The Modern Non-Invasive Diagnosis Of Endometriosis- Mini Review

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Abstract

Endometriosis, a chronic gynecological disease, affects millions of women worldwide, significantly impacting their quality of life. A reported delay, ranging from 4 to 12 years, exists between the onset of symptoms and the formal diagnosis. Characterized by the presence of endometrial-like tissue outside the uterine cavity, this condition often manifests with symptoms such as pelvic pain, dysmenorrhea, and infertility. Traditionally, the gold standard for endometriosis diagnosis has been surgical intervention involving laparoscopy and histological examination. However, the reliance on invasive procedures has led to delayed diagnoses, unnecessary surgeries, and the persistence of symptoms for many patients.

In recent years, the value of clinical diagnosis has been shown.

The aim is to explore and underscore the significance of clinical diagnostic methods, highlighting their potential for managing endometriosis.

Clinical history, questionnaires, imaging modalities, and biomarkers promise to reshape the diagnostic pathway for endometriosis, adopting a more patient-centric, non-invasive diagnostic approach.

Keywords: endometriosis; diagnosis; questionnaire; transvaginal ultrasound; magnetic resonance

Mini Review

Introduction

The diagnosis of endometriosis is frequently characterized by a substantial delay, with an average diagnostic lag of up to 12 years (1). This delay holds significant implications for patients, as over 90% of them exhibit moderate to severe symptoms upon diagnosis (2). The prolonged delay contributes to disease progression over several years, resulting in escalated treatment costs, extended adverse effects on quality of life and psychological well-being, and heightened risks of surgical interventions and infertility. This underscores the critical necessity for a non-invasive diagnostic tool to facilitate early identification of endometriosis.

In the modern diagnosis of endometriosis, a patient-centered approach is imperative, placing a primary emphasis on the clinical evaluation of the patient. This involves a comprehensive assessment that begins with a detailed medical history (including exploring risk factors and identifying associated comorbidities). In addition, the symptoms reported by the patient serve as the significant elements in the boxy of the diagnostic flow chart, also giving particular attention to the psychological impact of the condition. Utilizing questionnaires is invaluable for facilitating a nuanced understanding of the patient's experiences.

1. Questionnaires: A Tool For Screening

To prevent a delay in the diagnosis of endometriosis that may exacerbate the patient's clinical condition and symptoms, considering the costs and drawbacks associated with invasive diagnostic procedures, non-invasive diagnostic approaches utilizing the assessment of signs, symptoms, risk factors, and personal history should be increasingly prioritized. Specifically, the diagnostic scoring questionnaires can serve as an initial screening method or complement to the patient's clinical history.

The integration of diagnostic scoring questionnaires emerges as a practical and effective means of conducting an initial assessment. The questionnaires, designed to evaluate relevant symptoms and risk factors systematically, can enhance the diagnostic process. Moreover, their use is a valuable adjunct to the traditional clinical history, enabling healthcare providers to adopt a more efficient and patient-centered approach to diagnosis. As such, promoting non-invasive diagnostic avenues, mainly through the integration of diagnostic questionnaires, is a strategy to expedite the identification and management of endometriosis while minimizing the associated challenges of invasive procedures.

According to the most common risk factors (Table 1), the Florence Questionnaire includes information on genetic (family history), epigenetic (in utero exposure to stressors), age of menarche and characteristics of menstruations during adolescence, developmental stressors (psychological or physical) or exposure to environmental disruptors (chemicals).

To assess menstruation-related distress MEDI-Q (menstrual distress questionnaire) has been validated (3); it comprises 25 items; the questionnaire encompasses diverse aspects of menstruation-related symptoms, including pain, discomfort, psychological or cognitive changes, and gastrointestinal disturbances. Evaluation of distress level for each symptom considers its impact on functioning and quality of life during the menstrual phase compared to intermenstrual and premenstrual phases and its frequency. In addition to scores specific to individual symptom areas, the MEDI-Q furnishes four overarching indices, enabling a comprehensive evaluation of menstrual distress. Menstrual health is an integral part of overall health and physical symptoms (4), and bleeding during menstruation may have a relevant impact on stress perception and quality of life (5).

Consequently, this instrument proves valuable for application in both research and clinical settings, facilitating a comprehensive exploration and analysis of menstruation's impact. MEDI-Q into routine healthcare for women can enhance the identification and timely monitoring of menstruation-related

disorders, contributing to a more prompt and effective management approach.

Similarly, other patient questionnaires in the diagnosis of endometriosis have been proposed and utilized for evaluating the impact of endometriosis on quality of life:

- The Central Sensitization Inventory (CSI) is a validated self-administered questionnaire designed to evaluate the severity of symptoms and identify individuals with central sensitivity syndromes (CSSs), commonly known as chronic overlapping pain conditions (6).
- The Medical Outcomes Study Short Form 36 (SF36) (7).
- The Endometriosis Health Profile 30 (EHP30) (8).
- The EHP-5 questionnaire (9).
- Modified DELPHI survey (10).
- The Female Sexual Function Index (FSFI) (11).
- The Subjective Impact of Dyspareunia Inventory (SIDI) (12).

In endometriosis diagnosis and prevention, the emergence of technology, particularly mobile applications, has proven transformative. Applications enhance awareness, early detection, and overall management of endometriosis (13). Like the Endometriosis Risk Advisor (EndoRA), a free tool powered by an artificial intelligence (AI) algorithm. It categorizes patients into two main groups: those experiencing infertility or pain. A sequence of questions follows, covering symptomatology, family history, psychiatric history, past medical history, fertility issues, and previous fertility testing. The questionnaire dynamically adjusts based on the patient's responses, gathering additional information. The AI algorithm then computes the risk assessment, categorizing individuals as low risk (<50%), moderate risk (50–75%), or high risk (>90%) for potential endometriosis (14).

Key aspects underscoring the importance of technology in this context include symptom tracking and monitoring, early detection and diagnosis, education and awareness dissemination, improved communication with healthcare providers, personalized health insights, fertility tracking, community support, and regular updates and alerts. By leveraging these digital tools, individuals can actively participate in managing and preventing endometriosis, contributing to improved overall well-being and quality of life.

2. Symptoms and Physical Examination

Clinical questioning represents a straightforward and indispensable method for diagnosing endometriosis.

Pain and infertility are the most common symptoms. Using a Visual Analog Scale (VAS) score for dysmenorrhea, dyspareunia, dysuria, or dyschezia must be evaluated in the first clinical examination (15). The assessment of painful symptoms experienced by endometriosis patients may help predict pelvic organ involvement associated with deep infiltrating lesions in endometriosis patients. Therefore, employing questionnaires can serve as an effective means to identify patients who need radiological assessment.

Infertility is the other most common symptom in endometriosis patients and requires attention in terms of medical history, physical examination, and imaging. Factors such as altered pelvic anatomy, adhesions, disrupted ovarian function, and compromised endometrial receptivity contribute significantly to infertility in affected women (16). Furthermore, the coexistence of comorbidities such as adenomyosis (17), fibroids, autoimmune conditions, diminished ovarian reserve, and the occurrence of dyspareunia, and sexual dysfunction (18), can explain infertility in endometriosis.

The physical examination is indispensable after the evaluation of family and clinical history and the completion of questionnaires. Assessment of the pelvis in individuals suspected of having endometriosis should involve a comprehensive physical examination, including abdominal inspection and palpation. The pelvic examination incorporates a speculum assessment to identify posterior vaginal fornix (PVF) endometriosis, if present, and a digital

Table 1: Florence Questionnaire

Family History
- First-degree relative with endometriosis

In Utero Exposure
- Premature birth
- Preeclampsia
- Exposure to dietylstilbestrol

Early Life Factors
- Low Birth Weight (small for gestational age/fetal growth restriction)
- Formula-fed infant

Adolescent History
- Physical, psychological violence or sexual abuse in infancy and adolescence
- Severe dysmenorrhea interfering with daily life activities
- Genital tract abnormalities (e.g. obstructive Müllerian anomalies)

Gynecologic Factors
- Early menarche
- Severe dysmenorrhea
- Short menstrual cycle length
- Heavy Menstrual Bleeding
- Vulvodynia

Comorbidities-related Risk Factors
- Headache, migraine, and the chronic pain syndrome
- Autoimmune diseases (e.g., systemic lupus erythematosus, scleroderma, rheumatoid arthritis).
- Gastrointestinal disorders (e.g., ulcerative colitis, Crohn's disease, IBS, celiac disease)

Environmental and Stress Related Risk Factors
- Psychological stress and sexual abuse
- Endocrine disruptors and diet
- High intensity physical activity and low BMI

Previous Obstetrical History
- Adverse pregnancy and perinatal outcomes
- Miscarriage(s)
- Previous History of Pelvic Surgery

vaginal examination to detect nodules in various structures such as uterosacral ligaments (USLs), torus uterinus, PVF, rectovaginal septum (RVS), low rectum, and parametrium, is crucial. Additionally, a bimanual examination is conducted to evaluate uterine size, orientation, mobility/fixation, presence of adnexal masses, and site-specific tenderness in the pelvis, encompassing the pelvic floor musculature.

3. Imaging (TVS and MRI)

With the aim of a more rapid and non-invasive diagnosis of endometriosis, the development of 2D and 3D transvaginal ultrasound (TVS) served a major role. Transvaginal ultrasound enhances diagnostic accuracy when employed in conjunction with patient history, symptoms, and physical findings. This modality proves particularly adept at detecting ovarian endometriomas and deep infiltrating endometriosis. The International Deep Endometriosis Analysis (IDEA) group consensus outlined the standards for systematic sonographic evaluation of DIE localizations, offering a framework for expert-guided imaging. While traditional transvaginal ultrasound may be limited to endometrioma diagnosis, the IDEA group's approach contributes to a more comprehensive clinical assessment of various endometriosis manifestations. However, it is important to note that not all instances of endometriosis are visible through imaging, and this method cannot definitively rule out the presence of endometriosis (in particular superficial endometriosis, SUP) (19). Ultrasound serves as a dynamic test, providing real-time assessment. When considering diagnostic test accuracy (DTA), TVS has exhibited superiority over physical examination in comparative studies, particularly in diagnosing ovarian and posterior-compartment endometriosis (20).

The diagnostic test performance of TVS approached the criteria of a triage test for ruling endometriosis, thereby eliminating the necessity for performing laparoscopic surgery solely for diagnostic purposes in these individuals. This suggests that TVS can serve as an effective and reliable tool to identify

endometriosis, providing a non-invasive alternative to surgical procedures in cases where imaging strongly indicates endometriosis (21).

The dynamic TVS test, known as the uterine sliding sign, is highly accurate in discerning posterior deep endometriosis obliteration. The lack of sliding serves as a soft marker for rectal endometriosis presence. TVS has shown high sensitivity and specificity in identifying ovarian immobility, associated with ovarian endometriosis, posterior-compartment deep endometriosis, and ipsilateral superficial endometriosis. Endometriosis affecting the rectosigmoid, colon, or bladder can be subtyped into SUP or DIE. TVS has demonstrated excellent diagnostic accuracy for detecting DE in the rectosigmoid urinary tract involvement (bladder). TVS is feasible for identifying ureters and detecting pelvic ureteral involvement in DE cases; renal ultrasound is essential to exclude hydronephrosis (20).

In cases of advanced endometriosis, employing TVS based on the IDEA consensus is leading to considerable cost savings for healthcare systems, making it a favorable substitute for diagnostic laparoscopy (22).

Magnetic resonance imaging (MRI) is another non-invasive technology for diagnosing endometriosis, but the cost and the limited availability make it less commonly utilized for endometriosis diagnosis. MRI offers the advantage of evaluating endometriosis in multiple planes, which is particularly beneficial for imaging multifocal and extra-pelvic endometriotic lesions. It demonstrates overall high accuracy in detecting DIE and extra pelvic involvement (2).

4. Biomarkers and Gene Testing

Studies have shown promising results regarding the diagnosis of endometriosis based on biomarkers and gene testing. After several years of investigation, the evaluation of serum CA 125 is not recommended to exclude or diagnose endometriosis. The data on using microRNAs (miRNAs), a class of RNA molecules involved in gene regulation that emerged as potential biomarkers for various pathological conditions, including endometriosis, are promising. In the diagnostic context, the finding of miRNAs in serum and saliva are gaining interest as possible indicators of endometriosis, given that their gene expression profile may reflect disease-specific alterations. These miRNAs can be detected in easily accessible biological samples, offering a non-invasive approach to diagnosis.

Independent validation of serum miRNAs, including miR-125b-5p, miR-150-5p, miR-342-3p, miR-451a, miR-3613-5p, and let-7b, confirms their effectiveness as reliable biomarkers for endometriosis diagnosis (23). Furthermore, the expression of miRNAs has cyclic differences according to the stage of the menstrual cycle (24). A saliva-based miRNA signature for endometriosis offers a cost-effective and easily scalable method for sample collection, making it accessible to diverse populations.

The good sensitivity and specificity demonstrated by the saliva miRNA highlight its potential as a practical alternative and/or triage test; the application of Next-Generation Sequencing (NGS) and Artificial Intelligence (AI) in sequencing and analyzing miRNA provided a saliva-based miRNA signature for endometriosis (25).

Despite promising advances, further research is essential to confirm the effectiveness of miRNAs as biomarkers for endometriosis and better to understand their role in the disease's pathogenesis; miRNAs could contribute to a more accurate diagnosis and potentially pave the way for the development of new therapeutic approaches based on the molecular understanding of the disease.

5. Present and Future Perspectives

In the new Millennium, the non-invasive diagnosis of endometriosis appears a reality, and the combination of clinical examination plus 2D/3D TVS or MRI have facilitated detailed visualization of anatomical structures involved in endometriosis. The future integrated use of advanced imaging and artificial intelligence (AI)

may only improve the diagnostic capacity. Integrating these two technologies enables the creation of more accurate and efficient diagnostic models. For instance, AI can assist in detecting early-stage endometriotic lesions or differentiate between various phenotypes of endometriosis (26). Despite these positive prospects, ongoing research and validation of these new technologies are crucial to ensure their reliability and accuracy.

In addition, the diagnosis of endometriosis should be pursued across all levels of healthcare, starting with primary care practitioners, including general doctors, midwives, and nurses, who serve as the initial point of contact for patients. At the secondary level of care, specialists not only gynecologists but also professionals from diverse fields such as urologists, gastroenterologists, rheumatologists, psychiatrists, and psychologists, considering the comorbidities associated with the disease. At the tertiary level of care, the endometriosis care center serves as the focal point for specialized and comprehensive management.

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