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Endometriosis: Epidemiology, Diagnosis and Clinical Management

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Abstract

Purpose of review—Endometriosis is a disease of adolescents and reproductive-aged women characterized by the presence of endometrial tissue outside the uterine cavity and commonly associated with chronic pelvic pain and infertility. Here we review the epidemiology of endometriosis as well as potential biomarkers for detection and with the goal of highlighting risk factors that could be used in combination with biomarkers to identify and treat women with endometriosis earlier..

Recent findings—Early age at menarche, shorter menstrual length, and taller height are associated with a higher risk of endometriosis while parity, higher body mass index (BMI) and smoking are associated with decreased risk. Endometriosis often presents as infertility or continued pelvic pain despite treatment with analgesics and cyclic oral contraceptive pills.

Summary—Despite a range of symptoms, diagnosis of endometriosis is often delayed due to lack of non-invasive, definitive and consistent biomarkers for diagnosis of endometriosis. Hormone therapy and analgesics are used for treatment of symptomatic endometriosis. However, the efficacy of these treatments are limited as endometriosis often recurs. In this review, we describe potential diagnostic biomarkers and risk factors that may be used as early non-invasive *in vitro* tools for identification of endometriosis to minimize diagnostic delay and improve reproductive health of patients.

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Conflict of Interest

Parveen Parasar, Pinar Ozcan, and Kathryn L. Terry declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Endometriosis; Pain; Infertility; Biomarkers; Management

Introduction

Endometriosis is defined as the presence of endometrial glands and stroma like lesions outside of the uterus [1]. The lesions can be peritoneal lesions, superficial implants or cysts on the ovary, or deep infiltrating disease [2]. While there is no definitive etiology of endometriosis, there are several hypotheses regarding how endometriotic lesions develop. One possible mechanism is retrograde menstruation, a feature of the menstrual cycle in women and non-human primates, which is an outflow of the endometrial lining through the patent fallopian tubes into the pelvic space. This retrograde flow, along with potential hematogenous or lymphatic circulation, may result in the seeding of endometrial tissue in ectopic sites. However, retrograde menstruation is common (perhaps universal among menstruating women) while endometriosis is much less common. Therefore, other factors, such as hormonal, inflammatory, or immunologic milieu may determine whether lesions deposited in the pelvic cavity implant and persist [3–6]. Alternatively, endometriosis lesions may arise from Müllerian remnants that did not properly differentiate or migrate during fetal development or from circulating blood cells that transdifferentiate into endometriosis [7–9]. Similarly, the characteristics of the local environment would influence the maintenance of these endometriotic lesions. When considering these etiologic hypotheses, it is important to recognize that endometriotic lesions are antigenically similar to eutopic endometrium but not necessarily endometrium.

Endometriosis affects 10–15% of all women of reproductive age [1] and 70% of women with chronic pelvic pain [10]. Unfortunately, for many of these women there is often a delay in diagnosis of endometriosis resulting in unnecessary suffering and reduced quality of life. In patients aged 18–45 years, the average delay is 6.7 years [11]. As most women with endometriosis report the onset of symptoms during adolescence, early referral, diagnosis, identification of disease and treatment may mitigate pain, prevent disease progression and thus preserve fertility [12–14]. Barriers to early diagnosis include the high cost of diagnosis and treatment in adolescent patients and presentation of confounding symptoms such as cyclic and acyclic pain. Thus, a non-invasive tool to diagnose endometriosis could facilitate earlier diagnosis and intervention that could ultimately improve quality of life and preserve fertility.

The immunologic, genetic, and serum markers proposed to date for endometriosis diagnosis are not sufficiently sensitive and specific to justify their use as a screening test. In this review, we will discuss the epidemiology of endometriosis and current diagnostic tools and available potential diagnostic biomarkers for endometriosis that may be used to better clinically manage the disease to improve the quality of life of adult and adolescent patients.

Presentation and clinical course of endometriosis

Clinical presentation of endometriosis varies in women. Patients often present with symptoms such as intermenstrual bleeding, painful periods (dysmenorrhea), painful intercourse (dyspareunia), painful defecation (dyschezia) and painful urination (dysuria) [15]. Pelvic pain may present before menstruation begins. Often, endometriosis can be asymptomatic, only coming to a clinician's attention during evaluation for infertility.

Classification of endometriosis associated pain symptoms have been established by the American Society for Reproductive Medicine (ASRM) based on the morphology of peritoneal and pelvic implants such as red, white and black lesions, percentage of involvement of each lesion should be included. The pelvis is inspected in clockwise or counterclockwise fashion. Number, size, and location endometrial implants, plaques, endometriomas and adhesions should be noted. Endometriosis in bowel, urinary tract, fallopian tube, vagina, cervix, skin, or other locations should be documented per ASRM guidelines. Stages of endometriosis according to ASRM guidelines are stage I, II, III, and IV determined based on the point scores and correspond to minimal, mild, moderate and severe endometriosis [16].

Epidemiology and risk factors

Several reproductive factors have been consistently associated with risk for endometriosis (Table 1), suggesting hormonal variation may have a significant impact on the risk of developing endometriosis. For instance, early age at menarche (17, 18–20, 33) and short menstrual cycle length (19–23) are associated with an increased risk, while parity (20, 24–26) and current oral contraceptive use (27) are associated with a decreased risk. Circulating estradiol and estrone, which stimulate ectopic and eutopic endometrial tissue, are higher among women with an earlier age at menarche and in nulliparous women (28–32). Though not a reproductive risk factor, a consistent inverse association has also been observed between body mass index (BMI) and endometriosis (17, 18–19, 22, 33–38) may also relate to hormonal differences between heavy and lean women.

Unfortunately, the evaluation of tubal ligation, parity, and oral contraceptive use in relation to endometriosis risk have been plagued by methodologic issues. Tubal ligation has been hypothesized to decrease endometriosis risk through blocking retrograde menstruation from reaching the pelvic cavity. However, the association between tubal ligation and endometriosis is difficult to interpret since endometriosis is characterized by infertility and women who seek a tubal ligation are more likely to be parous than the general population (3, 39, 40). The association between oral contraceptive use and endometriosis risk is mixed with most (27, 41) but not all showing a decreased risk for current users but an increased risk for past users. However, oral contraceptives are used to treat endometriosis-associated pain and, therefore, this association may reflect suppression of endometriosis symptoms while on oral contraceptives that reappear after the oral contraceptives are stopped.

The association between smoking and endometriosis is unclear. Although smoking is deleterious to many other aspects of health, smoking is associated with a decreased risk of

endometriosis in some (42, 19, 22) but not all (43, 44, 26, 37) studies. Interestingly, exposure to cigarette smoke in utero is associated with an 80% reduction endometriosis risk, but passive smoking exposure during childhood increases risk (45–47). Although the mechanism is unknown, circulating estrogens are known to be lower in women who smoke (48) and could inhibit the growth and persistence of endometriotic tissue.

The association between alcohol and caffeine consumption is similarly mixed and may depend on fertility status. Among infertile women, several studies have reported increased risk with higher alcohol or caffeine intake (49–52). Increased bioavailable estrogen levels in women who consume moderate amounts of alcohol lend biologic credibility to the association. However, studies not restricted to infertile women have shown no association (33, 53–55).

Other lifestyle factors and dietary patterns that influence endometriosis risk may relate to their ability to mitigate inflammation. Physical activity and omega-3 dietary fatty acids may reduce levels of tumor necrosis factor alpha (TNFα), interleukin 6 (IL6) and other inflammatory markers [56–60]. While the association between physical activity and endometriosis is unclear (43), higher intake of long-chain omega-3 fatty acids has been associated with reduced endometriosis risk [61].

Despite recent advances in identifying risk factors for endometriosis, the field continues to be limited by requiring surgical diagnosis of the disease, often done laproscopically to confirm effected cases and appropriate controls (those that are sampled from the same base population as the cases). Validation is needed in large cohorts of women with laproscopically-confirmed endometriosis and appropriate control groups. Furthermore, as reproductive and lifestyle factors change, such as changes in contraception formulations and patterns of use as well as delayed childbearing, newer cohorts of young women are needed to understand how changes in established factors may influence endometriosis incidence as well as aid in the discovery of novel risk factors. Ultimately, the establishment of a defined set of endometriosis risk factors could lead to the identification of a group of women and girls with a high enough risk profile to warrant screening. Furthermore, these risk factors can also provide new insights into the etiology of the disease, which could lead to important advances in identifying potential screening biomarkers and treatment targets.

Diagnosis of endometriosis

Preliminary diagnosis of endometriosis is usually done on the basis of clinical history since most women show normal results of physical examination. Clinicians palpate for uterine or adnexal tenderness, a retroverted fixture, nodulating uterosacral ligament, and any pelvic masses. A tenderness on palpation of posterior fornix is the most common finding. Pelvic pain is also a symptom of other diseases such as pelvic adhesions, adenomyosis, and gastrointestinal or urologic disorders; therefore, differential diagnosis is important (7). Other causes of pelvic pain should be ruled out by carrying out appropriate diagnostic tests like urinalysis, Pap smear, pregnancy test, vaginal and endocervical swabs. Pelvic ultrasound scans are performed to facilitate diagnosis of an endometrioma, fibroids and ovarian cysts.

Pelvic masses are visualized by the use of transvaginal and transabdominal ultrasound. Transvaginal ultrasound is used to better visualize endometrium and uterine cavity and detect ovarian endometriotic cysts but does not rule out peritoneal endometriosis, endometriosis-associated adhesions and deep infiltrating endometriosis [66–70]. Occasionally, a magnetic resonance imaging and computed tomography scans are conducted to characterize the pelvic masses.

Despite the aforementioned tentative tests available, gold standard for confirmatory diagnosis of endometriosis is laparoscopic inspection with histologic confirmation after biopsy [66]. Endometriotic lesions are visualized by the use of laparoscope; however, the correlation between clinical symptoms and disease burden is poor [66, 71].

Since laparoscopy is not practical as a first line diagnostic tool, investigators have sought to identify non-invasive tools for early diagnosis that might prevent or delay progression of endometriosis (Table 2). Despite the range of blood tests that have been evaluated, a reliable test has yet to be identified for the diagnosis of endometriosis [72, 73]. A change in levels of analytes, proteins, microRNAs, and other markers corresponding to a disease state could be the basis for identifying novel biomarkers. Women with endometriosis show altered levels of CA-125, cytokines, angiogenic and growth factors compared to normal women, but none of the markers have been proven to be definitive clinical tool for diagnosis of endometriosis.

Biomarkers for the diagnosis of endometriosis

Current guidelines recommend that the histological examination of specimens collected from the suspicious areas during the visual inspection of the pelvis at laparoscopy is the gold standard for diagnosis of endometriosis [71]. However, laparoscopy may not be appropriate for all women with a history and physical examination suggestive of endometriosis. Therefore, care has been given to identify simple and reliable biomarkers of endometriosis for early noninvasive or semi-invasive diagnosis of this disease. Many studies have evaluated the diagnostic value of biomarkers for endometriosis but to date there is no reliable recommended biomarkers in endometrial tissue, menstrual or uterine fluids and immunologic markers in blood or urine for clinical use as a diagnostic test for endometriosis yet [74].

By using semi or non-invasive diagnostic tools to evaluate biomarkers from blood, urine, or menstrual fluid, a surgical procedure could be avoided and women with endometriosis, who could benefit from surgery to increase fertility and decrease pain, could be identified. Moreover, it provides data early in the disease process that could aid in treatment or prevent the progression of disease in particular for women with minimal-mild disease [75]. A list of candidate biomarkers for endometriosis diagnosis and progression are summarized in (Table 2). A combination of these biomarkers may improve the sensitivity and specificity over any single biomarker [74]. Moreover, stem cell, proteomic and genomic studies could provide advanced opportunities for discovery of the potentially new reliable diagnostic biomarkers with high sensitivity for endometriosis.

Clinical Management practices for associated pain and infertility

The management of endometriosis requires a multidisciplinary approach with [i] surgical diagnosis and debulking of disease load, [ii] hormonal treatment to suppress and delay recurrence and progression of disease, [iii] pain managment strategies best provided by a pain center clinic that develops individualized care plans and pelvic therapy. Symptomatic endometriosis is typically treated by surgical or medical treatment both equally effective. Despite the availability of treatments of associated pain, recurrence of endometriosis is not uncommon. Choice of medical treatments is done based on side effect profile, cost and personal preference. Non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose combined oral contraceptive pills (COCPs) such as ethyl estradiol and progestins are the first choice drugs [91]. If patients do not respond to NSAIDs in three months a second line of treatments is used which includes progestins (oral, injectable and intra-uterine), androgens, and gonadotropin releasing hormone agonists (GnRH) which reduce moderate to severe pain of endometriosis [92–94].

Surgical techniques include excision or removal of endometrial implants, ablation of uterosacral nerves by employment of endocoagulation, electrocautery or laser treatment, presacral neurectomy, and hysterectomy with bilateral salpingooophorectomy [95, 96]. They have 50–80% success rate in reducing symptoms. Unfortunately, endometriosis recurs in 5 to 15% of cases even after hysterectomy and bilateral oophorectomy.

The primary benefit of surgery for infertility associated with endometriosis is to enhance the probability of natural conception [97]. Surgery for infertility or pain increases the spontaneous post-operative pregnancy rate [98]. On the other hand, surgery for endometrioma could lead to reduced ovarian function and the possible loss of the ovary. Therefore, the decision of surgery should be made carefully, particularly in women with advanced age, bilateral disease, impaired ovarian reserve, who had previous surgery for endometriomas, or long-term infertility, who are incompatible with natural conception due to tubal or male factors.

Future Perspectives

With the advancement of technologies and novel research findings, novel markers have been reported which can potentially be developed as therapeutic targets of endometriosis. In this class, immunomodulators such as interferon alpha 2 (IFN- α 2) and tumor necrosis factor (TNF) – α inhibitors have been tested in animal models [99]. In one study [100], visceral sensitivity was measured in endometriosis patients and compared with patients with irritable bowel syndrome (IBS) and identified that patients who had pain associated with endometriosis had greater visceral hypersensitivity compared to IBS patients. This not only gives a way to differentially diagnose endometriosis patients but also provides a novel target for therapy of endometriosis. A recent study has shown that inflammation leads to elevation of components of signaling pathways such as mitogen-activated protein kinase (MAPK) in endometriosis [101, 102] and could be a potential targets of therapy for endometriosis. A combination of unique and specific diagnostic biomarkers and novel therapeutic targets will pave a path for better early diagnosis and more effective treatment of endometriosis.

Conclusions

In summary, endometriosis is a debilitating disease that impacts the quality of life of adult and adolescent patients. Diagnostic delays are common and may lead to a decline in reproductive potential and fertility. A semi/non-invasive diagnostic biomarker would be a useful tool to identify patients early in the disease process and thus improving outcomes, including less pain and better fertility. A myriad of biomarkers have been associated with endometriosis; however, they are not sensitive and specific enough for use in screening. These potential biomarkers would reduce the cost of surgical intervention by early diagnosing the cases and thus improve clinical management of the disease. Therefore, more research is needed in this area of medicine.

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Table 1

Risk factors for endometriosis

Factors associated with increased risk	References	Factors associated with decreased risk	References
Earlier age at menarche	[17, 18–20, 33]	Parity	[20, 24–26]
Shorter menstrual cycle length	[19–23]	Current oral contraceptive use	[27, 41]
Taller height	[33, 35]	Smoking	[19, 22, 26, 37, 42, 43, 44, 45–48]
Alcohol use	[36, 51, 52]	Higher body mass index	[17, 18, 19, 22, 33, 34–38]
Caffeine intake	[50]	Regular exercise	[22, 43]
		Fish and omega 3 fatty acids	[61]

Table 2

Potential diagnostic biomarkers for endometriosis

Biological groups	Biomarkers	References
Inflammatory markers-Cytokines	IL-1 β, IL-6, IL-8, IL-17, IL-21, RANTES, TNF-α, IFN-gamma, MCP-1, MIF, CRP	75
Steroids and hormones	ERs, 17 βHSD, aromatase	76
Growth factors	IGF, Activin, TGF β1, HGF, annexin-1	75.77
Cell adhesion and extracellular matrix molecules	Integrins, Vimentin, E-cadherin, osteopontin, ICAM-1 (CD54), β-catenin, FAK	78–80
Angiogenesis	VEGF, NGF, FGF-2, Leptin, IGFBP-3, glycodelin, M-CSF, angiopoeitin-1 and −2, MVD, endoglin and thrombospondin-1	81, 82
Apoptosis and cell cycle control	Telomerase activity, Pak-1, cyclin D1, Survivin, Bcl-2, MCL-1, Bax, Bcl-xL, Bcl-xS	83
Stem cell markers	CD9, CD34, Oct-4	84–86
Genomics	HOXA10, 3p, 5q, 7p, 9p, 11q, 16q, 17p, 17q, 18q, 19p, 19q	87
Proteomics	The analysis of different expression of certain peptides and proteins in endometriosis	88
Tissue remodeling	MMP-2, MMP9, TIMPs, urokinase	89–90

Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES), Monocyte chemotactic protein 1 (MCP-1), Vascular endothelial growth factor (VEGF), Microvessel density (MVD), Focal adhesion kinase (FAK), Insulin-like growth (IGF), Hepatocyte growth factor (HGF), Matrix metalloproteinase (MMP), Tissue inhibitors of metalloproteinases (TIMPs), Pak-1 (p21 activated kinase-1), 17 β hydroxysteroid dehydrogenase (17 βHSD), Estrogen receptors (ERs)