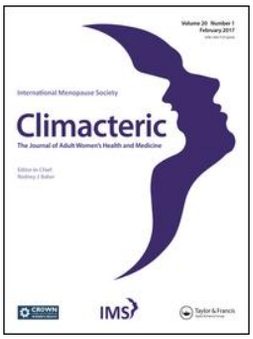

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REVIEW

Evaluation and management of endometriosis

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ABSTRACT

The initial diagnostic investigations for endometriosis are physical examination and pelvic ultrasound. The pelvic examination should include a speculum examination and vaginal palpation. Mobility, fixation and/or tenderness of the uterus and site-specific tenderness in the pelvis should be evaluated. Transvaginal ultrasound and pelvic magnetic resonance imaging are recommended to evaluate the extent of the endometriosis and to determine whether any urinary tract or bowel procedures might also be required during surgical resection. Quality of life should be assessed by using the Endometriosis Health Profile-30, its short version EHP-5 or the generic quality of life questionnaire SF-36. Management of endometriosis is recommended when it has a functional impact (pain, infertility) or causes organ dysfunction. Many gynecological societies have published different guidelines for the evaluation and management of endometriosis. However, the complexity of this disease together with the different available treatments lead to significant discrepancies between the recommendations. Postmenopausal endometriosis should be considered when a patient has a history of symptoms before menopause including dysmenorrhea, dyspareunia, dyschezia, infertility and chronic pelvic pain. Malignant transformation of endometriosis is estimated to occur in about 0.7–1.6% of women affected by endometriosis. Endometriosis is associated with an increased risk of ovarian cancer, specifically clear cell, endometrioid and low-grade serous types.

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Introduction

Endometriosis is defined as a disease characterized by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium, usually with an associated inflammatory process [1]. Endometriosis is seen in 78.37%, 12.55%, 4.54% and 2.55% of women in the age groups of 20–45, 45–50, 50–55 and over 55 years, respectively [2].

Endometriosis is an estrogen-dependent inflammatory disease defined by the presence of endometrial glands and stroma at extra-uterine sites. The disease causes dysmenorrhea, dyspareunia, dyschezia, chronic pelvic pain and infertility. Treatments targeting the hypothalamic–pituitary–gonadal axis or hormone receptors modulate the hormonal balance, consequently inhibiting estrogen synthesis [3].

Pathophysiology of endometriosis

Theories describing the etiology of endometriosis are: implantation of eutopic endometrium from retrograde menstruation; metaplasia of celomic pluripotential mesothelial cells lining the peritoneum into endometrial tissue at ectopic sites; development of misplaced endometrial tissue at the time of fetal organogenesis into endometriosis later in life (theory of müllerianosis); and endometriosis observed in non-traditional locations through hematogenous or lymphatic embolization of cells [4].

In endometriotic lesions, it is hypothesized that critical genes influencing progesterone and estrogen receptor expression have defective methylation. Coupled with increased aromatase expression in the ectopic endometrium, a higher concentration of local estradiol is the result. Furthermore, altered microRNA expression associated with gene transcription and post-translational events leads to cell proliferation or cell survival [4].

Moreover, there is decreased expression of 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) in endometriotic tissue when compared to eutopic endometrium. Consequently, there is a higher local estradiol bioavailability which will stimulate the production of prostaglandin E_2 (PGE_2), causing further stimulation of aromatase activity [5].

Subtypes of endometriosis

Endometrium-like tissue lesions involving the peritoneal surface are referred to as peritoneal/superficial endometriosis. Superficial endometriosis of the pelvic peritoneum is characterized by ectopic growth and function of endometrial tissue extending 5 mm or less under the visceral or parietal pelvic

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peritoneal surface [1]. An ovarian endometriotic cyst is either an invagination cyst or a true cyst with the cyst wall also containing endometrium-like tissue and dark blood-stained fluid. Endometrium-like tissue lesions in the abdomen, extending on or under the peritoneal surface, are defined as deep endometriosis [1]. They might invade adjacent structures, and are associated with fibrosis and disruption of normal anatomy. Deep endometriosis is historically defined as extending 5 mm under the peritoneal surface [1]. Bowel endometriosis is diagnosed when the disease is situated inside the bowel wall. The most affected section is the rectosigmoid area, but lesions can be found in other parts of the gastrointestinal system. The prevalence of deep endometriosis involving the bowel has been reported to be 5.3% and 12% of women affected by endometriosis. The rectum and sigma are the most frequently involved tracts, accounting for about 90% of cases [6].

If endometriosis involves the detrusor muscle and/or the bladder epithelium, the condition is called bladder endometriosis. Endometrium-like tissue can also be seen outside the abdominal cavity, categorized as extra-abdominal endometriosis. Lesions might arise from direct or indirect dissemination of the endometrium during surgery and cause iatrogenic endometriosis [1].

Adhesions (peritoneal) are bands of fibrous scar tissue bridging the abdominal and pelvic organs to each other. Finally, adenomyosis is defined as a form of endometriosis marked by the presence of endometrium-like epithelium and stroma outside the endometrium in the myometrium [1].

Clinical presentation and diagnosis

Endometriosis should be suspected in women (including young women aged 17 years and under) presenting with one or more of the following symptoms or signs: chronic pelvic pain; period-related pain (dysmenorrhea) affecting daily activities and quality of life (QoL); deep pain during or after sexual intercourse; period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements; period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine; and infertility in association with one or more of the aforementioned factors [7,8].

Unless endometriosis has a functional impact (pain, infertility) or causes organ dysfunction, management of endometriosis is not recommended. In the absence of symptoms, no screening is recommended for women at increased risk, either due to genetic factors (a relative with endometriosis) or menstrual risk factors (heavy menstrual bleeding, short menstrual cycle or early menarche). Moreover, patients who were previously treated for endometriosis and are currently asymptomatic do not need to be monitored systematically. Additionally, patients with endometriosis do not require screening for ovarian and breast cancer other than what is recommended in the normal cancer screening programs [9].

A thorough history including onset and duration of symptoms; bleeding pattern (regular, irregular or absent); last menstrual period; previous surgery for endometriosis (type, effect); previous myomectomy or Cesarean delivery; family history of endometriosis; previous non-surgical treatment for endometriosis (type, duration, effect); subfertility including duration of subfertility; treatment for infertility and outcome of fertility treatment; pain (dysmenorrhea, dyspareunia, dysuria, dyschezia, chronic pelvic pain); hematochezia and/or hematuria should be noted [10].

The intensity of the pain should be recorded by letting the patient use either a visual analog scale, a numerical rating scale, a verbal rating scale, the Biberoglu and Behrman score or the McGill Pain Questionnaire [11].

Patient QoL is impaired in those with symptomatic endometriosis [12]. The life course impact of untreated symptomatic endometriosis varies between individuals. A longer diagnostic delay is associated with low work ability and poorer health-related QoL, whereas the severity of pain is linked to impairments in sleep quality, work inside or outside the home, sexual function, mental health and QoL [12]. Two QoL questionnaires – namely the Endometriosis Health Profile-30 (EHP-30) and its short version EHP-5, and the generic QoL questionnaire SF-36 – have also been validated for use in endometriosis. The management of symptomatic endometriosis should include QoL assessment [9,13].

The diagnostic investigation for endometriosis starts with a physical examination consisting of a speculum examination (direct visualization of the cervix and vaginal fornices) and a bimanual pelvic examination. Mobility, fixation and/or tenderness of the uterus should be evaluated carefully. Site-specific tenderness in the pelvis should also be evaluated [10]. The vaginal examination can facilitate the detection of infiltration or nodules of the vagina, uterosacral ligaments or pouch of Douglas. The rectovaginal digital examination may allow the detection of infiltration or mass involving the rectosigmoid or adnexal masses. Rectal examination is highly recommended to assess the lateral and dorsal extension of the disease allowing detection of the patients who are at risk of hypogastric vessel injury and/or hypogastric plexus damage. It also allows the surgeon to evaluate the mobility of the nodule of the dorsal cul-de-sac and thus to predict how difficult the surgery may be [14].

Transvaginal sonography (TVS) is the initial imaging tool for the evaluation of endometriosis. The first step is the traditional evaluation of the uterus and adnexa for adenomyosis or endometriomas. Next, the location of specific tender spots which might reflect disease-specific sites is determined by the probe. Later the cul-de-sac (pouch of Douglas) is examined to determine whether there is deeply infiltrating disease or obliteration (assessment of the sliding sign) [10]. The final step is the evaluation of nodules in the anterior compartment (bladder) and posterior compartment. Fluid contrast in the vagina or rectum can improve visualization of bowel or bladder involvement.

Transvaginal ultrasonography with bowel preparation (TVUS-BP) can also be performed [15]. Saline contrast sonovaginography [16] and rectal water contrast transvaginal ultrasound (RWC-TVS) [17] are other transvaginal ultrasonography (TVUS) techniques available for endometriosis evaluation. By using TVUS, the sensitivity of finding the disease at

the rectocervical or rectosigmoid levels is higher than at the uterosacral ligaments. Magnetic resonance imaging (MRI) and TVUS have similar sensitivity and specificity of disease detection at the uterosacral ligaments (85% and 88%), vagina (77% and 70%) and colorectal region (88% and 92%) [10]. Similarly, MRI with an enema compared with RWC-TVS has similar sensitivity and specificity for the diagnosis of rectosigmoid endometriosis.

Furthermore, rectal endoscopic ultrasound or computed tomography-based virtual colonoscopy can be used [9]. Diagnostic accuracies are higher for TVUS-BP, RWC-TVS and 3.0 T MRI [14].

These investigations aim to determine the location, size and number of endometriosis lesions (nodules or plaques) as well as the level of infiltration (depth of invasion, length of infiltration, stenosis) into the organ/structure involved. Furthermore, the identification of lesions on/in the pelvic wall (i.e. sacral root) [18] and other extragenital localization (abdominal wall, inguinal canal, diaphragm, lung, etc.) with specific imaging techniques is relevant [14].

Before surgical resection of deep pelvic endometriosis, either a pelvic ultrasound performed by an expert or a pelvic MRI is required to determine whether any urinary tract [19] or bowel involvement is present [20]. While assessing the bowel involvement, such factors as multifocal or unifocal presence, lesion diameter, infiltration depth, size, circumference and stenosis will shape the surgical plan [9].

The multiplanar T2-weighted and T1-weighted MRI sequences with and without fat suppression are the technical requirements for diagnosing pelvic endometriosis. The sensitivities and specificities of both transvaginal ultrasound and MRI were compared for the anatomical regions such as the rectosigmoid, rectovaginal septum, uterosacral ligaments [21], vagina, urinary bladder and ovaries [22]. The diagnostic accuracy for the detection of endometriosis in these areas was found to be comparable.

Bladder or urethral endometriosis is best evaluated by MRI [19] or ultrasound imaging performed by an expert physician sonographer [9].

Kidney sonography is mandatory in every patient with deep pelvic endometriosis potentially involving the ureters to prevent overlooking silent hydronephrosis.

Classification systems

A classification system is necessary in order to standardize the optimal treatment strategy and compare the outcomes. Four standard classification systems – namely, the revised American Society for Reproductive Medicine (rASRM) classification, the ENZIAN classification, the Endometriosis Fertility Index (EFI) and the American Association of Gynecological Laparoscopists (AAGL) classification – are in use.

The rASRM classification lacks confirmation between histologically diagnosed endometriosis and the visually diagnosed stage. Secondly, the reproducibility of the rASRM score is poor. Third, severities of pain and infertility are not correlated with the rASRM stage. Fourth, the rASRM classification does not consider the presence of deep infiltrating endometriosis (DIE) in different sites [23].

The ENZIAN classification describes the retroperitoneal structures in detail, which is supplementary to the rASRM classification. The ENZIAN classification can be determined by imaging modalities and used for surgical planning. The disease localization and extent, as described by the revised ENZIAN score, are associated and correlated with the presence and severity of different symptoms. The ENZIAN score will not be accurate if the surgical dissection of the deep invasive lesions is incomplete, or if only imaging is done without surgery [23].

The primary objective of the AAGL Endometriosis Classification Score is to develop a user-friendly scoring system that will correlate anatomy-based finding with surgical complexity. Hence, a reliable preoperative method of determining surgical complexity would help the healthcare provider in planning the surgical approach and consulting the patient regarding the surgical outcomes [10].

The EFI system is used to predict the pregnancy rate in patients with surgically documented endometriosis. IVF outcomes were higher in patients with an EFI score of 6 or higher than in those with a score of 5 or less. Although the EFI score reflects the pregnancy rate better than the rASRM classification, it does not correlate with the pain. Moreover, the total score can vary by the surgeon for the function score given subjectively [23].

National and international guidelines of endometriosis

Recommendations for the diagnosis of endometriosis were compared between seven guidelines [24]. Symptoms, examination, imaging, biochemical and surgical recommendations were analyzed for mild to moderate, severe endometriosis and endometriomas. There was a substantial discrepancy between the recommendations [24].

Ten of the 152 different (7%) recommendations were comparable across the seven guidelines. Regarding the diagnosis of endometriosis, 4 of the 36 recommendations were described by all guidelines. Likewise, 3 of the 30 recommendations regarding the medical management of endometriosis were made across the guidelines [24]. Moreover, nearly a third of recommendations were either supported only by expert opinion or had no reference. Overall, none of the seven guidelines followed the standardized approach to guideline development. The differences between the guidelines are probably due to the lack of collection and reporting of comparable data in each individual work.

The Core Outcomes Measures in Effective Trials initiative have developed 13 core outcomes for endometriosis to standardize outcome selection, collection and reporting across future randomized controlled trials and systematic reviews evaluating potential treatments for endometriosis [25].

Hormonal treatments

The current medical treatments for the management of endometriosis symptoms are suppressive rather than curative. Medical therapy will not increase fecundity or resolve endometriomas or deeply infiltrating diseases. Medical therapy should be based on factors including patient age, patient preference, reproductive plans, pain severity and degree of disease. The intended duration, accessibility, risks, side-effects and cost of treatment are to be discussed. The medical treatment after surgery prevents recurrence and reduces symptoms, hence eliminating the need for repeat surgery or prolonging the time between surgeries [4].

For pain management, the medical therapies are estrogen–progestin combinations, progestins, gonadotropin-releasing hormone (GnRH) analogs, androgenic steroids (i.e. danazol), GnRH antagonists, aromatase inhibitors and selective progesterone receptor modulators [4].

The Endometriosis Guideline of the European Society of Human Reproduction and Embryology (ESHRE) [26] strongly recommends combined hormonal contraceptives, progestogens, GnRH analogs or GnRH antagonists for the reduction of endometriosis-associated pain.

The diminished conversion of arachidonic acid to prostaglandins with menses, causing a reduction in dysmenorrhea and pelvic pain, is achieved by hormonal treatments. No single route of administration (oral, transdermal or transvaginal) of hormonal treatments has been shown to provide superior pain relief [4]. When an estrogen–progestin combination is chosen, the preparation with the lowest possible ethinylestradiol (EE) dose and a second-generation progestin should be preferred [27].

The use of estrogen–progestins and progestins has been associated with a reduction in nerve fiber density, nerve growth factor concentrations and nerve growth factor receptor p75 expression in peritoneal endometriotic lesions, which will alleviate pelvic pain [27].

Progestin monotherapy provides similar ovulation inhibition and amenorrhea and improves dysmenorrhea and pelvic pain symptoms compared with combined oral contraceptives but has fewer unfavorable estrogenic effects than the latter. Progestin-only methods can be administered by oral, intrauterine, parenteral or implantable routes [4].

Between one-fourth and one-third of patients treated with these compounds do not respond to hormonal therapy, due to probable progesterone resistance. The progesterone receptors in endometriotic foci may have diminished activity, resulting in dysregulated progesterone response. Yet at least two-thirds of women with symptomatic endometriosis still respond to estrogen–progestin and progestin therapy [27].

The evidence on the dosage and the duration of GnRH analogs is limited and combined hormonal add-back therapy is to be prescribed. Similarly, the evidence is scarce for the duration and dosage of GnRH antagonist use. Aromatase inhibitors were recommended to those women refractory to other treatments and should be taken together with an oral contraceptive, progestogen, GnRH agonist or GnRH antagonist [27].

Estrogen–progestins were compared with progestins, GnRH analogs and the levonorgestrel-releasing intrauterine system (LNG-IUS) in terms of their effectiveness in reducing endometriosis-related pain, and no single preparation was found to be superior to the others [27]. Progestins were compared between each other, and also with GnRH analogs. The LNG-IUS was compared with GnRH analogs, and with Depo medroxyprogesterone acetate. Similar improvement in pain relief was reported [5].

Progestins do not increase the thrombotic risk, and can be safely used in many women with contraindications to estrogens and those who do not tolerate estrogens [27]. Comparative clinical trials comparing norethindrone acetate (NETA) with dienogest have not shown superior results for either agent [4]. However, the progestogenic effect of NETA is stronger than the dienogest. While NETA has androgenic activity, dienogest is antiandrogenic. Besides, dienogest seems to be equally effective as and better tolerated than NETA [27]. Since NETA is partly metabolized to estrogens it may prevent bone loss during prolonged periods of treatment. NETA and desogestrel have shown similar effects in reducing dysmenorrhea and also deep dyspareunia [27].

For reducing pain at deep penetration, estrogen–progestins might not always exert intended relief and progestins should be preferred for first-line treatment. Nevertheless, a substantial reduction in rectovaginal endometriotic nodules has been observed during the use of a low-dose monophasic oral contraceptive, oral NETA, desogestrel and an LNG-IUS [27].

Surgical treatment

Surgery is recommended by the 2022 ESHRE Guideline for the reduction of endometriosis-associated pain [26]. Excision instead of ablation of endometriosis and cystectomy instead of drainage and coagulation of endometrioma are strongly recommended. Care should be given to minimize ovarian damage.

Surgical removal of endometriosis is required when lesions are symptomatic, impairing bowel, urinary, sexual and reproductive functions. Surgical management of deep endometriosis depends on the location; that is, ureteral involvement, vaginal wall involvement, muscular layer involvement of bowel and bladder, and parasympathetic and somatic nerve invasion [6]. When endometriosis-related pain does not respond to medical treatment, surgery might be offered. The risks of intraoperative and/or postoperative urinary or intestinal complications should be discussed before surgery.

Segmental bowel resection is indicated in the case of large ($>$3 cm), multifocal nodules and stenosis of the lumen $>$40%. In cases of involvement of the muscular layer of the rectum or rectosigmoid, shaving the nodule from the wall of the affected bowel is preferred. When the shaving is not sufficient for removing the nodule from the rectal wall, discoid resection is carried out [6].

Segmental resection could be a feasible option in young patients with the desire to conceive, in whom the possibility of recurrence is greater than in aged women approximating

menopause. Conservative surgery (discoid resection and shaving) which has a higher recurrence rate could be more appropriate in perimenopausal women because of the lower possibility of recurrence. It is important to achieve a high success rate of treatment and low recurrence of disease with a low complication rate [6].

Postoperative hormonal treatment and recurrence reduction

Endometrioma recurrence [28] is seen after the excision of the ovarian cyst [27]. The recurrence seems to be age-related and can be prevented by hormone therapy [29]. The risk of cyst recurrence after excision of ovarian endometriomas is 10% per year for the first 5 years [27].

When hormonal suppression (combined hormonal contraceptive (CHC), progestin, LNG-IUS, GnRH agonist) is initiated within 6 weeks of endometriosis surgery, there is a significant reduction in endometriosis recurrence and pain scores at up to 1 year postoperatively. Medical suppression should be considered and discussed with patients not seeking pregnancy immediately after surgery [30]. Preoperative hormone treatment was not confirmed for use [26].

There is a benefit of postoperative medical treatment compared with no postoperative treatment, independently from the drug regimen used. There is the preventive effect of oral contraceptives on endometrioma reformation after surgical excision. Oral contraceptive users have an 8% risk of endometrioma recurrence in the long term, while never users have a 34% risk. The difference in the preventive effect of different progestins in the oral contraceptive is insignificant when desogestrel, gestodene and dienogest are compared [27].

The information available suggests that hysterectomy is effective in relieving endometriosis-related pain. However, there is a 15% chance that pain will persist and a 3–5% risk that pain might worsen or new symptoms may develop [31,32].

In premenopausal women, ovarian preservation carries a six times greater risk of additional surgery because of recurrent symptomatic disease compared with ovarian removal [33]. At the same time, the detrimental consequences of premature ovarian removal on cardiovascular risk and overall mortality should be carefully discussed with patients before making a shared decision [32,34,35].

Women should be informed that surgery may result in only partial or temporary pain relief and that about half of the patients who undergo surgery because of pain experience symptom recurrence at 2-year follow-up [31,32].

Fertility treatment

The ESHRE 2022 Guideline [26] states that operative laparoscopy might be offered as a treatment option for endometriosis-associated infertility in rASRM stage I/II endometriosis as it improves the rate of ongoing pregnancy. The evidence for the suggestion of intrauterine insemination with ovarian stimulation in infertile women with rASRM stage I/II endometriosis is weak, even though it increases pregnancy rates. Assisted reproductive technology (ART) can be performed for infertility associated with endometriosis, especially if the tubal function is compromised, if there is male factor infertility, in the case of low EFI and/or if other treatments have failed. The recurrence rate of endometriosis after ART is not increased. Ovarian suppression treatment to improve fertility is not confirmed. Furthermore, the extended administration of GnRH agonist prior to ART treatment is not approved. Performing surgery prior to ART to improve live birth rates in women with rASRM stage I/II endometriosis should not be routinely recommended. Likewise, surgery on endometriomas before ART should not be suggested.

When dealing with an endometrioma, some factors to consider are the malignant potential of the cyst, pain score, size of the cyst and family planning of the couple [36,37]. Fertility preservation either through egg or embryo freezing presents issues to counsel with the couple [34,38,39]. When cystectomy is an option, the likelihood of ovarian reserve being reduced should also be discussed with the couple. There is currently insufficient data to support fertility preservation for all women with endometriosis. Couples should be counseled about the possible choices [26].

Patient follow-up

Endometriosis should not be assumed to be progressive. The natural course of the disease might show either deterioration (31%), no change (31%) or improvement (38%) [4].

There is a very low risk of progression of deep endometriotic nodules infiltrating the rectosigmoid in women with amenorrhea induced by medical therapy, pregnancy or lactation [40]. In those patients for whom amenorrhea cannot be achieved, close surveillance with symptoms and routine imaging (every 1–2 years) can be offered to allow early detection of growth and progression of rectosigmoid nodules. Similar recommendations are applicable for endometrioma surveillance [41].

Postmenopausal endometriosis

Endometriosis can affect about 2–5% of postmenopausal patients. Postmenopausal endometriosis should be considered when a patient has a history of symptoms before menopause that could potentially be related to previously unrecognized endometriosis, including dysmenorrhea, dyspareunia, dyschezia, infertility and chronic pelvic pain [42].

Postmenopausal obesity may result in the stimulation of endometriosis lesions, subsequent symptoms or findings on imaging. The agonist activity on endometriosis lesions may occur in the setting of tamoxifen use, resulting in the development or progression of the disease [42]. Menopausal hormone therapy has been associated with postmenopausal endometriosis [43,44]. However, there are case reports of postmenopausal endometriosis in the absence of an identifiable source of systemic estrogen exposure or endogenous agonist activity [45].

Postmenopausal endometriosis is most commonly located in the ovary but is also found in other locations, such as the urinary tract, large and small bowel, stomach, vagina, skin, diaphragm and inferior vena cava [42].

If recurrence of endometriosis is detected while the woman is on menopausal hormone therapy, increasing the ratio of progestin to estrogen or discontinuation of the estrogen component are possible options for management in symptomatic postmenopausal endometriosis [44]. In those receiving tamoxifen, transition to an aromatase inhibitor could be considered [46]. Even in persons not taking tamoxifen, an aromatase inhibitor may be an effective treatment option for the suppression of extra-ovarian estrogen production, a main source of endogenous estrogen in postmenopausal women [42].

In patients with previously identified endometrioma on imaging who do not undergo surgical excision, the Society of Radiologists in Ultrasound recommends a minimum of one pelvic ultrasound per year to monitor the increases in lesion size or evidence of other worrisome changes over time since an estimated 1% of endometriomas undergo malignant degeneration [42].

In patients with previously identified deeply infiltrative endometriosis, a similarly elevated risk of malignancy can be suspected. An initial follow-up MRI in 6 months can be scheduled, followed by individualized intervals depending on the results. If minimal change is noted, repeat imaging in 2–3 years can be considered for follow-up. If there is evidence of change in size or features of the lesions present at 6 months, continued close surveillance with repeat MRI in 6–12 months could be performed [42].

The 2022 ESHRE Guideline gives a weak recommendation for the surgical treatment of endometriosis for postmenopausal women [26]. The use of aromatase inhibitors for postmenopausal women is offered as an option when surgery is not feasible. Estrogen-only preparations should be avoided while combined menopausal hormone therapy should be considered for the relief of postmenopausal symptoms. Nevertheless, even with combined menopausal hormone therapy, recurrence of endometriosis might occur [43,44].

Malignant transformation

Malignant transformation of endometriosis is estimated to occur in about 0.7–1.6% of women affected by endometriosis, with the ovary being the primary site in 79% while extra-ovarian sites account for about 20% of cases [37,47].

Malignant transformation is a rare condition, and the current evidence is available from only case reports and case series. Malignant transformation of endometriotic foci following menopausal hormone therapy was found in various regimens, including estrogen alone, combined estrogen and progestogen, and combined estrogen and testosterone [43]. Hence, the evidence did not support the concept of adding a progestogen to prevent malignant transformation. The pathophysiology of endometriosis is complex. The endometriotic foci can produce their own estrogen microenvironment, which makes them less responsive to progestogen [48]. Fortunately, malignant tumors arising from endometriosis are typically low grade and they have a generally better prognosis compared to ovarian malignancy [46].

The risk of ovarian cancer appears particularly elevated among subjects with a long-standing (>10 years) history of ovarian endometriosis, women with recurrent endometriomas, women with endometrioma over 9 cm in size or rapid growth of the cyst [49], or in the case of de-novo endometrioma in women aged >45 years [50,51].

Predictive indices are used to discriminate malignant epithelial ovarian tumors from benign ovarian endometriomas [52]. The Risk of Ovarian Malignancy Algorithm (ROMA), the Risk of Malignancy Index, the Copenhagen Index and the R2 Predictive Index were used for premenopausal and postmenopausal groups for the differentiation [53].

Artificial intelligence applications are being conducted for early detection [54,55], tumor differentiation [56] and prognostic prediction [57] of ovarian tumors.

The lifetime risk of ovarian cancer in women with a history of endometriosis is about 1.9% compared with 1.4% in the general population. Women with endometriosis are at about tripled risk for clear cell ovarian carcinomas and doubled risk for endometrioid ovarian carcinomas. Most clear cell ovarian carcinomas and endometrioid ovarian carcinomas would arise within ovarian endometriotic cysts that are detectable with TVUS, and they are confined to the ovary for a variable period of time [50].

Two different clinical approaches may be suggested for perimenopausal women with small (<5 cm), typical endometriomas. The first choice is the removal of the affected ovary/ovaries plus bilateral salpingectomy, especially in cases of long-standing endometriomas in women who are not using oral contraceptive or progestogens, or those who report a positive family history of ovarian cancer or infertility. The second option is surveillance with immediate surgery in the case of modifications of ultrasonographic cyst patterns (e.g. cyst volume increase and appearance of septa, papillary projections, mural nodules or changes in vascularization), or suspicious increase in serum CA 125 and human epididymis protein 4 (HE4) levels [50].

The absolute risk of developing breast, ovarian and thyroid cancer in a woman's lifetime is 12.8%, 1.3% and 1.3% for all populations and 13.3% (+0.5%), 2.5% (+1.2%) and 1.8% (+0.5%) for those women with endometriosis, respectively [26]. Colorectal cancer risk is the same among women with and without endometriosis. Cervical cancer risk is lower in women with endometriosis than in the general population [58].

The ESHRE 2022 Guideline suggests that endometriosis is not associated with significantly higher risk of cancer overall [26]. The increase in absolute risk compared with women in the general population is reported as being low. The existing population-based cancer screening guidelines are adequate to follow. There is evidence that complete excision of visible endometriosis might reduce the risk of ovarian cancer. However, the benefits should be discussed with the woman against the probable risks of surgery.

When asymptomatic endometriosis is incidentally found during surgery, routine excision/ablation of the lesion is not performed. Besides, no medical treatment should be given to

women with those incidental findings of endometriosis. The recommendation is weak for monitoring asymptomatic endometriosis [26].

Conclusion

Endometriosis affects 6–10% of reproductive-aged women [4]. The time from symptom onset to first physician visit and the time from first physician visit to diagnosis should be shortened [59] because a longer diagnostic delay is correlated with poorer health-related QoL. The disease might cause pelvic pain, organ dysfunction and subfertility. Non-invasive imaging methods are complementary to a thorough pelvic examination. Symptomatic women should be counseled about the medical–surgical treatment options, the need for prolonged suppressive treatments after surgery to prevent recurrences and additional surgeries. Treatment should be individualized according to the reproductive plans, pain severity, disease stage, needs, preferences and risk–benefit evaluation of the patient. Women with natural or surgical menopause should be informed on menopausal hormonal therapy choices, and risks of breast and ovarian cancers.

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