-related outpatient visits. An actuarial analysis revealed that women with endometriosis incur total medical costs that are, on average, 63% higher than medical costs for the average woman in a commercially insured group. Likewise, intangible effects of endometriosis cannot be dismissed. Fourquet et al previously assessed the burden of endometriosis through Patient Reported Outcome data, revealing that 72% reported having eight or more endometriosis-related or coexisting symptoms, being dysmenorrhea, incapacitating pain, and dyspareunia, with nonmenstrual pain that interfered with their daily life and work activities. Eighty-five percent of respondents noted a decrease in quality of their work and almost 20% reported being unable to work due to pain, while 69% reported that they continued work despite feeling pain. Forty percent of patients surveyed perceived that as a direct consequence of endometriosis, their career growth was negatively affected due to high rates of absenteeism and/or low performance, not being promoted, not receiving merit/excellence bonuses, missing professional seminars, and loss of clients. Others reported being “totally incapacitated” and even dismissed from or left their jobs due to symptoms.

Most recent data indicate that the total annual burden of endometriosis-associated symptoms in the United States has reached a staggering $119 billion. Moreover, endometriosis also accounts for a significant loss of productivity: 11 hours per woman per week; 38% more than for women with similar symptoms without endometriosis.

Endometriosis is among the leading gynecologic diagnoses in women with recurrent and progressive chronic pelvic pain. While studies aimed at calculating healthcare costs and health-related quality of life in women with endometriosis specifically are limited, the existing data should drive policy to improve the standard of care on a sustained basis, thus reducing the associated intangible and societal cost burden.

**COMORBIDITIES**

**Adhesions**

Adhesions are a common co-morbidity among endometriosis patients. In addition to pain, anatomic distortions, and surgical complications, adhesions may also play a role in the development of ovarian endometriomas and deeply invasive nodules. Thus, prevention, whether de novo or by re-formation, of adhesions is one of the most important—yet neglected—aspects of treatment in endometriosis.

Adhesions are defined as “connections between opposing serosal and/or nonserosal surfaces of the internal organs and the abdominal wall, at sites where there should be no connection. This connection can be a band, which is vascular or avascular, and filmy/transparent or dense/opaque, or it could be a cohesive connection of surfaces without an intervening adhesion band.”

In one study of patients diagnosed with adhesions, researchers found that 43% had had previous surgery, 13% had a history of pelvic inflammatory disease, and 2% had endometriosis; 47% of those who had adhesions at the time of laparoscopy did not demonstrate any recognized risk factor.

Without question, intrapelvic adhesions lead to significant morbidity. In a prior study, 303,836 hospitalizations resulted from surgeries that were performed primarily for adhesiolysis due to adhesions of the digestive and female reproductive systems, resulting in 846,415 days of inpatient care at a cost of $1.3 billion. The high incidence of adhesion formation after surgery for endometriosis underscores the importance of optimizing surgical techniques to potentially reduce adhesion formation.

The disruption of the peritoneal surface during surgical intervention, adhesiolysis, and local inflammation of endometriosis influence the formation of postoperative adhesions. Minimal and gentle tissue handling, use of barrier agents, precise microsurgical treatment with minimal blood loss, prevention of glove powder exposure, and copious pelvic irrigation can minimize
adhesion formation. In addition to optimized surgical techniques, which diminish risk of tissue injury, tissue devascularization, and subsequent inflammation, along with use of barriers, murine models have demonstrated the successful use of fish oil on endometriosis-associated adhesion development and secondary inflammatory responses within the uterus, effectively reducing not only experimental endometriosis-related postsurgical adhesion development but also inflammation inhibition within the uterus itself.\(^{50}\)

Kruschinski and colleagues\(^{51}\) investigated the feasibility and outcome of adhesiolysis in patients with severe and recurrent adhesions using gasless (lift) laparoscopy and a SprayGel\(^{®}\) adhesion barrier with promising results (a reduction in adhesion score at second-look laparoscopy was overall 89.8%; 90.1% reduction in extent, 89.3% reduction in severity, and 89.9% reduction in grade). SprayGel, however, is not available in the United States. Other barrier membranes and gels are routinely used in the United States, such as absorbable cellulose mesh (Interceed\(^{®}\)), combination hyaluronic acid and carboxymethylcellulose (SepraFilm\(^{®}\)), and 4% icodextrin (Adept\(^{®}\)), to name a few.

Despite the lack of data correlating adhesions to clear benefit of adhesiolysis, many surgeons still support the relationship and the value of adhesiolysis, as shown by Diamond et al.\(^{52}\) Similarly, Steege and Stout\(^{53}\) previously studied pain relief after adhesiolysis in patients with pain during their daily activity or with dyspareunia. Of the patients with pain during daily activity, 56% had either resolution of pain or at least a reduction in their pain of greater than 50%. In the patients diagnosed with dyspareunia, 70% had either resolution of pain or a reduction of at least 50% in pain.\(^{48,53}\)

Despite adherence to techniques for prevention and promising product development, adhesions remain a continued potential contributor to pain, even after endometriosis has been completely resected.\(^{49}\) It is expected that growing awareness will lead to the development of new products, improved surgical techniques, research data, and additional technologies to expand indications and favorable clinical outcome.

**Infertility**

It is estimated that up to 50% of women with endometriosis may suffer from infertility.\(^{54}\) Assisted reproductive technology, male factors, and other factors are outside the scope of this module; the focus herein is specifically on the role of endometriosis in infertility. Though the association is clear, mechanisms linking the two are uncertain. In general, biologic mechanisms connecting endometriosis and infertility include:

- Distorted pelvic anatomy, including adhesions resulting from endometriosis, which can impair oocyte release or inhibit ovum pickup and transport,\(^{54}\) as well as damaged or obstructed fallopian tubes or acquired or congenital uterine defects.\(^{19}\)
- Altered peritoneal function, including increases in fluid volume; concentration of activated microphages; prostaglandins; IL-1, IL-6, TNF-alpha, IgG, and IgA antibodies; lymphocytes; an ovum capture inhibitor preventing cumulus-fimbria interaction;\(^{54}\) RANTES; angiogenic activity; IGFBP protease; and related inflammatory milieu.\(^{55}\)
- Endocrine and anovulatory disorders, including luteinized unruptured follicle syndrome (LUF), luteal phase defect, abnormal follicular growth, and premature as well as multiple luteinized hormone surges. It has been hypothesized that LUF may not be a consequence of endometriosis, but, in fact, may be a cause or cofactor in the development of the disease.\(^{55}\)
- Impaired implantation, with evidence suggesting that endometriosis may be responsible for reduced expression of the \(\alpha\beta3\) cell adhesion molecule during the time of implantation.\(^ {54}\)

**Progesterone resistance.** The endometrial dysfunction in women with endometriosis may likely be attributed to a diminished response to progesterone. Changes in gene expression patterns noted in the eutopic endometrium of women with the disease reflect a defective progesterone action and exaggerated influence of estrogen,\(^{19}\) leading to hyperproliferative and anti-apoptotic changes. Thus, shed menstrual effluent may be more likely to establish, maintain, and recur. Progesterone receptor may also indirectly induce intracrine, autocrine, juxtacrine, or paracrine factors, including MIG-6.
By contrast, women with endometriosis have decreased levels of cellular immunity, including of NK cell functions and BAX-positive peritoneal macrophages, which may hold importance for the survival and proliferation of the aberrant, ectopic tissue. While controversy surrounds the relationship between endometriosis and infertility, growing data strongly indicate alterations in the eutopic endometrium of those women with the disease, which favor invasion and maintenance of the lesions.

**Risks of Adverse Pregnancy Outcome & Preterm Birth**

Previous uncontrolled studies demonstrated an increased incidence of spontaneous abortion in women with the disease. Subsequent data, however, have yielded contradictory results. More recently, endometriosis has been linked to a spectrum of pregnancy complications, originating either in the implants or in the uterus. Disorders of pregnancy associated with endometriosis include spontaneous hemoperitoneum in pregnancy (SHiP), bleeding, and preterm birth. A recent cohort study also provided further evidence that subfertile women who conceive spontaneously are at increased risk of pregnancy complications, including antepartum hemorrhage, cesarean delivery, pregnancy-induced hypertension, preeclampsia, and very preterm birth. The disease extends beyond the mere presence of ectopic endometrial glands and stroma, profoundly affecting the different cellular compartments in the uterus, including the junctional zone myometrium. While the majority of clinical focus on the consequences of uterine dysfunction associated with endometriosis has been on implantation defects and infertility, it is known that these ectopic lesions are a cause of specific pregnancy complications including SHiP, obstetric bleeding, and preterm birth. Infertile patients with endometriosis may require additional monitoring with increased attention when they become pregnant.

**Dyspareunia**

Dyspareunia, a prominent sequela of endometriosis, is characterized as sexual dysfunction manifesting as pain in the reproductive organs before, during, or soon after sexual intercourse. It is highly common in women with the disease; observational data have found that younger women ages 20 to 29 may suffer from dyspareunia twice as often as older women ages 50 to 60. Dyspareunia is a significant factor in the quality of life and relationships of women with endometriosis. For many, it may be severe and result in reduced sexual activity and enjoyment as well as reduced communication with the intimate partner.

Dyspareunia may be classified in accordance with location of pain: shallow, when pain is located in the vestibule of the vagina; deep, which is highly common in endometriosis, wherein pain presents in the vaginal vault; and general, when pain is present throughout the entire vagina. The dysfunction may manifest early, appearing at the beginning of intercourse and subsiding soon after, or late, presenting at the end or after intercourse and lasting as many as several hours postcoitus.

Primary dyspareunia is present from the first sexual intercourse; secondary dyspareunia arises later. More than half of women with endometriosis have suffered primary deep dyspareunia during their entire sex lives, severely impairing their quality of sexual life.

Often depicted as psychogenic in nature, the true etiopathogenesis may well be the result of organic, multidisciplinary causes. In women with endometriosis, dyspareunia is often among cardinal symptoms along with pelvic pain and dysmenorrhea; among disorders connected with dyspareunia, endometriosis brings about the greatest difficulty in diagnosis. Deep dyspareunia is a frequent component of endometriosis-associated pain, affecting 60% to 80% of patients undergoing surgery and between 50% and 90% of those using medical therapies. In women with the disease, deep dyspareunia is often most severe before menstruation; is usually positional, decreasing with changing coital positions; and has been associated with the presence of deep lesions of the uterosacral ligaments. Women with this type of lesion have a higher intensity of dyspareunia than those with lesions in other locations. The disorder may also be caused by traction of scarred inelastic uterosacral ligaments during intercourse or by pressure on nodules imbedded in fibrotic tissue. Similarly, immobilization of pelvic organs during sex may contribute to pathogenesis.
Contributing to the diagnostic difficulty, there are a number of other organic pelvic disorders that may cause or contribute to dyspareunia as well, including but not limited to interstitial cystitis, pelvic congestion syndrome, levator ani muscle myalgia, adenomyosis, leiomyoma, ovarian remnant syndrome, uterine retroflexion, irritable bowel syndrome, and mechanical trauma.

Dyspareunia should be routinely investigated during endometriosis consultations even in absence of patient complaint. Asking if there is pain present during or after intercourse may address emotional and physical concerns the patient herself has left unspoken.

Medical treatment, surgical intervention, and combination therapy may improve deep dyspareunia in women with the disease. GnRH-A may temporarily decrease the state of the disease thus reducing pain with intercourse, while continuous oral contraceptive therapy or the levonorgestrel-releasing intrauterine device may also reduce intensity of deep dyspareunia with limited side effects. Aromatase inhibitors, more recent to the realm of endometriosis treatment, were shown in combination with norethisterone acetate to though pain recurred after cessation of treatment. In particular, laparoscopic excision of deep endometriotic lesions has been demonstrated to significantly improve not only deep dyspareunia but also the quality of sex life.

The “Evil Triplets” of Chronic Pelvic Pain: Interstitial Cystitis, Levator Neuralgia, & Endometriosis

Interstitial cystitis, which has emerged as a more common disorder than previously recognized, is estimated to affect upwards of 2.5 million women in the United States. Characterized by urinary urgency and frequency, pelvic pain, and dyspareunia without presence of infection, interstitial cystitis is a progressive disorder that worsens if left untreated. Studies have long demonstrated the high prevalence of and association between interstitial cystitis and endometriosis, termed the “evil twins” of chronic pelvic pain syndrome.

Interstitial cystitis has long been ignored as a major contributor to chronic pelvic pain. Studies have shown through cystoscopy and hydrodistention findings that over 90% of chronic pelvic pain patients have interstitial cystitis; moreover, 80% of CPP patients have biopsy-confirmed endometriosis.

According to the International Pelvic Pain Society, in patients with pudendal neuralgia, connective tissue restrictions (subcutaneous panniculosis) are present. Upon examination, the tissue presents with tenderness and trophic changes, including abnormal skin texture and structure, reduced blood flow, tissue ischemia, thickening of subcutaneous tissue, and underlying muscle atrophy. Functionally, ischemic tissues are hypersensitive to touch and may cause pain upon compression (peritoneal pain elevated by sitting, reduced by standing). Increased sympathetic activity from painful stimuli, for example, the pudendal nerve, pelvic floor, or myofascial trigger points, may cause local vasoconstriction and the release of inflammatory agents with resultant tenderness and restriction. The visceral-cutaneous reflex causes tissue changes in locations distant to the involved organ or nerve; for example, inflamed bladder or pudendal nerve causing panniculosis in lower extremities.

The significant incidence of pudendal neuralgia (88.5%) in chronic pelvic pain studies suggests that disease entity should be added to the differential diagnosis for chronic pelvic pain syndrome, updating the classification as the “evil triplets.”

Cancer & Autoimmune Connection

Endometriosis, more than simply “killer cramps” as it is so often trivialized, may be related to a number of hereditary, environmental, epigenetic, and menstrual characteristics, some sharing certain common processes with cancer. Indeed, it is important to note that endometriosis is not cancer. The disease does, however, correspond to a variety of co-morbid conditions, ranging from autoimmune disease to food and environmental allergies to malignant concerns. Multiple prior studies have indicated an association between endometriosis and a number of autoimmune diseases, multiple chemical sensitivities, inflammatory bowel disease, food intolerances, allergies, and chronic fatigue.

Less clear is the potential link between endometriosis and certain cancers. Much debate continues to surround the cancer-endometriosis link, with researchers calling the “histogenesis of endometriosis and endometriosis-associated ovarian cancer [one of the] most mysterious aspects of pathology.” Current evidence is insufficient
to draw any definitive conclusions whether this association represents causality or the sharing of similar risk factors and/or antecedent mechanisms. Nonetheless, it has been well established that the disease is indeed associated with an increased risk for non-Hodgkin lymphoma and certain malignant tumors, notably ovarian, with 15% to 40% of endometrioid ovarian carcinoma cases being associated with endometriosis. Based on this frequent association, many reports implicate endometriosis as a precursor lesion to ovarian cancer.

The risk of ovarian cancer among those patients with endometriosis is higher than those without the disease by 30% to 40%. One analysis of benign ovarian endometrioid tumors found frequent coexistence of endometriosis and endometrioid neoplasms, supporting a genetic link between the two. In an estimated 60% of endometriosis-associated ovarian cancers, the cancer is adjacent to or directly arising from the endometriotic tissue, lending credence to the fact that malignant transformation can and does occur.

Animal studies suggest that common molecular genetic pathways, specifically K-RAS/MAPK and PTEN/PI13, are involved in the pathogenesis of both endometriosis and endometrioid ovarian carcinoma. Separate studies have identified upregulation of multiple genes within the RAS/RAF/MAPK and PI3K pathways in endometriosis patients, as compared to controls. Of note, PTEN and K-RAS mutations were found to play a role in the development of low-grade ovarian endometrioid carcinomas; synchronous mutations were also identified in uterine and ovarian endometrioid carcinomas associated specifically with endometriosis. Moreover, loss of the PTEN tumor suppressor gene has been implicated in progression from endometriosis to endometrioid ovarian cancer.

Endometriosis does present serious risk factors that can accelerate the development of ovarian cancer by 5.5 years. Still, epidemiological findings on the association between endometriosis and cancer remain elusive, with modifications to the standard treatment regimens for the disease unjustified at this time. Nonetheless, providers from all disciplines should be aware of this increased risk profile and strive for early detection.

### DIAGNOSIS

#### Barriers to Diagnosis

Due to lack of awareness, endometriosis is an often underappreciated diagnosis. Women and girls with the disease suffer a delay in diagnosis, on average, of 7 to 12 years and may present to five or more physicians before their pain is addressed. Moreover, the disease may be mistakenly dismissed as routine menstrual pain, particularly in younger women. It is not possible to triage women with chronic pelvic pain effectively on history alone; such women may benefit from referral to a specialist center for careful clinical assessment and investigation; the gold standard remaining laparoscopic pelvic examination and, where appropriate, peritoneal biopsy.

In particular, data reflect that general practitioners’ knowledge about endometriosis is limited, with possible direct consequences on the delay of diagnosis. In survey findings, 63% of general practitioners indicated they felt ill at ease in the diagnosis and follow-up of patients with endometriosis. One-half could not cite three main symptoms of the disease out of dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. Only 38% of general practitioners indicated that they perform a clinical gynecologic examination for suspected endometriosis, and 28% recommended MRI to confirm the diagnosis.

In that endometriosis requires a surgical diagnosis, use of biomarkers has recently been described as the highest priority in research due to the continued lack of noninvasive diagnostic means. Lack of nonsurgical markers contributes significantly to the delay in diagnosis and timely intervention, though proteomics and genomics are establishing the basis for future study related to biomarker development.

#### Clinical Diagnosis: Pelvic Examination & Pain Mapping

Though physical examination has poor sensitivity, specificity, and predictive value in the diagnosis of endometriosis, findings may suggest the benefit of imaging prior to surgery. Indeed, the poor negative predictive value of the pelvic exam was demonstrated in one study of 91 patients, in which 47% of patients with surgically confirmed endometriosis and chronic pelvic pain had normal bimanual examinations.
The most common areas involved with endometriosis include the cul-de-sac and uterosacral ligaments, usually very accessible on pelvic exam. When probed, the patient may exhibit pain. A thorough combination of history, physical examination, and laboratory and additional diagnostic studies as indicated can determine the cause of pelvic pain and rule out other nonendometriosis concerns. The physical exam should include pain mapping, a helpful procedure used to identify location of the pain with various diagnostic modalities. While some studies have proposed that uterosacral nodularity is better palpated during menses, no studies have conclusively demonstrated this observation; however, hallmark findings of nodular masses along thickened uterosacral ligaments, posterior uterus, or the posterior rectovaginal septum may be present. Obliteration of the cul-de-sac in conjunction with fixed uterine retroversion may also imply extensive disease.

Rupture of an ovarian endometrioma may present as an acute abdomen. Extensive involvement of the rectum and other areas of the gastrointestinal tract may cause adhesions and obstruction.

**Imaging Studies**

As effects of the disease may be devastating, radiologists should be familiar with the various imaging manifestations of endometriosis, particularly those that allow its differentiation from other pelvic lesions. Still, whilst diagnostic imaging may be helpful in the endometriosis diagnosis, it is not without drawbacks and limitations.

In terms of best imaging modality, MRI enables very small lesions to be detected and can distinguish the hemorrhagic signal of endometriotic lesions due to its very high spatial resolution. Indeed, in certain views, it is no longer acceptable to operate on severe endometriosis without exploring the uterus by MRI to exclude the presence of uterine adenomyosis. Moreover, it performs better than the CT scan in detecting the limits between muscles and abdominal subcutaneous tissues. MRI has been shown to accurately detect rectovaginal disease and obliteration in more than 90% of cases when ultrasonographic gel was inserted in the vagina and rectum.

Siegelman and Oliver offer expert pearls concerning use of MRI for detection and characterization of pelvic endometriosis: first, inclusion of T1-weighted fat-suppressed sequences for all imaging examinations, because such sequences facilitate the detection of small endometriomas and aid in their differentiation from mature cystic teratomas. It must also be remembered that benign endometriomas, like many pelvic malignancies, may exhibit restricted diffusion.

Although women with endometriosis are at risk for developing clear cell and endometrioid epithelial ovarian cancers, imaging findings such as enhancing mural nodules should be confirmed before a diagnosis of malignancy is offered. The presence of a dilated fallopian tube, particularly one containing hemorrhagic contents, is often associated with pelvic endometriosis. Deeply infiltrating endometriosis can involve the pelvic ligaments, anterior rectosigmoid colon, bladder, uterus, and cul-de-sac, as well as surgical scars; the lesions often have poorly defined margins and T2 signal hypointensity as a result of fibrosis. The presence of subcentimeter foci with T2 hyperintensity representing ectopic endometrial glands within these infiltrating fibrotic masses may help establish the diagnosis.

MR imaging has high specificity for identifying endometriomas, which are characterized by high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. Correlation of the radiologic imaging features of endometriotic lesions with their laparoscopic appearances may help improve individual proficiency in the radiologic diagnosis of endometriosis.

Transvaginal or endorectal ultrasonography may also reveal ultrasonographic features of endometriomas, varying from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of vascularity. Computed tomography scanning may reveal endometriomas appearing as cystic masses; however, appearances are nonspecific and imaging modalities should not be relied upon for diagnosis.

As technologies improve, clinical symptomatology combined with characteristic imaging features in appropriate patient populations may facilitate minimally invasive and noninvasive diagnoses. Current areas of research include predictive biomarkers for early diagnosis utilizing a metabolomics approach, specific plasma biomarkers obtained during menses, dynamic contrast-enhanced imaging studies, identification and validation of novel serum markers for early diagnosis, and more.
Surgical Diagnosis & Staging

Laparoscopic intervention remains the standard for diagnosis. Histologic confirmation of both endometrial glands and stroma in biopsy specimens is typically required to make the diagnosis, though the finding of fibrosis in combination with hemosiderin-laden macrophages may be sufficient for a presumptive diagnosis.82

Due to the subtle appearance of some implants, accuracy of diagnosis depends on the ability of the surgeon to adequately identify the disease. A thorough and systematic examination of the pelvis and abdomen is essential in all patients to identify and document all lesions, with care taken not to overlook peritoneal pockets and ovarian fossae.82

The American Society for Reproductive Medicine’s current classification of endometriosis in stages 1 to 4 is the most widely used and accepted staging system. The classification system, using point scores based on size and number of lesions and bilaterality, as well as associated adhesion formation noted at the time of surgery, is a fairly accurate method of recording surgical findings. However, the current staging system does not correspond well to pain and dyspareunia, and fecundity rates cannot be predicted accurately.10

As a result, attempts to develop a staging system that meets the need to establish a common language in endometriosis surgical findings, enable specificity of diagnosis, standardize comparisons, and facilitate research have been undertaken. Adamson and Pasta83 have subsequently developed a validated, clinically useful tool for surgically confirmed patients with endometriosis attempting non-IVF conception (Figure 3). Further efforts are required to develop similar staging systems that will help predict outcomes for patients with endometriosis and pelvic pain for both surgical and nonsurgical treatment.

TREATMENTS

Surgical Intervention

Indications for the surgical management of endometriosis include:

- Diagnosis of unresolved pelvic pain
- Severe, incapacitating pain with significant functional impairment and reduced quality of life
- Advanced disease with anatomic impairment (distortion of pelvic organs, endometriomas, bowel or bladder dysfunction)
- Failure of expectant/medical management
- Endometriosis-related emergencies, that is, rupture or torsion of endometrioma, bowel obstruction, or obstructive uropathy

The goals of conservative surgery include removal of disease, lysis of adhesions, symptom reduction and relief, reduced risk of recurrence, and restoration of organs to normal anatomic and physiologic condition.84 This may be achieved through a variety of instruments and techniques. If endometriosis is histologically confirmed and is of the deeply infiltrating kind, the recommended management is to refer the patient to an endometriosis center.85

Laparoscopy

When endometriosis is diagnosed at the time of surgery, surgical destruction is recommended,86 with the objective to remove endometriotic lesions, preserve uterus and ovarian tissue, and restore normal anatomy. This may be achieved through standard or robotic-assisted laparoscopy. Rarely is laparotomy indicated.

Laparoscopy remains a generally safe procedure, well-tolerated and associated with reduced hospital stays, complications, and postoperative morbidity. Complications are becoming ever-increasingly less common; approximately 3.2 per 1000 cases.87 However, traumatic complications may uncommonly occur (eg, bowel, bladder, or gastric perforation; large vessel or ureteral injury).88 When complications do arise, they are primarily related to three categories: complications of access, physiologic complications of the pneumoperitoneum, and complications of operative procedure.89

A multidisciplinary team approach (eg, gynecologic endoscopist, colorectal surgeon, urologist) can reduce risk and facilitate effective treatment.19 Likewise, advanced surgical skills and anatomical knowledge are required for deep resection and should be performed primarily in tertiary referral centers. Careful preoperative planning, informed consent, and meticulous adherence to “best practice” technique is requisite to reduce morbidity and ensure effective management of potential complications.90
### Figure 3. Staging: American Society for Reproductive Medicine Revised Classification of Endometriosis

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<tr>
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<td>Dense Adhesions</td>
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*Point assignment changed to 16
**Point assignment doubled

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LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

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<th>Description</th>
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<tr>
<td>Fimbria</td>
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<td></td>
</tr>
<tr>
<td>Ovary</td>
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To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

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<td>If there is no history of a prior pregnancy</td>
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EFI = Total Historical Factors + TOTAL SURGICAL FACTORS:

ESTIMATED PERCENT PREGNANT BY EFI SCORE

Although excisional biopsy and resection offers a higher success rate in treating the disease, surgical excision also requires a higher level of surgical skill. As a result, many patients receive incomplete treatment, which in turn may lead to persistent symptoms and recurrent disease. It should be noted that many women who have undergone repeated surgeries and had a hysterectomy still suffer. The need to improve surgical approach and/or engage in timely referrals is unquestionable.

Surgery to debulk and excise endometriosis may be “more difficult than for cancer.” Complete removal of implants may be difficult due to variation in appearance and visibility. True surgical resection and treatment poses formidable challenges, even the hands of experienced clinicians. In particular, deep disease is often difficult to treat due to close proximity of and common infiltration in and around bowel, ureters, and uterine artery. Potential adenomyosis should also be included in the preoperative workup, as it can influence postoperative improvement patterns of pain and symptoms associated with endometriosis.

Lesions may present as “powder burn” implants, foci of inactive disease containing glands embedded in hemosiderin deposits and stroma; nonpigmented lesions appearing as clear vesicles; and as pink, white, red, brown, yellow, and blue implants. Microscopic disease may be identified in otherwise normal-appearing peritoneum by light and electron microscopy. “Blood painting” or use of staining agents such as indigo carmine or methylene blue may also improve detection. Cellular activity is believed to be greater in superficial and deep implants versus intermediate lesions.

Upon visual diagnosis, laparoscopy is usually extended to an operative procedure, beginning with adhesiolysis between bowels and pelvic organs in order to expose the pelvic cavity. Ovaries may then be dissected from the cul-de-sac or pelvic sidewall, tubes freed from adhesions, and implants resected or otherwise destroyed. Bowel and genitourinary lesions should be removed. If appropriate, presacral neurectomy or laparoscopic uterosacral nerve ablation may also be performed to treat central pelvic pain. Removal of endometriomas on the ovaries may also be performed. Peritoneal implants should be destroyed using the most effective, least traumatic manner to minimize and reduce risk of postoperative adhesion formation.

Complete excision of endometriosis, including vaginal resection, offers a significant improvement in sexual functioning, quality of life, and pelvic pain, including in those symptomatic patients with deeply infiltrating endometriotic nodules in the posterior fornix of the vagina. As well, the technique offers good results in terms of reduced bladder morbidity and bowel symptoms. However, in that this kind of surgery requires advanced skills and anatomical knowledge, again, it should be performed only in selected reference centers.

Randomized controlled trials also demonstrate that excision is associated with a higher pregnancy rate and lower rate of recurrence, though it may cause injury to the ovarian reserve. Improvements to this aspect may be represented by a combined excisional-vaporization technique or by replacing coagulation with surgical ovarian suture.

In general, laparoscopic excision significantly improves general health and psycho-emotional status at 6 months from surgery without differences between patients submitted to intestinal segmental resection or intestinal nodule shaving. Pain, sexual function, and quality of life were demonstrated to improve significantly in at least one study, and these symptoms were associated with a good fertility rate and a low complication and recurrence rate after a CO₂ laser laparoscopic radical excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis.

**Hysterectomy/Oophorectomy/Salpingo-oophorectomy**

Nearly 600,000 hysterectomies are performed annually in the United States, with endometriosis as the second leading cause following fibroids. Though not curative, hysterectomy with or without bilateral oophorectomy and adhesiolysis may be appropriate for those patients in whom the disease is uncontrolled through surgery or medical suppression. However, probability of pain persistence after hysterectomy is 15% and risk of pain worsening 3% to 5%, with a six-time higher risk of further surgery in patients with ovarian preservation as compared to ovarian removal.

Excision of endometriosis with uterine preservation is almost always possible. However, hysterectomy may be considered for those patients in whom severe pelvic pain affects the quality of their life and who do not
desire fertility preservation. The goal at hysterectomy is the same as in any endometriosis surgery, that is, to remove all disease.

Common approaches include:

- **Removal of uterus and cervix**: removing only the uterus with hysterectomy has the same risk for recurrence as conservative surgery. Subtotal hysterectomy involves removing the uterus but keeping the cervix intact.

- **Bilateral oophorectomy or bilateral salpingo-oophorectomy**: for endometriosis treatment, removal of ovaries is often performed in combination with hysterectomy.²

Hysterectomy may be performed abdominally, vaginally, or through laparoscopic-assisted vaginal hysterectomy. Recovery times for vaginal and LA VH are shorter than for abdominal hysterectomy. However, hospital stays may be longer with LA VH than standard vaginal hysterectomy.²

The surgeon must first free the ovaries, ureters, and rectum from the posterior vagina to the rectovaginal septum. Deeply fibrotic nodular disease involving the cul-de-sac requires excision of the fibrotic tissue from the uterosacral ligaments, posterior cervix, posterior vagina, and rectum. Hysterectomy with excision usually results in relief of the patient’s pain, and oophorectomy is not usually necessary. The most severely affected ovary may be removed, however, especially if on the left, as this ovary frequently becomes adherent to the bowel. Bilateral oophorectomy is rarely indicated in women under age 40 undergoing hysterectomy for endometriosis.²

Hysterectomy should not be done for extensive endometriosis with extensive cul-de-sac involvement, unless the surgeon has the skill and time to resect the deep fibrotic endometriosis from the posterior vagina, uterosacral ligaments, and anterior rectum. In these patients, excision of the uterus using an infravesical approach leaves the deep fibrotic endometriosis behind to cause future problems. Furthermore, it may be more difficult to remove deep fibrotic endometriosis when there is no uterus between the anterior rectum and the bladder. After hysterectomy, the endometriosis left in the anterior rectum and vaginal cuff frequently becomes densely adherent to, or invades into, the bladder and one or both ureters.²

As with any procedure, patients should be counseled extensively on all the risks, benefits, and long-term outcomes of the hysterectomy option.

### Nonsurgical Therapies

#### Medical Therapies

Endometriosis relapse is a matter of debate, since superficial surgical and medical treatments often fail. The high rate of recurrence suggests that a combination of surgical and medical management might provide maximized outcomes, and any of the agents can be used before, after, or both before and after either conservative or radical surgery. There is no evidence that medical treatment of endometriosis improves fertility; moreover, fertility is essentially eliminated during treatment because all medical treatments inhibit ovulation.⁵ Selection of medical therapy for the patient depends on therapeutic effectiveness, tolerability, drug cost, physician experience, and expected patient compliance.

The rationale for medical therapy is to induce amenorrhea and create a hypoestrogenic environment that will theoretically inhibit endometrial growths and promote regression of disease. Symptoms recur once therapy is discontinued.

The primary goal of medical suppression is to impede the growth and activity of endometriotic lesions. Gonadotropin-releasing hormone agonists (GnRH), oral contraceptives, Danazol, aromatase inhibitors, and progestins are the mainstays in endometriosis treatment, all with the potential to reduce pain and estrogen production.⁷ All have similar clinical efficacy in terms of reduction in pain-related symptoms and duration of relief.⁷

Endometriotic implants express aromatase and consequently can generate their own estrogen, which can maintain their own viability and growth. In contrast to medical suppressives that target ovarian estrogen production, aromatase inhibitors inhibit local estrogen production in endometriotic implants themselves as well as in the ovary, brain, and adipose tissue.⁹ A systematic review showed that aromatase inhibitors also significantly reduced endometriosis-associated pain when compared with GnRH
Aromatase inhibitors are administered in varying doses, including 2.5 mg daily for letrozole and 1 mg daily for Anastrazole\(^6\). Aromatase inhibitors given to reproductive-age women will cause increased follicle-stimulating hormone levels and subsequent superovulation. Other concerns about prolonged therapy are associated bone loss and multifollicular ovarian cyst development due to the initial FSH rise. For this reason, aromatase inhibitors are combined with an FSH suppression agent, such as COCs, progestins, or GnRH agonists.\(^{103}\) They are well tolerated by patients and may represent a promising therapy for endometriosis.\(^{107}\)

Oral contraceptive pills have been used empirically to alleviate dysmenorrhea for many years. They are generally well tolerated and confer fewer metabolic and hormonal side effects than Danazol or GnRH therapy. Open clinical trials have shown that oral contraceptives relieve dysmenorrhea, through ovarian suppression and continuous progestin administration. A study by Guzick et al\(^{108}\) examined a head-to-head comparison of Lupron and continuous oral contraceptives for the treatment of endometriotic pelvic pain; both were found to be equally effective. Treatment with GnRH analogues is limited to only 6 to 12 months because these agents induce a hypoestrogenic state that substantially decreases bone mineral density, whereas oral contraceptives may be a simple and effective way to manage the disease through avoidance or delay of menses for upwards of 2 years.\(^{109}\)

Progestins inhibit the growth of endometriotic lesions by inducing decidualization followed by atrophy of uterine-type tissue. When compared to GnRH therapy, both treatment modalities show comparable effectiveness in the treatment of endometriosis-related chronic pelvic pain.\(^{110}\)

Medroxyprogesterone acetate has proven efficacy in pain suppression in both the oral and injectable depot preparations. Oral doses of 10 to 20 mg/day can be administered continuously. The time to resumption of ovulation is longer and variable with depot preparations. Adverse effects include weight gain, fluid retention, depression, and breakthrough bleeding. Megestrol acetate has been used in doses of 40 mg with similarly good results. The levonorgestrel intrauterine system (Mirena\(^8\)) has been shown to reduce endometriosis-associated pain. When inserted at the time of laparoscopic surgery, it has been found to reduce the recurrence of dysmenorrhea by 35\%.\(^{10}\)

The Mirena intrauterine device may also be considered an alternative to hysterectomy in patients with adenomyosis. Anecdotal use in the adenomyosis community has shown promise among those suffering from related dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and pelvic indurations. In one study, LNG-IUS demonstrated significant and comparable improvement in hemoglobin levels to hysterectomy in treating adenomyosis-associated menorrhagia during the first year. Although both treatments led to improvements in health-related quality of life, LNG-IUS had superior effects on psychological and social life, thus making it a promising alternative therapy to hysterectomy.\(^{111}\)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been studied extensively in randomized controlled trials for the treatment of primary dysmenorrhea and are of proven efficacy.\(^{112}\) Although studies that focus solely on use of NSAIDs for endometriosis are lacking, these agents are widely used because of their acceptable side effects, reasonable cost, and ready availability.\(^{104}\)

Danazol acts by inhibiting the midcycle follicle-stimulating hormone and luteinizing hormone surges and preventing steroidogenesis in the corpus luteum. Though dated, Danazol has been shown to be as effective as any of the newer agents, but with a much higher incidence of adverse effects including androgenic manifestations such as oily skin, acne, weight gain, deepening of the voice, and hirsutism. Hypoestrogenic features due to Danazol include emotional lability, hot flashes, vaginal dryness, and reversible breast atrophy. The recommended dose is 600 to 800 mg/day though smaller doses have been used with success.\(^{104}\)

GnRH agonists work by producing a hypogonadotropic-hypogonadic state by downregulation of the pituitary gland. They have emerged as a first-line medical therapy for endometriosis-associated pain in moderate to severe disease in recent decades. Therapy may be administered via intramuscular, subcutaneous, or intranasal routes. Efficacy is limited to pain suppression, however, with no improvement on fertility rates.\(^{10}\) Similar efficacy has been observed concerning the various medical therapies used for endometriosis.\(^{113}\)
With “add-back” therapy, GnRH agonists have a better side effect profile versus other hormonal therapies, and many series have demonstrated that add-back therapy does not interfere with the GnRH agonist’s ability to relieve pelvic pain. Disadvantages of long-term use include the high cost of medication, bone mineral density loss, and hypoestrogenic side effects. It has also been recently suggested that combining progressive muscular relaxation with GnRH-A therapy may improve anxiety, depression, and health-related quality of life in women with the disease.

Preoperative GnRH therapy may reduce pelvic vascularity and size of endometriotic lesions, reducing intraoperative blood loss and decreasing the amount of surgical resection needed. Postoperative therapy has been advocated as a means of eradicating residual endometriotic implants in patients with extensive disease in whom resection of all implants is impossible or otherwise inadvisable.

Alternative Therapies
The role of alternative therapies has not been validated; hence an in-depth discussion is outside the scope of this presentation. Yet, anecdotal experience and early evidence suggest that herbal medicine, physical therapy, certain diet and nutrition measures, acupuncture, hypnotherapy, use of specific supplements, Traditional Chinese Medicine, and other complementary approaches may indeed result in some reduction of pain and contribute to the treatment of endometriosis. In general, however, weak evidence exists regarding efficacy of complementary treatments on impact of health-related quality of life in women with the disease.

Still, promising research continues to emerge in this area, including one recent study that reviewed the potential use of resveratrol and epigallocatechin-3-gallate (EGCG) as natural treatments. In this animal model, both treatments were found to significantly reduce the mean number and volume of established lesions, consistently diminish cell proliferation, and increase apoptosis within the lesions, as well as induce reduction in human endometrial epithelial cell proliferation. Such present findings are promising and will assist in the future development of novel alternative treatments for the disease.

Likewise, it is expected that the increasing number of related studies will lead to development of additional therapeutic agents for treatment including growth factor inhibitors, angiogenesis inhibitors, cyclooxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, and other compounds that hold great promise for the future treatment of endometriosis.

**CONCLUSION**

Despite receiving very little mention in historical compendiums of disease, endometriosis has impacted lives of women for centuries. It is without question the disease remains, even now, a chronic, costly illness requiring long-term, multidisciplinary treatments. Endometriosis, a complex disorder that may go undiagnosed for years, with no absolute cure and a high recurrence rate, continues to be a significant reproductive health concern with highly negative and far-reaching effects.

The profound economic impact and significantly impaired quality of life of the affected contribute to the urgent need for continued research and improvement in diagnostic and treatment modalities. Focus on better clarifying pathogenesis and pain mechanisms as well as links to certain morbidities, for example, malignancies and autoimmune disease, is necessary.

Though prevention remains elusive, increasingly sophisticated research efforts will lead to more timely intervention and appropriate, multifactorial treatments to restore quality of life, preserve or improve fertility, and lead to long-term effective management of this enigmatic disease.
REFERENCES


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