



CODEN [USA]: IAJPB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4394908>Available online at: <http://www.iajps.com>

Research Article

**ENDOMETRIOSIS: ADVANCES AND CONTROVERSIES IN
CLASSIFICATION, PATHOGENESIS, DIAGNOSIS, AND
TREATMENT.**¹Dr Mamuna Ayub,²Dr Saira Sundus,³Dr Humaira Ilyas¹MBBS, Nawaz Sharif Medical College, Gujrat.^{2,3}MBBS, Services Institute of Medical Sciences, Lahore.**Article Received:** October 2020 **Accepted:** November 2020 **Published:** December 2020**Abstract:**

Endometriosis is a perplex disorder with unascertained root and complex pathological processes. Generally, it has association with pelvic pain and sub fertility. The exact prevalence rate in common population is not truly while on the base of symptoms its prevalence rate is 10% for all and 30%-40% for symptomatic premenopausal women¹ it is described by the many theories such as ectopic implantation of menstrual shreds flow to the abdominal cavity through the uterine tubes.

Laparoscopy is considered most preferable standard of diagnosis of endometriosis proved by the histological performances of surgical biopsies. Further, this article will illustrate the pathogenesis, treatment, diagnosis of endometriosis by reviewing the previous history.

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Please cite this article in press Mamuna Ayub et al., Endometriosis: Advances And Controversies In Classification, Pathogenesis, Diagnosis, And Treatment., Indo Am. J. P. Sci, 2020; 07(12).

INTRODUCTION:

Endometriosis is a perplex disorder with unascertained root and complex pathological processes. Generally, it has association with pelvic pain and sub fertility. The exact prevalence rate in common population is not truly while on the base of symptoms its prevalence rate is 10% for all and 30%-40% for symptomatic premenopausal women¹ it is described by the many theories such as ectopic implantation of menstrual shreds flow to the abdominal cavity through the uterine tubes. Another theory stated that in endometriosis, embryonic cells of paramesonephric ducts are at abnormal position.³ Endometriosis is also illustrated as hormone dependent inherited disorder. A meta-analysis reported the association of five specific loci are involved in sex steroid pathway with the increasing risk to develop endometriosis. However, deficit of authentic marker for disease diagnosis while ultra sound is more reliable with 82% to 89% sensitivity and history of ultra sounds for the deep infiltrating endometriosis, rectovaginal septum, vagina and bladder manifest the overall responsiveness is 53 to 93%.⁴ Laparoscopy is considered most preferable standard of diagnosis of endometriosis proved by the histological performances of surgical biopsies. Further, this article will illustrate the pathogenesis, treatment, diagnosis of endometriosis by reviewing the previous history.

Pathogenesis

In the influence of emerging research on endometriosis it is stated that hormonal and immune factors erect a pro-inflammatory micro environment assist the perseverance of endometriosis. Its most salient symptoms are pain and infertility. New drugs has been unlocked the investigation pathway to further proceed the pathogenesis of endometriosis.

A theory coelomic metaplasia has indispensable part to elucidate the pathology of endometriosis, the modification in normal peritoneal to abnormal endometrial tissue because of disruption of endocrine chemical which plays an important part to bring these changes.³ One more theory addressed this condition and reported that endocrine influence the formation of endometriotic lesions during the migration of residual cell from the embryonic paramesonephric duct.³

Inflammatory disease

Endometriosis is also considered a pelvic inflammatory state with growing concentration of macrophages (activated) of peritoneal fluid and enhanced the cytokine inflammatory response. Escalate the formation of interleukin-6, tumor necrosis, and fluctuate the macrophage migration

inhibitory factor. The endometrial epithelial progenitor tissues have a potential role in pathogenesis of endometriosis.⁵

Endometriomas

The formation of endometriomas has been described by various theories. As formation of pseudocysts by assembling the menstrual debris which involve active implants at the area of inversion. Few authors proposed that endometriomas might be originated through the ovarian follicles, yet its obvious description has not been given.⁶

Deep infiltrating endometriosis

In deep infiltrating endometriosis a distinct phenotype of similar disease was found, divide into endometriomas and peritoneal lesions. Inclusive position are anterior (bladder) and posterior (vagina, uterosacral ligaments, rectum, and ureters) component of disorder. Some properties of endometriosis include the appearance of matrix metalloproteinases may escalate in deep filtrating endometriosis.⁷

Diagnosis

Anamnesis

Listen to the patient. Carry on a detailed anamnesis in a very slow fashion. This simple action gives us the best approach to the disease. She has so much to tell, to show with her face and expression. In most cases, the disease can be understood just by listening. The omnipresent symptom is pain: cyclic pelvic pain, dysmenorrhea, periovalatory pain, chronic non-cyclic pelvic pain, dyspareunia (positional or permanent), dyschezia, and dysuria. There are many other pain presentations that nobody even thinks of until confronted with an endometriosis patient who, incidentally, has exactly "that type of pain". A young girl we operated last year referred to right shoulder pain at menstruation. At laparoscopy, a large diaphragmatic series of blue and red lesions was excised. She was relieved after surgery. A similar case was reported recently by Singh *et al.* 27. This publication elucidates the use of MRI for the clinical diagnosis of endometriosis, which will be shown extensively in this review. Involuntary infertility, even when not the cause for consultation, should also be regarded as one of the frequent symptoms of endometriosis. Less frequently, cyclic nasal bleeding, umbilical bleeding, cyclic hemoptysis, cyclic constipation, and urinary urgency are reported by patients with endometriosis.

Biomarkers

As of today, of the many biomarkers for endometriosis proposed in peripheral blood and endometrium, not

one has been validated for endometriosis¹⁸. This could be due to patient selection, sample collection, or analytical procedures. There is a current need to develop a non-invasive test for patients with symptomatic endometriosis. We still lack a reliable marker for the disease. Ca 125, considered a marker for endometriosis, is helpful only in postoperative follow-up. It usually decreases after surgery and rises when the disease recurs or progresses. Clinical presentations vary. Signs, symptoms, and markers do not correlate well with the extent of disease, as stated by Taylor *et al.* ¹⁹. In 58 consecutive cases of endometriosis, Hirsch *et al.* ²⁸ found increased values of Ca 125. This group concluded that Ca 125 of at least 30 units per milliliter is “highly predictive of endometriosis” in symptomatic patients¹⁹. The authors propose it as mandatory but consider it “unable to rule out endometriosis”¹⁹.

Genetics

For many years, there has been a search for genetic testing that could identify a population prone to develop endometriosis. A simple literature search identifies more than 3000 publications from 2018 linking genetics to endometriosis. Recently, an Australian group presented a summary of 17,045 cases included in a meta-analysis³⁰. In them, 14 genomic regions were identified, supported by results from multiple studies. The group found that “no independent associations were identified from direct genotyping of common and low-frequency protein-coding variants”³⁰. According to them, the most common genetic factors related to endometriosis risk are located in regulatory DNA sequences. This, they say, alters the regulation of gene transcription. They conclude that the target genes are present in three chromosome regions: “LINC00339 and CDC42 on chromosome 1, CDKN2A-AS1 on chromosome 9, and VEZT on chromosome 12”³⁰. Using single-nucleotide polymorphism (SNP) array technology, a 2017 publication³¹ describes genomic aberrations linked to the development of endometriosis. These investigators performed SNP array genotyping of pooled DNA samples from 100 patients with endometriosis and 50 controls. The authors detected 49 copy number variation (CNV) loci that were present in patients with endometriosis but that were absent in the control group. Six novel CNV loci in the subtelomeric regions representing gains and losses were identified

Imaging

Ultrasound.

In 1979, Walsh *et al.* presented their findings in 25 patients with surgically confirmed endometriosis or

adenomyosis or both³². Sonolucent zones within the uterus representing blood lakes described adenomyosis. Other cases had cystic images, five of which were of mixed characteristics. At that time, “ultrasound alone could not differentiate endometriosis from diseases such as tubo-ovarian abscess, ruptured ectopic pregnancy, other ovarian cysts or tumors”³². The authors stated that the clinical history contributed to the non-surgical diagnosis of endometriosis. Today, some authors state that TVS “allows a better accurate diagnosis of rectosigmoid endometriosis than MRI”³³. For this group, it is less reliable in the case of uterine, Douglas pouch, and uterosacral ligament disease. Nevertheless, they propose it as a first-line imaging technique because of its low cost and feasibility

Magnetic resonance imaging

In 1999, a pioneer article described the use of MRI for the preoperative diagnosis of endometriosis⁴⁰. The authors described, in 20 patients, MRI findings of DIE at the uterosacral ligaments, the pouch of Douglas, the rectum, and the bladder that were histologically proven at surgery. Diagnosis was accurate except when contrast was not used (two of three patients with rectal endometriosis).

A decade before, Arrivé *et al.* ⁴¹ published the first report of MRI use for the clinical diagnosis of endometriosis. Using only 0.35 Tesla, they prospectively studied 30 consecutive women with symptomatic disease. In 25 cases, endometriosis was confirmed by surgery. A sensitivity of 64% and a specificity of 60%, with an accuracy of 63%, were shown. Most endometriomas were correctly identified. Only 14 of 29 cases of adhesions and 6 of 45 cases of peritoneal implants were diagnosed by MRI. “MRI findings did not correlate with the surgically determined severity of the disease”⁴¹. In 1989, the authors concluded that MRI could not be used as the first study to detect endometriosis. For them, laparoscopy was the procedure of choice.

Classification

Management

Hormones.

The guideline recommends prescribing hormonal treatment—combined OCs, progestagens, anti-progestogens, or GnRH agonists—“as one of the options, as it reduces endometriosis-associated pain”⁶⁰. It also “recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain”⁶⁰. Combined estrogen and progestin OCs are

recommended, as they reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain, in a continuous protocol. Also, vaginal contraceptive rings or transdermal estrogen/progestin patches are suggested.

Anti-hormones.

According to the guideline, evidence regarding dosage or duration of GnRH agonists is limited. “Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment” since this will not reduce the effect of the pain treatment⁶⁰. The guidelines recommend giving “careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density”⁶⁰.

Aromatase inhibitors.

These options are considered for those who have pain from rectovaginal endometriosis, refractory to other medical or surgical treatment. They should be prescribed in combination with OC pills, progestagens, or GnRH analogs. Analgesics. The guideline asks a simple question⁶⁰: “Are analgesics effective for symptomatic relief of pain associated with endometriosis?” Then it tells us that evidence on the use of NSAIDs for endometriosis is scarce. The authors of the guidelines present a referenced publication from 1985 and one study on the cyclooxygenase-2 (COX-2) inhibitor rofecoxib (withdrawn from the market in many countries because of severe side effects). For the guideline, NSAIDs have a “favorable effect on primary dysmenorrhea and are widely used as a first-line treatment of endometriosis-associated pain”⁶⁰. However, it recommends the use of NSAIDs or other analgesics to reduce endometriosis associated pain. Clinicians should discuss the associated side effects with the patient.

Elagolix

The elagolix phase III clinical trial⁶⁶ introduced a new and promising treatment for endometriosis. Oral anti-gonadotrophic agents have a sound future. They arrest the progression of the disease and dramatically reduce pain. Relief is fast and significant. New clinical trials for similar drugs are ongoing. In the publication of reference, elagolix compared with placebo showed a significant decrease from baseline in the mean pain score. This significant effect was seen at months 3 and 6 of treatment. One adverse side effect, bone density damage⁶⁷, was dose dependent. Decrease in lumbar spine bone mineral density (BMD) following 6 months

of treatment with elagolix compared with placebo was significantly different for each elagolix dose. “The proportion of participants with lumbar spine BMD decrease from baseline greater than 3% was also dose-dependent”, as was the case of decreases in BMD of the total hip and femoral neck⁶⁸.

Proellex

Selective progesterone receptor modulators are a class of drugs with progesterone antagonist activity that may confer therapeutic benefit for reproductive disorders in premenopausal women. Endometrial structure, which is dynamically controlled by circulating sex hormones, is likely to be perturbed by progesterone receptor modulators through their progesterone antagonist properties. A selective progesterone receptor modulator, CDB-4124, telapristone acetate (Proellex), was clinically studied recently⁷¹. Its performance as a treatment for endometriosis was proven. It is a drug with progesterone antagonist activity. A major concern was the alteration of the eutopic endometrium. The structure

Lifestyle: diet and exercise

No interventions on lifestyle, exercise, or diet have demonstrated with an acceptable evidence grade that they can be of help to improve QOL. On the other hand, most patients believe in them and find them useful. Cognitive therapies and yoga are favorites. Only small retrospective observational studies suggest that exercise “might be effective in reducing dysmenorrhea”¹¹. Weight reduction or specific dietary interventions have no clearly demonstrated effects except for the fact that diet after surgery, with vitamins, minerals, salts, and lactic ferments, appears to be effective in pain reduction in comparison with hormonal treatment. There is a consensus that gluten-free diets improve symptoms in some women who have endometriosis and gastrointestinal complaints.

Fertility

The opportunity, quality, and extension of the first surgery are determinant when fertility is the issue. Milani and Cesana *et al.*⁷⁵ recently evaluated the reproductive prognosis during the first three years after conservative surgery. In a retrospective study, they surveyed 140 patients operated for endometriosis (with histological confirmation). With no other infertility factors, the pregnancy rate in a group of previously infertile patients was 53%: 48 spontaneous pregnancies and 10 with ARTs. Those patients who had not sought pregnancy before surgery were also followed and 71% of them became pregnant. Only three in a group of 31 required ART

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