



Literature review: diagnostic and treatment challenges of endometriosis in premenopausal women

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Abstract

Background and aim. Endometriosis is an inflammatory disease that highly decreases the quality of life. The gold standard of diagnosis is considered laparoscopy with tissue biopsy, which can often lead to excess surgical interventions. To this day there is an ongoing discussion about the best treatment for endometriosis, which has led to multiple different guidelines and no clear conclusion. The aim of this review is to discuss whether diagnostic laparoscopy can be safely replaced by non-surgical imaging techniques and to compare different treatment guidelines for endometriosis.

Materials and methods. To evaluate whether transvaginal ultrasound and magnetic resonance imaging can take the role of diagnostic laparoscopy with tissue biopsy, the literature research using PubMed and Google Scholar databases was performed. We also reviewed different endometriosis treatment algorithms to try and depict the best treatment method of today.

Results. Radiological endometriosis diagnosis although highly sensitive and specific does depend on the disease location. Nevertheless, it should be the primary choice for diagnosis as it carries less risk for the patient. Most of the treatment algorithms are based on the main symptoms: pain and infertility. The guidelines agree that medical therapy should be the primary choice of treatment. However, surgery is still irreplaceable while removing already existing endometriotic lesions.

Conclusion. Non-surgical diagnosis can safely replace diagnostic laparoscopy with tissue biopsy in diagnosing endometriosis. Pharmaceutical therapy is the first choice for treatment when the primary symptom is pain. If the main complaint is infertility treatment should depend on the size of the endometrioma and fertility.

Keywords: peritoneal endometriosis, endometriomas, transvaginal sonography, magnetic resonance imaging, first-line therapy.

1. Introduction

Endometriosis is an inflammatory disease defined as lesions of endometrial-like tissue outside the uterus. The condition is associated with infertility and pelvic pain (2). This topic is important to discuss as it is estimated to affect about 10% of reproductive-age women and the main symptoms highly decrease life quality by damaging personal relationships and productivity (3). Furthermore, a definitive diagnosis of endometriosis requires diagnostic laparoscopy with tissue biopsy. Therefore, the actual prevalence is uncertain. Also, the average time between the first symptoms to diagnosis is about seven years; thus, most of the time, the diagnosis is late (2,4,5).

Endometriosis may manifest with various symptoms such as dysmenorrhoea, dyspareunia, ovulation pain, chronic pelvic pain and infertility, or it may also be asymptomatic. Even in symptomatic cases, it is challenging to diagnose endometriosis based on manifestation alone because those are not pathognomonic symptoms, and they overlap with pelvic inflammatory disease and irritable bowel symptoms (6). Historically, there are many mentions of women having symptoms characteristic of endometriosis. However, there are two main reasons to consider historical context critically. Firstly, as mentioned previously, endometriosis has similar symptoms to irritable bowel syndrome and pelvic inflammatory disease. The second reason closely related to the first one is that to this day, the only definitive diagnostic test for endometriosis is considered laparoscopy with tissue biopsy, and it started being performed only recently compared to the first mentions of endometriosis-like manifestations, which date more than 4000 years ago (3,6). As the understanding of the disease changed, it is important to mention that the first person to diagnose endometriosis microscopically in 1860 was Karl von Rokitansky (3).

Nevertheless, Cullen was the first to precisely describe peritoneal endometriosis mentioning ten places in the pelvis where he had found endometrial-like lesions (7,8). He also found endometriotic lesions in myomas and the uterus and called it "adenomyoma" (7). Later, Sampson described several cases of ovarian endometrioma, which he called "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary". Sampson also proposed implantation theory which states that a retrograde flow of blood mixed with full endometrial tissue going through Fallopian tubes into the peritoneal cavity is the main cause of the disease (3,7). The celomic theory is another attempt to explain the cause of endometriosis, except in this theory, the endometrial tissue does not come from the uterus. Coelomic metaplasia describes the transformation of normal peritoneal tissue to ectopic endometrial tissue; this transformation happens because of hormonal or immunological triggers (7,9). There are even more theories, theory of abnormal embryogenesis, stem cell theory, autoimmune disease, or immune deficiency theory. The reason for such a variety of possible theories is that none of the mechanisms can fully explain this disease (7). Therefore, it is important to discuss today's diagnostic and treatment standards because with the changing comprehension of the disease, arising new theories and genetics playing a role in pathogenesis, some diagnostic and therapeutic methods may have outlived their usefulness and others may have just recently come into play.

2. Materials and Methods

A search was performed using PubMed and Google Scholar databases using these terms: peritoneal endometriosis, endometriomas, non-invasive diagnosis, pharmaceutical therapy and diagnostic laparoscopy. Only articles in English were included.

3. Results

3.1. Diagnosis

To this day, diagnostic laparoscopy with tissue biopsy is considered the gold standard for diagnosing endometriosis (10). Nevertheless, medical equipment has immensely improved over the years, so in this part, the main question is whether laparoscopy is still the gold standard or maybe some other diagnostic techniques have caught up with it, thus, allowing doctors to avoid invasive diagnoses. Only the diagnosis of superficial and ovarian endometriosis will be considered in this article. The term superficial endometriosis in this review includes both superficial peritoneal lesions and lesions on the ovarian surface. Also, the term will be used as a synonym for peritoneal endometriosis as more studies have focused on superficial peritoneal endometriosis, and superficial ovarian endometriosis is poorly described; therefore, many authors chose to use these terms as synonyms (11).

3.1.1 Anamnesis and clinical examination

Before discussing imaging techniques and other diagnostic methods, we will concentrate on anamnesis and clinical examination, which are often neglected. Often the primary manifestation of endometriosis is pain which can be dysmenorrhea, dyspareunia or chronic pelvic pain. However, the pain is not pathognomonic to endometriosis and can be caused by non-gynecological conditions. Another common complaint is infertility. Charles Chapron et al. (2019) suggest a specific questionnaire to evaluate the possibility of endometriosis in women (12). According to the patient's history, all the points in this questionnaire are indicators of possible endometriosis. The questionnaire must be detailed and involve the family history of endometriosis, in utero or early childhood factors, adolescent history, phenotype,

infertility, pain characteristics, menstrual symptoms, fatigue syndrome, associated comorbidities, previous obstetrical history and previous history of pelvic surgery (12). When considering clinical examination, it is best to perform it during menstruation as this improves detection. The physicians should look for bluish lesions on the vaginal fornix suggesting superficial endometriosis. Also, palpable nodules of the rectovaginal wall, posterior cul-de-sac, uterosacral ligaments and retroverted uterus may point to deep infiltrative endometriosis. If adnexal masses are detected, ovarian endometrioma should be considered. However, normal physical examination does not exclude endometriosis diagnosis. Therefore, it should be done at least twice if a woman is complaining of pain or infertility. The first time it may be done by a physician who is not an expert in endometriosis as a routine examination. If, after this examination, the results are normal, then transvaginal ultrasound should be performed; again, the physician sonographer does not have to be an expert in the field of endometriosis. Finally, if the results after the clinical examination and initial ultrasound are normal, then both of these steps should be repeated by an expert. Nevertheless, if endometriosis is found by clinical examination, the extent of it must be evaluated by more precise methods such as transvaginal ultrasound, magnetic resonance tomography (MRI) or diagnostic laparoscopy. The same methods should be used if the clinical examination is normal, as this does not exclude the diagnosis. (12,13).

3.1.2 Imaging or diagnostic laparoscopy

Before comparing imaging techniques with diagnostic laparoscopy, it is important to mention why it would be beneficial to avoid surgery. First of all, surgical intervention laparoscopy carries certain risks, such as

pelvic organ injury (about 2% risk), damage to major blood vessels (0,001% risk) and very small, nonetheless, existing risk of mortality (0,0001%). It also requires full anesthesia and may cause adhesions after the surgery. Furthermore, laparoscopy is expensive, and even though it is considered the gold standard for the diagnosis of endometriosis, only about one-third of the women who undergo diagnostic laparoscopy are diagnosed with endometriosis (1,14). Finally, the sensitivity and specificity of laparoscopy highly depend on the surgeon's skills and must be followed by histological evaluation. However, it is essential to mention that diagnostic laparoscopy can be extended to remove endometriotic lesions, managing two procedures simultaneously (1,13). Therefore, it is critical to determine whether any non-invasive imaging techniques have enough sensitivity and specificity to diagnose endometriosis and single out the cases where diagnostic laparoscopy would be necessary.

3.1.3 Transvaginal ultrasound

Considering transvaginal ultrasound (TVUS), the diagnosis process should be divided into two parts first-line diagnostic investigation and second-line diagnostic investigation. The first-line diagnostic investigation consists of a physical examination and TVUS. During the ultrasound, the operator should evaluate the uterus and ovaries as well as the adnexa and the mobility of the uterus (normal, reduced or fixed). The second-line diagnostic investigation involves targeted pelvic examination and TVUS performed by an expert clinician along with pelvic MRI (13,15). Supposing endometriosis is not detected during the first-line investigation. In that case, it is vital to investigate by an expert because the variance of endometriotic lesions and distorted anatomy caused

by adhesions and fibrosis complicates sonographic evaluation (16). Ovarian endometrioma and adenomyosis are probably the easiest forms of endometriosis to diagnose by TVUS. In premenopausal women, it can be seen as cystic lesions with ground glass echogenicity (17). The challenge arises if an endometrioma is smaller than 2 cm, as it may be overlooked. It can also be confused with corpus luteum or luteum cysts, ovarian fibroid, tubo-ovarian abscess, teratoma or dermoid cystadenoma. Also, it is imperative not to mistake malignant tumors for endometrioma in postmenopausal women (11,13). For differential diagnosis of endometrioma, cystic corpus luteum and malignant tumor, Color Doppler can be helpful as it shows the vascular flow (17,18). Corpus luteum cyst typically has a circular flow, and malignancy should be suspected if there is the presence of vessels in papillations (17). Also, for TVUS diagnosis, the International Ovarian Tumor Analysis (IOTA) group's simple descriptors perform well in differentiating adnexal masses suspected to be endometrioma (19). Alternatively, #Enzian classification may be used for TVUS endometrioma diagnosis as well as for diagnosing pelvic endometriosis (20). Patients with endometriomas are likely to have deep endometriotic lesions; therefore, they should be evaluated for DE (13).

In 2016 Vicki Nisenblas et al. meta-analysis TVUS qualified as a SpPin triage test, with 93% sensitivity and 96% specificity, and approached the criteria for replacement and SnNout triage test (1). Nonetheless, for pelvic endometriosis, TVUS showed high heterogeneity in sensitivity and specificity. The mean sensitivity was estimated to be 65% and specificity 95%, thus not qualifying as a replacement test but approaching the criteria for SpPin triage test (Table 1) (1). The possibility of diagnosis highly depends on the

site of endometriosis; also, some newer publications suggest that TVUS can replace diagnostic surgery, which may be attributed to improved technology and

skills. However, none of the publications specifies on TVUS models they were using, and clinicians' skills are complicated to determine objectively (1,17).

TVUS	Sensitivity	Specificity	SpPin triage test	SnNout triage test	Replacement
Endometrioma	93%	96%	Qualified	Approached the criteria	Approached the criteria
Pelvic endometriosis	65%	95%	Approached the criteria	Did not qualify	Did not qualify

Table 1. The sensitivity and specificity of TVUS diagnosing endometrioma and pelvic endometriosis. For neither of types of endometriosis TVUS met the replacement criteria but qualified as SpPin triage test and approached the criteria for both SnNout triage test and replacement for endometrioma and only approached the criteria for SpPin triage test for pelvic endometriosis (1).

3.1.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is typically considered the second-line investigation of endometriosis because of the cost and smaller availability. However, it has better diagnostic accuracy than TVUS in detecting pelvic endometriosis according to some authors and is less operator-dependent (21). Considering the preparation for MRI, the patient should fast for about 2 – 3 hours prior to the examination only if evaluating deep pelvic endometriosis. Some studies showed more precise results if the examination is performed not during menses; however, these results differ in different studies; therefore, it is not considered a strong recommendation, but it may be helpful if MRI is not performed during menses. Fat-suppressed T1-

weighted sequence in some studies was considered the gold standard for diagnosing endometriomas. It is also helpful for differential diagnosis from dermoids which are fat-containing lesions; therefore, they will be ruled out (22,23). T2-weighted sequence without fat suppression should be used for pelvic endometriosis detection (23).

In Vicky Nisenblas et al. (2016) meta-analysis MRI for endometriomas showed 95% sensitivity and 91% specificity, meeting the criteria for a replacement test and SnNout triage test as well as approaching the criteria for SpPin test (1). As for pelvic endometriosis, the sensitivity was only 79% and specificity 72%, which did not meet or approach any of the criteria (Table 2) (1).

MRI	Sensitivity	Specificity	SpPin triage test	SnNout triage test	Replacement
Endometrioma	95%	91%	Qualified	Approached the criteria	Qualified
Pelvic endometriosis	79%	72%	Did not qualify	Did not qualify	Did not qualify

Table 2. The sensitivity and specificity of MRI diagnosing endometrioma and pelvic endometriosis.

Diagnosing endometrioma MRI qualified for both replacement and SpPin triage test as well as approached the criteria for SnNout triage test. For pelvic endometriosis sensitivity and specificity was low, therefore, it did not qualify for any of the tests (1).

None of the tests was accurate enough for the overall diagnosis of endometriosis. However, depending on the sight and type of the endometriosis TVUS and MRI can replace diagnostic laparoscopy (1,24). Furthermore, according to the 2022 Guideline of European Society of Human Reproduction and Embryology (ESHRE), laparoscopy is no longer the gold standard and is only recommended in cases where imaging results were negative or empirical treatment was either unsuccessful or inappropriate (25).

3.2. Treatment

When considering the treatment of endometriosis, there are two main categories: non-surgical treatment, which involves analgesics as well as hormonal treatment, and surgical treatment. Hormonal therapy is mainly based on ovary suppression as endometriotic lesions are estrogen-dependent (3). In this part, we will not go into specifics of different treatment options. The main goal is to discuss for which patients only non-surgical treatment will suffice and in which cases surgery is necessary.

3.2.1. Pharmaceutical and empirical treatment

There are a few limitations of the existing pharmaceutical treatment. Firstly, it is mainly used for pain management and has little effect on reducing

endometriotic lesions. Also, no medical therapy today is effective enough to treat already existing endometriomas and does not affect pelvic adhesions (3,26,27). Also, almost all of these treatment options, except for non-steroidal anti-inflammatory drugs, dydrogesterone and dienogest, inhibit ovulation; therefore, are not helpful for women trying to conceive (3,28). However, pharmaceutical treatment should be the primary choice as both diagnostic laparoscopy and endometriosis surgery carries certain risks. The main surgical complications of removing endometriomas include diminished ovarian reserve, which may lead to infertility or premenopause, as well as basic laparoscopic complications (3,29). Women experiencing only pain with no other symptoms and no other indications for surgery should be considered for medical therapy without histological endometriosis confirmation. However, effective empirical therapy does not prove endometriosis diagnosis (3). Medical therapy can be divided into first-line and second-line. The first-line consists of combined oral contraceptives and progestins with or without NSAIDs which can be prescribed empirically. The Second-line treatment consists of GnRH analogs and aromatase inhibitors which are only prescribed if the first-line therapy is ineffective or not tolerated as they have more side

effects and GnRH analogs need add-back therapy after six months of use (3,28). Empirical therapy should usually start when a patient complains of dysmenorrhea, and an initial examination is performed without any diagnosis of pelvic pathology. NSAIDs and/or hormonal suppression are prescribed as, most of the time, it is primary dysmenorrhea. If symptoms do not improve in 3 – 6 months with empirical treatment, secondary dysmenorrhea should be suspected; which most common cause is endometriosis (30). S. Chaician et al. (2017) conducted a systematic review and meta-analysis comparing surgical and medical therapy for patients experiencing pain (31). No statistically significant difference was seen between pharmaceutical therapy and surgery. However, the author emphasizes that studies were based on follow-up, and all patients that did not come back to clinicians were considered cured. Nevertheless, this assumption is not necessarily valid, and there is a high chance that these patients went to other clinics or decided to seek alternative treatment methods. Therefore, it is quite difficult to evaluate the exact impact of both medical therapy and surgical treatment (31). Some experts suggest that starting medical therapy with progestins should be the primary choice, especially Dienogest, as it has shown promising results in reducing pain symptoms and increasing overall life quality. Dienogest also has advantages over combined oral contraceptives, such as not having an estrogen component that may stimulate the disease as well as not suppressing ovaries (32–34). An overview of Cochrane reviews also concluded that current data is insufficient to evaluate the effectiveness of oral contraceptives compared to placebo (35).

3.2.2. Ovarian endometriosis: pain and infertility

For many women suffering from endometriosis pain is the first symptom. S. Cosma et al. (2020) suggest an

algorithm based on the two primary symptoms pain and infertility (which will be discussed later) when considering the treatment of endometrioma (36). According to this algorithm, if pain is present, then the size of the endometrioma should be considered. If it is smaller than 3 cm, then medical therapy is the first choice. A fertility scan should be conducted if an endometrioma is larger than 3 cm. In the case of a normal fertility scan, the first choice is medical therapy. If it fails, then surgery should be considered. Given that the fertility scan is abnormal, the patient should be referred to a specialized psychologist for counseling, and further treatment choices should be based on pain management and infertility (36). In this algorithm, if a fertility scan is normal, the first choice is always medical therapy. However, C. E. Miller et al. (2021) suggested an algorithm in which the central aspect dividing surgical and non-surgical patients is the size of an endometrioma when pain is present (37). If endometrioma is 3 cm or smaller, medical therapy should be chosen. In the case of endometrioma being larger than 3 cm, the first choice should be ovarian cystectomy (37). Both articles have analyzed either multiple studies or already approved guidelines and still present differences in their suggested algorithms, thus, presenting the main issue of endometriosis treatment – the lack of an equal systematic approach. C. E. Miller et al. (2021) suggest this algorithm if fertility is desired. If an endometrioma is 3 – 4 cm or smaller, then pregnancy should be attempted without removal of an endometrioma because there is a high chance that this size endometrioma will not cause fertility problems (37). Furthermore, if surgery is performed, it can damage the ovarian reserve. However, if an endometrioma is larger than 3 – 4 cm, ovarian cystectomy should be performed due to the risk of rupture or torsion, and then pregnancy should

be attempted. Assisted reproductive technologies should be considered if pregnancy attempts are unsuccessful despite 1 – 1.5 years of trials (26,38). Another question to be considered if endometrioma was not removed because of the small size is whether there is a chance of endometrioma rupturing during egg retrieval as this may cause pelvic infection or abscess. Also, does endometrioma negatively affect antral follicle count compared to the non-affected side. Finally, the last question C. E Miller et al. suggest asking is whether there is a high risk of implantation failure caused by endometrioma. If any of these last questions are positive, then ovarian cystectomy should be considered (26). S. Cosma et al. (2020) suggest a similar algorithm for infertility treatment (36). If infertility is the main symptom, a fertility scan should be conducted; if it is normal, the patient should attempt natural conception. If natural conception is unsuccessful, assisted reproductive technology can be used. In the case of an abnormal fertility scan, assisted reproductive technology is considered the only choice (36). For patients who do not wish to conceive or have another endometrioma in the same ovary, unilateral oophorectomy may be suggested as it is the best preventative measure for endometrioma recurrence (38).

3.2.3. Peritoneal endometriosis

R. M. Kho et al. (2018) compared major gynecological society guidelines and presented a superficial endometriosis treatment algorithm based on the main symptoms (39). If the patient's primary symptom is pain, then medical therapy is the first choice. If the primary symptom is infertility, then assisted reproductive techniques should be considered. If a woman suffers from both symptoms, she is eligible for medical therapy and assisted reproductive techniques.

Laparoscopic surgery is indicated only when medical therapy fails in relieving pain and in vitro fertilization fails twice (39).

3.3. Surgical techniques

When considering surgical treatment, it is important to remember that incomplete removal of endometriomas can lead to recurrence, and too aggressive treatment can cause hormonal imbalance and damage the ovarian reserve resulting in fertility problems. This is very important if a small endometrioma is found accidentally during a routine examination as it may not cause any symptoms because of the small size; therefore, surgical removal should be considered more damaging than therapeutic (26). If surgery was deemed necessary, then ovarian cystectomy should be performed instead of drainage and coagulation because it is considered to have a lower recurrence rate, better pain relief after surgery and increased spontaneous pregnancy rates (40–42). If there was a previous ovarian surgery, the endometriosis surgery should be considered carefully and individually as reoperation may lead to reduced ovarian function or complete loss of the ovary (39). M. F. Shaltout et al. (2019) conducted a randomized controlled trial dividing women with endometriomas into four groups (43). The first group of patients underwent laparoscopic drainage surgery, the second group had laparoscopic cystectomy, the third group had laparoscopic drainage with insertion of Surgicel inside the remaining ovary, and the fourth group also had the insertion of Surgicel, but instead of drainage, laparoscopic cystectomy was performed. The patients received a two-year follow-up for both recurrence of endometriomas and ovarian reserve evaluation. Women who underwent laparoscopic cystectomy and had Surgicel insertion in the remaining ovary had the

lowest recurrence rate compared to the other groups. However, the drainage and Surgicel group had the smallest decrease in ovarian reserve. This study shows that the best option for recurrence prevention is laparoscopic cystectomy, and it can be even more efficient by adding Surgicel. However, it is essential to evaluate ovarian reserve before surgery as cystectomy causes higher depletion than drainage (43). Patients with big endometriomas or challenging anatomy may benefit from a two- or three-stage surgical treatment to preserve fertility. Laparoscopic endometrioma drainage and coagulation are the first steps in the two-stage approach, followed by adjuvant GnRH analogue therapy. The third stage can be carried out if endometrioma persists following treatment, in which case a second laparoscopy can be done (44).

Regarding peritoneal endometriosis, there is still a debate on which technique is superior as there was seen no difference in pain, recurrence, or fertility outcomes after surgery, either ablation or excision (39,45). Probably the best option when operating peritoneal endometriosis is to evaluate the depth of the endometriosis lesion. For more superficial lesions, ablation may be sufficient, and for deeper ones, excision should be the first choice as ablation emits much energy, which damages surrounding structures (41).

3.1 Medical therapy after surgery

According to some articles, there is no substantial evidence that post-surgical medical therapy improves pain after 12 months compared to surgery alone, though there might be a lesser chance of recurrence if medical therapy is used post-surgery. Only moderate evidence shows improved pregnancy rates using medical therapy after surgery (46,47). However, based

on A. Zakhari et al. (2020) meta-analysis and A. Murji et al. (2020) literature review and expert commentary, the use of Dienogest postoperatively significantly reduces the risk of endometriosis recurrence compared to those who receive no medical treatment (32,48).

4. Conclusion

Non-surgical diagnosis of endometriosis even though in some cases highly sensitive and specific is very dependent on endometriosis location, therefore, diagnostic laparoscopy cannot be yet fully replaced. Nevertheless, TVUS and MRI should be the first choice to avoid excess operations and, therefore, according to the 2022 ESHRE guideline, it is the primary choice for diagnosis. One of the shortages we found in all the research is that the specific models of TVUS and MRI are not mentioned or compared which could be helpful to make results more standardized. Also, for both non-surgical and laparoscopic diagnostic the importance of a specialist is emphasized, however, this criteria is fairly difficult to evaluate objectively. When it comes to treatment the research and guidelines agree that medical therapy should always be the first choice, preferably starting with Dienogest. Surgical treatment should only be considered if medical therapy fails or the size of an endometrioma is larger than 3 – 4 cm as medical therapy most likely will not reduce the size of it and it has a higher chance of rupture. It is important to evaluate the ovarian reserve irrespective of the primary symptom when choosing a surgical technique for endometriomas as they may impact it differently, thus, impacting future fertility. The main aspect of peritoneal endometriosis surgery should be the depth of the lesion.

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