The Diagnostic Tools in Endometriosis

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1. Clinical symptoms and physical examination in endometriosis

Endometriosis is defined as the histological presence of endometrial glandular tissue and stroma outside the uterus.[1] It affects about 10% of all woman in reproductive age. [2]Endometriotic lesions are commonly seen on the peritoneum, ovaries, fallopian tubes, uterus, uterine ligaments, bladder, intestines, ureters, and rectum.[3] It can also be seen outside the pelvis, e.g.; in the lungs, diaphragm, and pericardium. [4,5] Although there is no precise information about the etiology of endometriosis, the theory of retrograde menstruation has been emphasized for years. Immunological and genetic studies on its etiology have recently focused on the stem cell theory.[4] According to this theory, stem cells can transform into endometriotic cells due to their plasticity, proliferation, and differentiation capacities. [4,6, 7]

Endometriosis lesions are commonly seen on the peritoneum, ovaries, fallopian tubes, uterus, uterine ligaments, bladder, intestines, ureters, and rectum.

It is also thought that hormonal variations may play a role in the development of endometriosis. [8] For example, early menarche [9,10] and short menstrual cycle [9,10] were associated with increased disease risk. In contrast, parity [10, 11] and oral contraceptive use [12] were associated with decreased risk for endometriosis. The diagnosis of the disease often delayed, which causes patients to live with low quality of life for years. Although the symptoms usually begin to appear in the adolescent period, the average delay time for

diagnosis is about 6.7 years. [13] The most important reason for this delay is that a non-invasive diagnostic test has not been developed to diagnose the disease.

Endometrial implants are affected by circulating estradiol and estrone. [8] Implants, just like the endometrial tissue, can cyclically undergo proliferation, and hemorrhages may be seen in these foci. Due to non-draining hemorrhages, irritation, and inflammation in the surrounding tissue may form, leading to adhesion formation to develop. These formations can cause pain just before or during menstruation.

In patients with endometriosis, chronic pelvic pain [2], severe dysmenorrhea, dyspareunia, or dysuria or dyschezia can be seen, according to the location of the endometrial foci.[14] Apart from pain symptoms, approximately 40% of patients with endometriosis have complaints of infertility.[2]

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The other possible symptom of endometriosis is excessive and prolonged menstrual bleeding. Abnormal uterine bleeding can be both associated with a risk factor and symptom of endometriosis. [4,15] There is no correlation between the severity of all these clinical signs mentioned above and the stage of the disease. [16]

Since endometriosis could also be observed in patients without the disease, it is necessary to take a detailed history to imply endometriosis and perform a careful pelvic examination.

While taking the patient history, age, the age of menarche, menstrual pattern, parity, pain characteristics, severity of the symptoms, history of surgery, systemic diseases, and

current medications should be questioned and recorded. Apart from a detailed history, appropriate diagnostic tests such as BhCG test, pap smear, vaginal, and endocervical sampling and urinary analysis should also be used in the differential diagnosis. [8] It will be useful to use visual pain scales when evaluating the pain. Since endometriosis can decrease the quality of life, the implementation and recording of validated quality of life scores will guide treatment planning.

In most of the patients, generally, no significant physical examination finding is observed. [8] The most common finding on physical examination is tenderness during posterior fornix palpation. [8] Apart from this, physicians should pay attention to findings such as uterine and adnexal tenderness, nodule and tenderness in the sacrouterine ligaments, and pelvic mass. It is essential in terms of differential diagnosis that chronic pelvic pain may be due to many different causes such as pelvic adhesions, urological or gastrointestinal diseases. [17]

Following physical examination, pelvic ultrasonography can be performed to diagnose ovarian endometriosis, adenomyosis, ovarian cysts, fibroids, and other pelvic pathologies. [8,18] Sometimes, magnetic resonance imaging (MRI) or computed tomography (CT) can be used in the diagnosis, especially to determine the character of the pelvic masses and to detect endometriotic nodules. Endometriotic lesions and implants that are not seen on ultrasound can be detected with MRI, mainly due to high-resolution imaging and excellent tissue characterization.[19] This imaging modality enables planning and mapping before surgery, especially in deep infiltrating endometriosis. [19]

The gold-standard method in the diagnosis of endometriosis still consists of histopathological examination of the biopsy taken following the inspection of the pelvic

cavity during laparoscopy. Since laparoscopy is an invasive procedure, researchers are seeking other methods for the diagnosis of endometriosis. [20,21]

In this review, we aimed to give information about serum markers, imaging methods, and ongoing studies used as a guide in the diagnosis of endometriosis.

2. Biomarkers in endometriosis

To prevent a delay in the diagnosis of endometriosis, the development of non-invasive diagnostic methods is aimed, and thus many researches have been performed on serum biomarkers. It is thought that a highly sensitive marker might be useful for detecting patients with endometriosis, especially in cases of pelvic pain and subfertility, where radiological findings are normal. However, in the light of current literature, a single serum biomarker or a panel of several markers that allows diagnosing endometriosis has not been identified yet. [16, 22]

Previously, it has been reported that the concentration of cancer antigen-125 (Ca-125), a glycoprotein, may be increased in patients with endometriosis (>35 units/ml). However, it has been shown that Ca-125 may be increased due to many benign conditions such as menstruation, fibroids, pregnancy, and gastrointestinal tract pathologies. Since this biomarker may also be increased for malignant disorders as ovarian cancer, its specificity and sensitivity is quite low. [23] Thus, this biomarker does not play a primary role in the diagnosis of endometriosis. [23-25] It is not recommended to evaluate the recurrence and the risk of malignant transformation. [26,27] Another glycoprotein studied in the diagnosis of endometriosis is Ca-19.9. Although some studies showed the increasing level of Ca 19.9 during the follow-up of endometriosis, its sensitivity was lower than Ca-125. [22] On the other hand, Ca-19.9 may be increased in pathologies such as dermoid cysts and benign ovarian cysts like Ca-125 and especially in pathologies of the gastrointestinal tract.

Human Epididymal Secretory Protein 4 (HE4), another epithelial ovarian cancer marker, was evaluated if it was useful in distinguishing endometriosis from ovarian malignancies. [28] Studies show that the combination of HE4 and Ca-125 biomarkers has 94% sensitivity and 78.6% specificity in the differential diagnosis of endometriosis from ovarian cancers. [29] However, the Risk of Ovarian Malignancy Algorithm (ROMA) index, calculated using menopausal status, HE4, and Ca-125, has found to be with 15% false positivity in endometriosis. Therefore, it has been reported that the evaluation of these serum biomarkers with ultrasonography and MRI findings can be more accurate. [30, 31]

Some studies have shown that cytokines, angiogenic factors, and growth factors in peripheral blood are expressed differently in patients with endometriosis. [22,32] However, the results in these studies are not generalized due to the limited number of patients, evaluation of variables at different periods of the menstrual cycle, and inclusion of patients at various stages of endometriosis. [22] The reliability of the results, obtained from the combination of several serum biomarker panels, is limited due to the number of biomarkers, single variated statistical analysis, lack of validation in the independent test set. [33-37]

Vodolazkaia et al. evaluated 28 plasma biomarkers classified as glycoproteins, inflammatory and non-inflammatory markers, adhesion molecules, angiogenic factors, and growth factors in different menstrual cycle phases according to their biological functions. [38] They demonstrated that two different models consisting of four biomarkers in each (annexin-V, VEGF, Ca-125, glycodelin, annexin-V, VEGF, Ca-125, and sICAM-1) during menstrual phase are associated with 81-90% sensitivity and 63-81% specificity in undiagnosed endometriosis cases by ultrasonography.

The increased levels of inflammatory and immunological markers such as IL-1, Il-6, IL-8, TNF-α, MCP-1, and interferon-γ (IFN-γ) were reported in the literature. However, the results were not confirmed by subsequent studies.[39] There is no consensus yet on whether the cytokines are helpful to distinguishing endometriosis from other pelvic pathologies.

In endometriosis, oxidative stress may be increased in the pelvic cavity due to the retrograde iron-containing menstrual fluid flow. Studies have shown the decreased levels of paraoxonase (PON-1), high-density lipoproteins and plasma superoxide dismutase, and the increased levels of total cholesterol, triglyceride, low-density lipoprotein, and lipid peroxidase.[39] Apart from this, ICAM-1, one of the cell adhesion molecules, was suggested to be increased in the early stage of endometriosis, whereas to decreased in stage III-IV endometriosis.[22] Some studies show that matrix metalloproteinases (MMP) facilitate the invasion of endometrial tissue fragments into the peritoneum and produce remodeling in the extracellular matrix; some reports showed no difference in the expression of MMP-2 and MMP-9 in endometriosis.[39] Additionally, although there are studies about Vascular Endothelial Growth Factor (VEGF), an angiogenic factor; Pigment Epithelium Derived Factor (PEDF), an angiogenesis inhibitor; Epidermal Growth Factor (EGF) and Platelet-Derived Growth Factor, they are not specific and sensitive to endometriosis and not accepted as serum biomarkers.[39]

In a recent Cochrane review, 122 serum biomarkers were compared.[20] These biomarkers are angiogenesis, growth factors, apoptosis markers, cell adhesion molecules, hormonal markers, immune system and inflammatory markers, oxidative stress markers, microRNAs, tumor markers, and other proteins have been evaluated in small sample-sized studies. In addition, a meta-analysis of these biomarkers could only be performed on anti-

endometrial antibodies, IL-6, Ca 19.9, and Ca-125, since a different cut-off value was used in each study. Unfortunately, the diagnostic value of each marker could not be generalized, as they differ significantly between studies. [20,41]

As a result, there is currently no serum biomarker to diagnose endometriosis.

> Many serum biomarkers, such as angiogenesis factors, growth factors, glycoproteins, inflammatory markers, and oxidative stress markers, have been evaluated to develop a non-invasive diagnostic method for endometriosis. However, there is currently no single serum biomarker or panel of serum markers to

3.Sonographic Evaluation in Endometriosis

The most crucial goal in surgery for endometriosis is maximum cytoreduction, taking into account the patient's future expectations. For that reason, the first step is to map the spread and location of the disease preoperatively.[41] Transvaginal ultrasonography (TVS) and magnetic resonance imaging (MRI) are utilized with high sensitivity in preoperative mapping and diagnosis of the disease. Ultrasonography is used as a first-line diagnostic tool in endometriosis with its reasonably high sensitivity, noninvasive technique, and available to employ at any time.[42,43] In addition to detailed clinical examination, kidneys should be evaluated by transabdominal ultrasonography in deep infiltrating endometriosis (DIE).[41,44]

Most of the endometriosis societies worldwide have been published of their opinions about the imaging techniques. TVS has limited value in peritoneal endometriosis. However, it can be used both to make and exclude the diagnosis of an ovarian endometrioma.[45] Besides, it is useful in DIE that infiltrates the vagina, rectum, and the rectovaginal septum.[46-49] To detect silent hydronephrosis, sonography is useful in the evaluation of ureters and kidneys.[50] MRI

should be specially reserved for patients with indeterminate ultrasonography results with rectovaginal, ureteral, and bladder involvement.[46,47] In imaging methods, histopathological evaluation is mandatory in cases with the heterogeneous complicated ovarian mass and in cases where malignancy cannot be excluded.[44,51]Ultrasonographic views of endometriosis are briefly summarized in table 1 (Table 1).

The Cochrane review emphasized that none of the imaging methods were alternative to surgery in the diagnosis of pelvic endometriosis. According to this review, the sensitivity and specificity of pelvic ultrasonography for endometrioma, DIE, and Douglas obliteration are 93%, 79%, 83%, and 96%, 94%, 97%, respectively.[52] The biggest challenge for TVS is that it depends on the experience of the practitioner and has low reproducibility.[49,53] Therefore, the International Deep Endometriosis Analysis Group reorganized the terminology to standardize the pelvic ultrasonographic examination to minimize the margin of error and achieve high accuracy.[42] This examination includes dynamic ultrasonography and covers the following steps, respectively; 1) Standard evaluation of the adnexa and uterus (sonographic findings of the presence and absence of endometrioma and/or adenomyosis) 2) Evaluation of 'soft markers' 3) Real-time evaluation of the Douglas based on the 'sliding sign' 4) Evaluation of the DIE nodules in the anterior and posterior compartments.42 'Maneuvers to detect 'sliding sign'; firstly, the transvaginal probe is placed in the anterior fornix. The uterus is moved between the probe and the hand placed in the suprapubic area. When it is recognized that the posterior bladder wall slides over the anterior uterine wall, the anterior compartment (ureterovesical area) is free, and this is called "sliding sign". Otherwise, 'sliding sign' is specified as the negative and anterior compartment is obliterated. The same approach is applied to the posterior compartment (rectovaginal area).[49,53] Bowel preparation before TVS

has no additional benefit to the examination.[54] Unlike the posterior compartment, the adequacy of this technique is less for the anterior (especially bladder) and middle (torus uterus and round ligament) compartments. [49,51,53] The 'soft markers' investigated by TVS are as follows; presence of adenomyosis and endometrioma, decreased ovarian movement, presence of 'kissing over' and absence of 'sliding sign'. [55]

Ultrasonography is used as the first-line diagnostic method for the diagnosis of pelvic endometriosis.

In ultrasonography, the typical appearance of ovarian endometrioma has been described as unilocular or multilocular, homogeneous, and low-level echogenicity (ground glass appearance) cystic masses with low-to-moderate vascularization. [44,46,56] This typical image can be seen in 95% of endometriomas and 19% of non-endometrioma cysts.[53]

The 'soft markers' investigated by TVS are as follows; presence of adenomyosis and endometrioma, decreased ovarian movement, presence of 'kissing over' and absence of 'sliding sign'.

The ultrasonographic image described as atypical endometrioma is unilocular cystic masses with papillary projections. These papillary projections are blood clots, cholesterol residues, or fibrin residues, unlike extensions of solid tissue. These are often smooth-rounded and do not contain vascularisation in Doppler sonography.[56] This atypical ultrasonographic image appears in 36% of endometriomas, and 6% of non-endometriomas.[53] Sonographic characteristics of ovarian endometriomas may vary with age. While typical ultrasonographic findings appear mostly at a young age, atypical sonographic findings such as papillary projections, nodularity, and increased septa thickness are encountered more frequently with

advancing age. Surgical options, including both benefits and risks, should be counseled with the patient in perimenopausal patients with long-term (approximately ten years or more) and recurrent endometrioma. Cystic masses with a ground-glass appearance in the postmenopausal period have a high risk of malignancy.[56]

> The sensitivity and specificity of pelvic ultrasonography for endometrioma, DIE and Douglas obliteration are 93%, 79%, 83%,and 96%, 94%, 97%, respectively.

Endometriomas with complex echogenicity and papillary projection may be misinterpreted as a dermoid cyst or malignant mass. Conversely, dermoid cysts, malignant masses, or serous cysts can be misclassified as endometrioma. The presence and distribution of vascularization in papillary projections on the cyst wall should be evaluated by Doppler ultrasonography. Color Doppler ultrasonography examination optimally depends on the proper settings and quality of the ultrasonography device, and the experience of the practitioner. Therefore, an adverse doppler finding may not guarantee that the cyst is benign.[53,57,58] MR should be taken into consideration as an additional tool in the management of cases, which is evaluated as insufficient, and malignancy cannot be excluded. [53,56]

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In the ultrasonographic evaluation of endometriosis, other techniques include rectal contrast bowel-transvaginal ultrasonography (RCW-TVS), transrectal ultrasonography using a transvaginal probe (TRUS), sonovaginography with saline or gel and 3D (3D) ultrasonography. [56] In the review of Deslandes et al., it was emphasized that few studies were

investigated alternative techniques and the accuracy rates of these techniques were not significantly different from conventional TVS.[49] In a study comparing TRUS, TVS, and MR, it was stated that the significant superiority of TRUS over TVS is exclusively on the evaluation of the uterosacral ligament. It was also asserted that both TRUS and TVS revealed comparable outcomes with MRI in the diagnosis of DIE. [59] It has been suggested that the use of TRUS, TVS, and RCW-TVS may help in the diagnosis of rectum infiltrating DIE.[46,50] Although many lesions in the lower colon can be detected with high sensitivity and specificity with these methods, they may remain insufficient in the upper colon. MR can be considered as an additional imaging method in such complex cases. [50]

Guerriero et al. established the first comparative studies on 2D and 3D TVUSG. According to this study, no significant difference was found between the two techniques in the anterior, posterior, and intestinal compartments. [60] However, 3D sonography is significantly more reliable compared to 2D sonography on the diagnosis of adenomyosis. [61] In this study, morphologically thickened and altered junctional zone (JZ) in adenomyosis was evaluated more effectively with 3D sonography. In another study, it was suggested that patients who had early-stage endometriosis could be diagnosed by observing the changes that occurred in JZ.[62] Although it was shown that 3D sonography was more successful in the posterior compartment than 2D, it was emphasized that 2D and 3D sonography were performed to investigate the presence of rectosigmoid nodule is very dependent on the practitioner and care should be taken in this regard.[63,64] Besides, the study comparing the diagnostic efficacy of MRI with 3D recto-sonography emphasizes that 3D recto-sonography is as successful as MRI but should be utilized by experienced physicians. [65] In a study with 3D Doppler sonography, it was revealed that there was an inverse relationship between

vascularization rate in endometrioma and the severity of painful symptoms.[26] There is currently no research to support this study.

In conclusion, ultrasonography should be used as a first-line imaging modality in the diagnosis of pelvic endometriosis. Likewise, to map the disease using imaging methods before surgery allows for optimal operation and personalized treatment.

Tablo1. Ultrasonographic Findings in Endometriosis

Pathology	Ultrasonographic Findings
Endometrioma	- Unilocular cyst (most common) - Multilocular, multilocular-solid, unilocular-solid cyst (less common) - Ground-glass echogenicity - Absence of vascularization in color doppler
DIE	- Hypoechoic lesions with or without a smooth surface - Hourglass-shaped or diabolo-like nodule - Moose Antler sign / Indian headdress sign (nodule with prominent spikes towards the bowel lumen) - Comet sign (nodule with progressive narrowing, like a tail) - Thickened and hyperechogenic uterosacral ligaments
Adenomyosis	- Enlarged uterus - Uterine wall asymmetry (not related to myoma) - Presence of uncertain areas with decreased or increased echogenicity - Hypoechogenic linear lines - Myometrial cysts (1-7 mm round anechoic areas) - Adenomyotic lesions - Endometrial-myometrial zone (JZ) irregularities
Decidualizeden dometrioma	- Unilocular-solid or multilocular-solid cyst

	- Ground-glass echogenicity
	- Smooth surface papillary projections
	- Vascularization in cyst

4. Magnetic resonance imaging in endometriosis

Although endometriosis is usually seen in the pelvic region, it can also be found in various extra pelvic areas, including the perineum, liver, pancreas, lung, and even the central nervous system, and in such cases, it is difficult to diagnose. While considering the surgery, for effective treatment, the goal should be removal all of the endometriotic lesions. [67]MRI is one of the best imaging techniques for the preoperative evaluation of endometriosis due to the possibility of evaluating the entire pelvic region at once.

The European Society of Urogenital Radiology (ESUR) association has established optimal criteria for the diagnosis of pelvic endometriosis [68]; Torus uterinus, thickening or mass in the middle upper part of the posterior cervix; Uterosacral ligament involvement shows fibrotic thickening or nodularity with regular or irregular borders compared to the contralateral ligament; Vagina, thickening behind the posterior wall of the cervix, or obliteration of a mass or hypointense signal of the posterior vaginal wall / posterior vaginal fornix; Rectovaginal septum, thickening or nodule passing through the lower border of the posterior lip of the cervix; The disappearance of the adipose tissue plane located between the rectosigmoid, uterus and the rectum / sigmoid colon, replacement with a mass of tissue that forms a wide angle with the rectosigmoid wall, or loss of the hypointense signal of the anterior wall of the rectum / sigmoid colon; Douglas pouch, partial or complete obliteration with the presence or absence of lateralized fluid accumulation; Parametrium, low signal intensity, pelvic wall involvement and ureteral dilatation; The bladder, usually with a wide

angle with the nodule or mass, bladder wall extension at the level of the vesicouterine sac or protrude into the lumen by invading the bladder wall containing the muscle layer or the mucosal layer. Round ligament shows fibrotic thickening or nodularity with regular or irregular borders compared to the contralateral ligament.

Endometrioma: MRI has a high specificity (> 90%) in determining of the endometriomas. However, in the differential diagnosis, hemorrhagic cyst (there are no dark spot marks in T2), teratoma (fat sign is pathognomic), and ovarian cancers (chelates containing gadolinium are used, contains solid areas) must be considered. It should be remembered that nodules within the cyst, which is a suspicious finding for ovarian malignancy, can be found generally in 20% of endometriomas. The nodules in the endometrioma are usually a retracted coagulum and do not retain with gadolinium-containing chelates. [69]

Posterior Pelvic Compartment: In a meta-analysis of the use of MRI to evaluate rectovaginal septum (RVS) endometriosis, the sensitivity and specificity of MRI to detect RVS involvement were reported as 81% and 86%, respectively. In the same meta-analysis, the sensitivity and specificity of MRI for vaginal endometriosis were reported as 77% and 97%, respectively, while for Rectosigmoid endometriosis, it was reported as 92% and 96%, respectively. [70]

Anterior Pelvic Compartment: Medeiros et al. [71] reported sensitivity and specificity as 64% and 98% in the meta-analysis included by a total of 1,819 women from 20 studies. However, these values are stated to be higher in retrospective studies. [72, 73]

Lateral Pelvic Compartment: Low signal intensity, presence of pelvic wall involvement, and ureteral dilation on MRI suggest the diagnosis of parametric endometriosis. In a study by

Barot et al. [73], MRI had 83.3% sensitivity and 98.6% specificity in diagnosis of endometriosis located in lateral pelvic compartment.

Magnetic Resonance Imaging (MRI) is one of the best imaging techniques for the preoperative diagnosis of endometriosis. MRI has a high specificity (> 90%) in determining endometriomas. The sensitivity and the specificity of MRI to detect RVS involvement has been reported as 81% and 86%, respectively.

5.Other Diagnostic Methods in Endometriosis

Although endometriosis is known as a benign disease, complications like rectovaginal fistula, primer or seconder colostomy, ileostomy, sepsis, heavy blood loss, and bladder or bowel dysfunction can be seen after endometriosis surgery. [74]

Preoperative evaluation of rectovaginal endometriosis, particularly in patients with bowel infiltration, is the optimal approach for surgical planning.[74]

Many authors believe that colonoscopy is a useful method in excluding other diagnoses rather than confirming the diagnosis of intestinal endometriosis due to the rare occasion of mucosal infiltration in endometriosis.[75] The results of a study by Kim et al. [76] demonstrated that the most common colonoscopic finding of colorectal endometriosis is distortion, recess, intestinal lumen, and granulation-like mucosal changes with polyps, mass, and erythema. Histological diagnostic value of endoscopic biopsy increases with the presence of surface nodularity. In a study which set out to determine intestinal involvement by colonoscopy in patients with endometriosis, X et al. found that in 76 patients, 38 had serosal, 28 had muscular, 8 had submucosal, and only 2 had mucosal involvement.[75] Sensitivity,

specificity, positive predictive and negative predictive values related to colonoscopy use in the diagnosis of intestinal endometriosis were reported as 7%, 98%, 85%, and 58%, respectively.[75]

Given all that, colonoscopy is not routinely recommended in patients with deep pelvic endometriosis. The necessity of bowel resection should not be excluded by obtaining only a negative colonoscopy result.

Cystoscopy

Deep endometriotic involvement in the urinary system is seen in 1-5% of women with all endometriosis. [77] The most common endometriosis location in the genitourinary system has been reported as bladder (84%) and ureters (10%).[74] Urethral involvement is divided into two forms as follows: extrinsic form (80%), which occupies submucosa and adventitia, and intrinsic form, which (20%) occupies mucosa and muscularis propria.[77] Decreased urinary frequency, urgency, dysuria, and hematuria are among the urinary system symptoms in bladder involvement. Urethral involvement should be considered in the presence of flank pain. It should also be remembered that 50% of patients may be asymptomatic. [77]

Although history and imaging methods are considered sufficient in the diagnosis of endometriosis-related genitourinary lesions, cystoscopy is also recommended to confirm the lesion and make a differential diagnosis and histological diagnosis with biopsy.[78]

Contrast Agents

Recognition of peritoneal endometriosis lesions during laparoscopy can be difficult because the lesions are polymorphic and have microscopic dimensions. In order to overcome these difficulties in the diagnostic process, endometriotic tissues, which cannot be detected during surgery, can be distinguished from healthy tissue using contrast agents.[79]

In the review of 9 studies in which intraoperative endometriotic lesions were evaluated by using contrast agents; In 4 studies, 5-aminolevulinic acid (5-ALA), in 2 studies, methylene blue (MB), in one study, indigo carmine (IC), and in 1 study, bloody peritoneal fluid was used. [6]Besides, the use of Indocyanine green (ICG) has also been used to evaluate sentinel lymph node involvement in cases with both endometriosis and gynecological cancers in recent years.[79]

5-ALA, the precursor of Protoporphyrin IX, has been used in a wide range of treatments in urology, dermatology, gastroenterology, neurosurgery, and gynecology. [80,81] It is applied as an oral solution dissolved in mineral water or juice before surgery. The solution dose in the application ranges from 1 to 30 milligrams per kilogram, as there is no consensus. [82,83] Due to the risk of phototoxicity, it is necessary to filter the operating room lights and cover the skin. Methylene blue has been used for several purposes for years, such as imaging sentinel lymph nodes in breast cancer surgery, imaging ureters in urology, and a long evaluation of tubal patency in gynecology. [84,85]Using a methylene blue together with fluorescent imaging, it is reported that the endometrial tissue is retained more than normal peritoneal tissue. [86]

Indigo Carmine (IC) is used in urology to localize ureteral openings during cystoscopy and ureter catheterization. In addition, IC solutions are occasionally utilized in obstetric surgery to detect amniotic leaks. [87,88]

Indocyanine green (ICG) was used as a contrast agent by the FDA in 1959. It was then used in medicine since the late 1950s for various purposes, such as measuring cardiac output, examining liver function, and examining the role of retinal vessels. In gynecology, it is used in sentinel lymph node mapping with fluorescence imaging methods in patients with endometrial cancer. [89]

Fine Needle Biopsy

Fine needle biopsy, is a fast and accurate method not only in diagnosis of endometriosis before and during surgery, but also, to certain the location of the lesion, particularly, in case of incisional endometriosis.[90]

Colonoscopy, cystoscopy and contrast agents can be very useful ancillary tools in planning of surgery, particularly in cases with deep endometriosis. Colonoscopy may be insufficient for diagnosing endometriosis with intestinal involvement, and cystoscopy should be recommended in patients with hematuria.

6. New methods for the diagnosis of endometriosis

The current gold standard diagnostic method of the endometriosis is laparoscopic surgery, which allowed visual evaluation of the peritoneal cavity and histological diagnosis of endometriotic tissue[91-94]. Although vaginal ultrasonography and MRI have sufficient diagnostic capability, they are inadequate to the determination of peritoneal nodules and adhesions, especially for deep infiltrative endometriosis patients.[16] Some biomarkers deliberated to play a role in the pathophysiology of endometriosis have been investigated in peripheral blood and endometrial tissue samples. [93] However, a meta-analysis reported that anti-endometrial antibodies, peripheral blood biomarkers such as interleukin-6 (IL-6), CA-19.9, and Ca-125, have insufficient sensitivity and specificity for diagnosing. The final results of recent studies have failed to present satisfying outcomes, and the development of new technologies led to intensifying the studies for the latest diagnostic methods.

One of the first trials is micro RNA (miRNAs) studies. [95] miRNAs are short, non-coding RNA structures that can be released into tissue and circulation. They are included in exosomes that protected from endogenous RNase degradation due to their combination with specific protein complexes. [96] Known RNA fragments consisting of 18-23 nucleotides to modulate gene expression. [97] Up till now, approximately 2500 miRNAs have been identified in the human genome. [98] They may be responsible for gene expression involved in the development of endometriosis.[99] miRNAs expressed in all tissues and regulate many cellular functions, including cellular differentiation, proliferation, and apoptosis. [100]Most miRNAs are localized in the cell, but significant miRNAs have also been detected in extracellular body fluids such as plasma, spinal and follicular fluid, saliva, and urine. [101]

Many studies in recent years have found that [102-104] miRNAs are abnormally expressed in endometriotic lesions, tissues, plasma, and other body fluids; hence their diagnostic value has become the center of interest in recent years.[105, 106]However, general agreement could not be reached due to different results conducted on this subject. [107]

A meta-analysis, which designed to investigate the diagnostic rate of circulating miRNAs in endometriosis patients showed that [108], specificity 0.86 (95% CI 0.79–0.90), sensitivity 0.88 (95% CI 0.80–0.93), positive predictive value 7.05 (95% CI 4.20– 11.84), the negative predictive value is 0.16 (95% CI 11–0.24). The area under the ROC curve was 0.93. The results indicated that miRNAs have a high diagnostic value in endometriosis. [108] Also, Burney et al. evaluated that miRNAs of ectopic endometrium with or without endometriosis patients, miR-21-5p, are the most differently expressed miRNA in the endometriosis. [108] On the other hand, Liang et al. found that many miRNAs, including miR-200c and miR-638 and let-7, were abnormally expressed in the disease.[109]

Moustafa et al., designed a prospective study including six miRNA levels by quantitative polymerase chain reaction (PCR), in 41 endometriosis patients and 59 healthy control groups.[95] The study showed that levels of miR-125b-5p, miR-150-5p, miR-342-3p and miR-451 were significantly higher in endometriosis patients. At the same time, miR-3613-5p and let-7 were found considerably lower. Also, they examined the relationship between miRNA expression levels and ASRM stages of endometriosis, all miRNAs were expressed differently in patients with Stage I / II and Stage III / IV endometriosis compared to the control group. Still, the difference between Stage I / II and Stage III / IV was not significant.

Furthermore, they showed that miRNA expression levels were not significantly affected by menstrual cycle phase or hormonal drugs.[95] These studies showed that expression changes, especially in Let-7 and miR-200 family, occur as promising new serological markers. [111- 115] On the other hand, some studies have found lower sensitivity and specificity results in miRNAs values. Vanhie et al. reported that miRNA diagnosis was limited in endometriosis patients since the area under the curve was 60% for 42 miRNA expression. [106] Besides, miRNA expressions can be affected by many factors, including ethnicity, age, body region, and sample processing procedures (qPCR and NGS). [99, 106,116]

Although the initial results of mi RNA studies are fairly promising, it is unlikely to use them in daily practice because of the insufficiency of available data, defined various miRNA types and depending miRNA expressions on tissue and technique difficulties.

Another non-invasive diagnosing method is the Raman spectrophotometer. Raman spectrophotometry provides information on the molecular structure and chemical bonds of

substances by detecting inelastic distributed photons. [116] Based on this hypothesis amount of protein and antigen biomarkers in the blood changes of endometriosis, different chemical contents in the blood or tissue can be detected by Raman spectrophotometry.[117]Parlatan et al. showed that sensitivity 80.5% and specificity 89.7% diagnosis of endometriosis using Raman spectrophotometry. [117] Besides, Lieber et al. reported that using Raman spectrophotometry can detect either normal or endometriotic tissues from benign-cystic or malignant tissues. [118]Notarstefano et al. showed that the Raman micro-spectrophotometer could distinguish luteinized granulosa cells and endometrioma. [119]

Recent studies showed that genetic polymorphism might have played a role in the development of endometriosis. [120] Transcriptomic and proteomic analysis of blood and endometrial fluids, which categorized "omic" approaches, have been used to evaluate disease severity of endometrial diseases and even implantation for endometriosis patients. [121]

Genomic study is a biotechnological approach of an organism that examines the whole genes by various techniques and different genetic features in the target groups. [121] Various techniques are used in this investigation; Genome-Wide Association Studies (GWAS), Whole Genome Sequencing (WGS), Next Generation Sequencing (NGS), Whole Exome Sequencing (WES), Single Nucleotide Polymorphisms (SNPs) and RNAseq which consists of many different techniques.[122] Based on the studies on twins, heredity in endometriosis patient was estimated approximately 50%. [123]

Genomic fields, especially on 10q26, 20p13 and 7p15.2 chromosomes, may be associated with the risk of endometriosis. [124] Eight GWAS analysis performed on women with different ethnic origins, and these studies emphasized that there were increased signals in the presence of stage III / IV endometriosis. [125] Genes closest to risk have been reported as

GREB1, VEZT, FN1, IL1A, LINC00339-WNT4, KDR, SYNE1, CDKN2BAS1, PARP1P2, CCDC170, CDC42, and FSHB genes. [121-125]Rahmioglu et al. showed their meta-analysis [126] total of 58,115 cases, and 733,480 control groups use 15 GWAS, 27 genetic loci associated with endometriosis, and infertility patients which stage I / II and stage III / IV endometriosis. 78 % locus were found larger effect sizes in stage III / IV compare to stage I / II endometriosis. Besides, a greater locus rate as 63% was observed in cases with endometriosis-associated infertility compared to patients with endometriosis-only. These results suggest that specific variants can cause subtypes of endometriosis through different pathways.

Some studies studying those epigenomic modifications such as DNA methylation and histone modification, which affected expression without changing the DNA sequence, can cause endometriosis by altering genes.[121-127] Dyson et al. [128]reported the changes in methylation of HOX gen family, nuclear receptor genes, and transcription factors in GATA family (GATA 6) of total 403 genes for the pathogenesis of endometriosis. They concluded that a higher methylation rate was observed in stromal cells of the endometrium.

In addition, the nuclear receptor of Steroidogenic factor 1 (SF1) methylated 12,000 times higher than that in endometriotic stromal cells was found in the relevant studies. [129] Furthermore, some studies have discovered highly elevated estrogen receptor beta (ERb) expression in endometriotic stromal cells, depending on the hypomethylated promoter region in the ESR2 gene [130] which level was 142 times higher than the normal endometrium.[121] Similarly, RAS / RAF / MAPK and PI3 kinase signaling pathway genes irregularity were detected, and it may have an effected on the pathogenesis of the disease. [131]

Although all studies on omics and endometriosis also seem promising in defining new therapeutic targets, establishing personalized treatment protocols, and predicting response to treatment, results cannot be generalized due to gaps in the studies such as designs and comparability of data.

Hundreds of nominate gene association studies have been tried, but most of the results of presumed genes have not been repeated. [133] Although it is deliberated that GWAS studies may a primary role causing endometriosis for genetic disorders, various biased approaches such as designing different groups and differences same phenotypic features eliminate the reproducibility of the same results. [121] Therefore, not only genes to the development of endometriosis but also hormonal, functional, autoimmune, angiogenetic, inflammatory, proliferative and apoptotic processes, effects of oxidative stress and metabolism, various polymorphisms in the gene loci affecting the cell cycle phase, changes in tumor suppression genes have been associated with endometriosis. [134]

Consequently, using a biomarker panel with good sensitivity and specificity would be more useful than the use of a single biomarker for the diagnosis of a complex disease such as endometriosis. New "omics" technologies and multiplex immunoassays may help to discover more biomarker panels.

The main goal of these studies is to find a new biomarker by combining large numbers (up to 1000) and a wide variety of proteins (cytokines, chemokines, adipokines, growth factors) using antibody sequence technology. However, no biomarkers have been approved for clinical use yet. Although blood tests can be practiced, there is not any blood test being provided superior to anamnesis, physical examination, and high-quality imaging. More and further researches are needed to be carried out to evaluate new biomarkers related to how it is changing after endometriosis treatment, their levels in infertile patients, stage of the endometriosis disease, or their relationship with pain scores.

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