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RECCOMENDATIONS

Ginekologia Polska
2024, vol. 95, no. 9, 729–758

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.100261

Guidelines of the Polish Society of Gynecologists and Obstetricians on the management of women with endometriosis

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Guidelines of the Polish Society of Gynecologists and Obstetricians present the most up-to-date treatment and management recommendations, which may be modified after detailed analysis of a specific clinical situation, which in turn might lead to future modifications and updates.

DIAGNOSIS OF ENDOMETRIOSIS

Patient medical history

— At the initial stages of the diagnostic process for endometriosis, it is advisable to use the endometriosis questionnaire.
— If dysmenorrhea is the sole symptom and the patient has no immediate reproductive plans, the diagnostic process for endometriosis need not be initiated if the complaints may be effectively alleviated with well-tolerated hormonal contraceptive therapy.
— Targeted clinical evaluation is recommended if the patient presents with symptoms indicative of endometriosis.

Clinical evaluation

— Targeted clinical evaluation should include:
  - pelvic inspection and palpation;
  - double-bladed speculum test;
  - bimanual pelvic examination.
— Imaging tests should always be performed in women with suspected endometriosis based on the questionnaire score, even if clinical evaluation revealed no abnormalities.

Imaging tests

— Transvaginal ultrasound should always be performed in women with suspected endometriosis.

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Received: 15.04.2024 Accepted: 15.04.2024

— In certain cases, when deep endometriosis is suspected based on patient-reported symptoms and ultrasound findings, the following tests may be recommended:
  • endometriosis protocol-based ultrasound assessment;
  • endometriosis protocol-based MRI to determine disease advancement before elective surgical treatment.

Of note, negative results of the imaging tests do not exclude the presence of superficial endometriotic foci.

Other diagnostic tests

— The use of other diagnostic markers (including CA-125) from blood, saliva, urine, and endometrium (including uterine fluid) for endometriosis should take into account the current state of knowledge about their diagnostic efficacy, along with the possibility of differentiating between other pathologies.
— CA-125 may be applicable in the diagnostic process but only as an element of the overall clinical picture.
— When in doubt, pharmacological suppression of the ovulation should be the test of choice.
— If the pain persists after pharmacological suppression of the ovulation, other than endometriosis-related causes need to be considered.

PHARMACOTHERAPY

— Treatment for endometriosis should be based on a long-term plan, with optimal pharmacotherapy and minimal number of surgical interventions.
— The choice of pharmacological treatment should be tailored to the patient needs, depending on their response to therapy, adverse effects, cost, and patient wishes.
— Combined oral contraceptives should be the drug of choice to treat chronic pain of endometriosis [preferably combined oral contraceptive (COC) with dienogest].
— Progestogen therapy is recommended in patients with contraindications to estrogens in COC.
— Pharmacotherapy before elective surgery to improve the surgical outcome is not recommended.
— Long-term hormonal therapy (COC, progestogens) is advised postoperatively to lower the risk for disease recurrence, if it is well-tolerated by the patient and not contraindicated.
— Hormonal therapy for endometriosis is no longer recommended after surgical intervention if the patient has reproductive plans. Monotherapy with nonsteroidal anti-inflammatory drugs (NSAIDs) may be used in those patients to reduce chronic pain.

SURGICAL THERAPY FOR ENDOMETRIOSIS

— Diagnostic laparoscopy only to confirm the diagnosis of endometriosis is not advised without first attempting pharmacotherapy.
— Laparoscopy remains the method of choice in surgical treatment of endometriosis.
— Hormonal therapy before surgical intervention to improve visualization is not recommended.
— Hormonal therapy should be implemented postoperatively in patients with no immediate reproductive plans.
— Surgical treatment of endometrial ovarian cysts in patients with reproductive plans should carefully preserve the ovarian cortex, while removing the hydrosalpinx.

Peritoneal endometriosis

— In patients without immediate reproductive plans, diagnostic laparoscopy to confirm the diagnosis of endometriosis is not recommended without first attempting pharmacotherapy.
— Diagnostic-therapeutic laparoscopy is only indicated in patients with suspected endometriosis **if pharmacotherapy was ineffective or not well-tolerated, and in patients who failed to conceive**.
— During diagnostic laparoscopy, it is recommended to biopsy the endometriotic foci to confirm the diagnosis with histopathology.
— It is not advised to take samples from a **normal peritoneum**.
— Due to a comparable effect on endometriosis-related pain, excision or ablation of the peritoneal endometriotic foci is the recommended laparoscopic technique.

Endometrial cyst

— Regardless of the surgical method used to treat endometrial cysts, minimal impact on the ovarian reserve needs to be prioritized.
— Before surgery for endometrial cysts, especially bilateral and recurrent, it is prudent to evaluate the ovarian reserve and discuss the possibility of preoperative harvesting and freezing of the oocytes for future use if the patient has reproductive plans. Careful preservation of the ovarian cortex and removal of the obstructed Fallopian tube or the hydrosalpinx should be achieved during surgery for endometrial cysts in such patients.
— Every nullipara with an endometrial cyst, as well as every patient with endometrial cysts in both ovaries, should be referred to a high-level care center for a specialist consultation before surgery.

— During a laparoscopic intervention for endometrial cysts, a thorough pelvic evaluation to check for concomitant types of endometriosis and treatment of all lesions is advised.
— Excision/coagulation of the endometriotic foci is the recommended surgical treatment in infertile patients with peritoneal endometriosis, as it increases the pregnancy and birth rates.
— Laparoscopic excision is the method of choice for endometrial cysts.

Histopathology of the excised cyst or its fragment is necessary to confirm or exclude malignant transformation.

DEEP ENDOMETRIOSIS

— Patients with deep endometriosis (DE) should be diagnosed and treated at specialized, high-level care centers for endometriosis — multidisciplinary hospitals which offer highly specialized, multidisciplinary care.
— All patients undergoing surgery for DE should receive comprehensive information about the potential benefits — improved quality of life — as well as the possible serious complications associated with the surgery. These factors determine the choice of the optimal treatment strategy.
— Indications for surgical intervention in patients with DE include high-intensity pain resistant to pharmacotherapy, hydronephrosis, and symptomatic and/or critical (> 80%) intestinal stenosis.

ENDOMETRIOSIS AND INFERTILITY

— Surgical treatment of deep endometriosis in infertile women should be considered only in case of high-intensity, chronic pain.
— In infertile women with endometriosis, preoperative pharmacotherapy which suppresses ovulation does not improve the chances for conception.
— In women with reproductive plans but treated for infertility, postoperative hormone therapy should not be recommended merely to improve fertility.
— In case of patients with no immediate reproductive plans after surgical intervention, hormone therapy does not lower the chances for pregnancy later on and may significantly alleviate the endometriosis-related pain.
— In infertile women with minimal and mild endometriosis [revised American Society for Reproductive Medicine (rASRM) grades I and II], laparoscopic excision of the endometriotic foci may increase the probability of conception.
— Surgical treatment of endometrial cysts may be considered in case of severe pain and difficulty in accessing the gonad during the *in vitro* fertilization-embryo transfer (IVF-ET) procedure, however surgery for only the endometrial cyst most probably does not increase the chances for pregnancy in IVF-ET programs.
— During a preoperative consultation, the following aspects should be discussed and considered:
  • surgical history;
  • pain complaints;
  • ovarian reserve;
  • patient age and wishes.
— The probability of spontaneous conception after surgical treatment should be calculated using the Endometriosis Fertility Index (EFI).
— Ovulation induction and intrauterine insemination (IUI) increase fertility and pregnancy rates in infertile women with minimal and mild endometriosis (rASRM grades I and II) and with good prognosis.
— If the treatment proves to be ineffective, especially in patients > 35 years of age and/or with unfavorable prognosis, *in vitro* fertilization (IVF-ET) should be recommended.
— The choice of ovulation induction protocol does not affect the efficacy of the IVF-ET programs in women with endometriosis.
— Prolonged desensitization with gonadotropin-releasing hormone (GnRH) analogues before IVF-ET to improve the outcome is no longer recommended, as there is no evidence to confirm the befits of such management.

ADENOMYOSIS

— An up-to-date algorithm for the diagnosis of adenomyosis should be based on the following parameters:
  • clinical data;
  • pelvic exam;
  • ultrasound test, performed in accordance with the consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group.
— When in doubt, diagnostic hysteroscopy is advised to confirm the presence of changes which are typical for adenomyosis.
— When in doubt, MRI test — which has high predictive value — should also be included in the diagnostic process.
— If the patient has no reproductive plans, the most effective methods include total laparoscopic hysterectomy or supracervical laparoscopic hysterectomy, if the glands and stroma of the cervix are disease-free and there are no signs of endometriosis of the rectovaginal septum.
— If pharmacotherapy is considered, progestogen therapy (preferably dienogest and norethindrone acetate or medroxyprogesterone acetate), GnRH analogues and antagonists, selective estrogen receptor modulators (SERMs), as well as levonorgestrel-releasing intrauterine device are used.

— If the patient has reproductive plans but presents with concomitant infertility, the treatment should be individually tailored to her needs.
— If the patient has reproductive plans but presents with concomitant infertility, uterus-sparing surgery, conducted at a high-level care center, is recommended.

ADJUNCTIVE TREATMENT IN ENDOMETRIOSIS

Endometriosis, which induces localized as well as systemic inflammation, necessitates the implementation of an appropriate diet aimed at modulating the gut microbiome. This dietary approach serves primarily as an adjunct to pharmacotherapy. Similarly, implementation of targeted physiotherapy and psychological counseling should become integral components of the therapeutic process for patients with endometriosis. Such approach not only improves the likelihood of successful pharmacotherapy, but also plays a crucial role in prehabilitation, preparing patients for the surgical intervention if pharmacological management proves ineffective.

ENDOMETRIOSIS AND THE RISK OF MALIGNANCY

— The percentage increase in risk for developing ovarian, thyroid, and breast cancers in women with endometriosis does not indicate a need to modify and update the guidelines for cancer prevention in women with endometriosis.

INTRODUCTION

Endometriosis is an estrogen-dependent disease, defined as the presence of endometrial-like tissue outside of the uterus, with an accompanying inflammatory process [1]. In the absence of a specific biochemical marker, it is not possible to determine the disease prevalence [2]. It has been estimated that endometriosis affects approximately 10% of all reproductive-age women worldwide [3]. Endometrial involvement may be found in typical and non-typical locations [4], with pelvic area as the most commonly affected site.

Endometriosis is a heterogeneous disease, with three phenotypes:
— superficial peritoneal lesions (SUP);
— ovarian endometriomas (OMA);
— deep endometriosis (DE).

In rare cases, endometrial implants may be found in extrapelvic sites such as the liver, lungs, brain, and other locations. Adenomyosis is a specific type of endometriosis in which the implants are located directly in the uterine muscle [5].

Since endometriosis is an estrogen-dependent disease, the endometrial tissues, just like the endometrium, are governed by the changes in estrogen and progesterone concentrations and are characterized by recurrent ectopic bleeding [6, 7]. That, in turn, activates the innate immune system and triggers a chronic inflammatory state [8], leading to pain [9] and infertility [10], although some women who are diagnosed with endometriosis present with no complaints [11]. The widely accepted rASRM classification of endometriosis differentiates between four stages of disease advancement (I–IV), based on lesion size, location, degree of involvement, and presence of adhesions [12]. Notably, there is no correlation between pain intensity and advancement of the disease classified with the help of the rASRM scale [13, 14].

Other classification systems include the #ENZIAN scale, which is a descriptive tool for staging deep endometriosis that takes into account the depth of the infiltration, and the EFI, a validated scoring system for predicting spontaneous pregnancy rates in infertile women after endometriosis-related laparoscopy [15, 16]. None of the recognized scores describes disease activity.

Earlier this year the #ENZIAN scale was recognized by a consensus of experts as the best tool to assess the severity of deep endometriosis and to plan surgical management. This classification system describes both clinical findings and changes observed in ultrasonography or magnetic resonance imaging [17].

Due to its chronic nature, endometriosis has a detrimental effect on the emotional wellbeing and quality of life of the affected patients, as well as their functioning in personal and professional environments [18, 19]. Also, endometriosis is associated with high social costs due to absenteeism from work [20]. Endometriosis and the related complaints not only impede on social functioning, but also negatively affect the relations between intimate partners as well as willingness to engage in sexual activity [21].

Since the pathogenesis of endometriosis has not been fully elucidated, causal treatment options for endometriosis remain unavailable [22]. Recent years have brought reports about the role of adequate diet in endometriosis, both in the context of disease prevalence and as a form of auxiliary therapy [23]. Therapeutic options include pain management as well as hormonal and surgical interventions and need to be tailored to the individual needs of the patient, symptom intensity, everyday functioning, patient wishes, and reproductive plans [24]. Slightly different treatment methods should be selected if the main goal of therapy is to lower the intensity of the pain and daily discomfort, and yet others if pregnancy is the desired outcome.

Until recently, laparoscopy — with or without histopathology — has been the diagnostic "gold standard" for endometriosis [25–28], which often resulted in delayed treatment [29, 30].

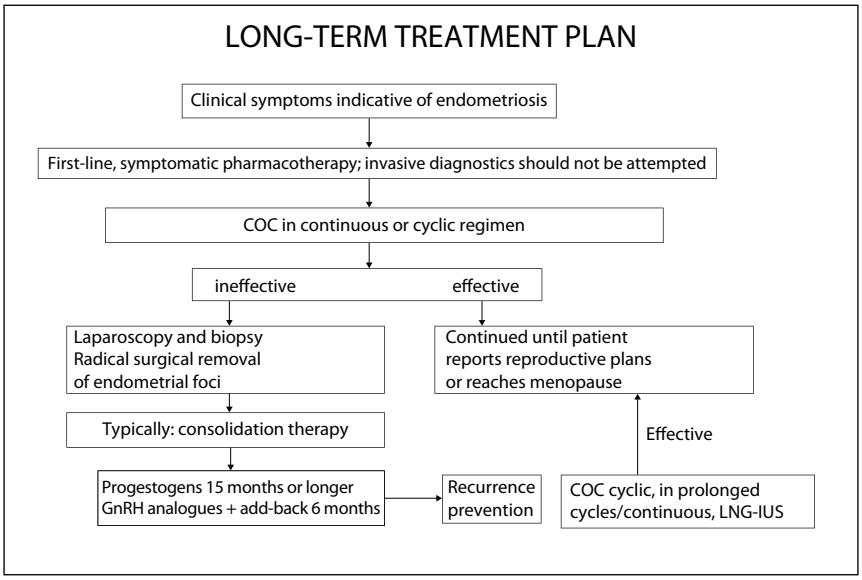

Figure 1. Long-term treatment plan for endometriosis; GnRH — gonadotropin-releasing hormone; COC — combined oral contraceptive; LNG-IUS — levonorgestrel-releasing intrauterine system

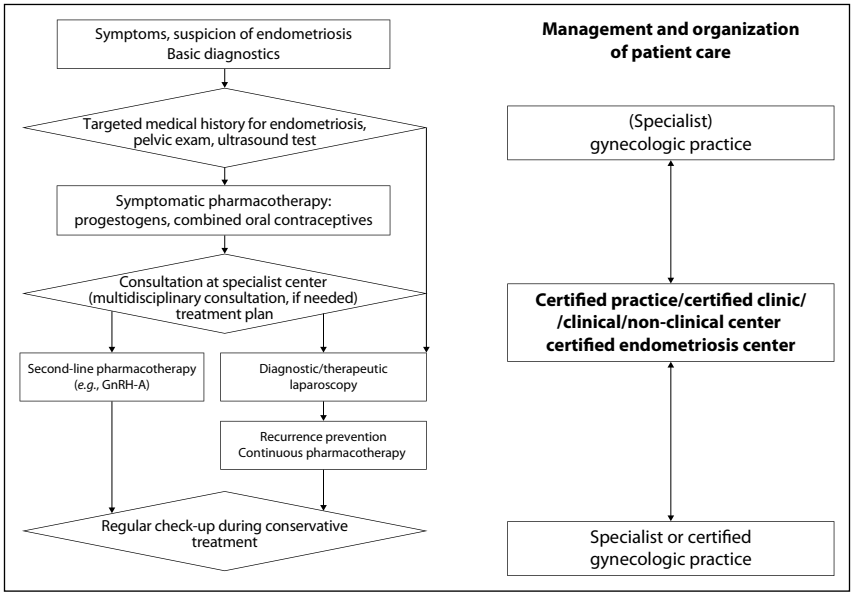

Figure 2. Management of patients with endometriosis, depending on the experience of the center

The 2017 National Institute for Health and Care Excellence (NICE) and the 2022 European Society of Human Reproduction and Embryology (ESHRE) updates of the guidelines on the diagnosis and management of endometriosis allow the use of empiric therapy in the diagnostic and therapeutic processes, if the patient has no reproductive plans [24, 28]. That crucial change in the approach to patients with endometriosis has also been discussed in the present guideline. Figures 1–3 present Evidence Based Medicine (EMB) notions and summarize the current recommendations for patient care management protocols.

The aim of this guideline is to help physicians select the optimal, up-to-date diagnostic and therapeutic management for women with the suspicion or diagnosis of endometriosis.

THE DIAGNOSIS OF ENDOMETRIOSIS

Personal medical history

Obtaining a detailed medical history from a patient is a vital, preliminary step in the diagnostic process for endometriosis. Studies which analyzed the role of patient medical history and the Patient-Reported Outcome Measures in

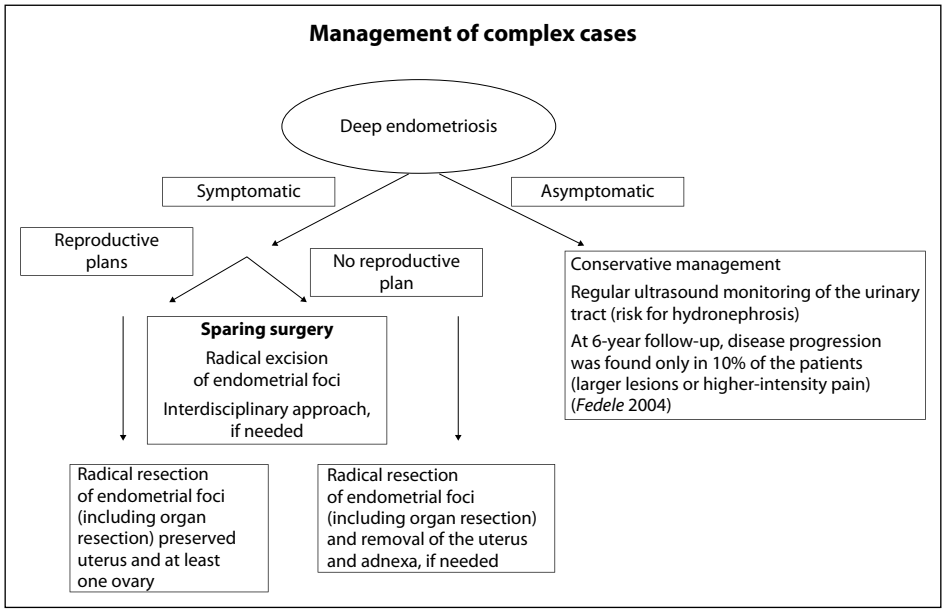

Figure 3. Management of patients with deep endometriosis

Endometriosis (PROME), emphasize their high usefulness in clinical practice [31].

The following symptoms are listed as important PROME parameters:

— quality of life;
— pain;
— quality of sexual life;
— fatigue;
— depression and irritability;
— gastrointestinal and urinary tract complaints;
— impact on patient professional life [32].

The concept of an interview-based approach to endometriosis with the help of the original questionnaire — designed for general practitioners to aid diagnosis and referral for a specialist consultation - may be used to assess PROME [33].

Apart from the questions about the most characteristic symptoms of endometriosis, *i.e.*, painful (dysmenorrhea) and/or profuse (menorrhagia) menstrual bleeding, and dyspareunia, it is necessary to add questions about frequent (including nocturia) and/or painful urination (dysuria) and defecation (dyschezia), and other symptoms which persist for at least 6 months, regardless of the phase of the menstrual cycle, such as:

— flatulence, diarrhea;
— diarrhea/constipation;
— pain localized mainly in the lower abdomen and the sacral region;
— urinary urgency/polyuria;
— sciatica;
— bleeding from atypical locations.

The probability of endometriosis increases with the number of symptoms reported by the patient [34].

While taking patient history, it is recommended to pay attention to high-risk factors for endometriosis such as:

— low body mass index (BMI);
— positive familial history;
— high BMI with accompanying infertility [35, 36].

Endometriosis in the mother increases the risk for developing the disease by 7-fold in the daughter, 5-fold in the sister, and 1.5-fold in the cousin [37, 38]. Mothers of the affected women were significantly more often diagnosed with endometriosis and uterine myomas [39]. Importantly, pre-term labor, preeclampsia and nicotine use during pregnancy are statistically significantly more often reported for mothers of women with endometriosis [40]. Women with endometriosis had significantly lower birthweight and more often received infant formula.

Information about the period of adolescence — including very painful menarche, absenteeism from school due to painful menstruation, and ineffective pharmacotherapy with hormonal contraceptives or NSAIDs to alleviate the pain - may also prove to be valuable [41, 42]. Based on the patient-reported information, it is essential to determine whether the patient experienced difficulty conceiving, miscarriage, or obstetric failure, as these factors also increase the risk for endometriosis [43, 44].

Adequate medical history should include questions about comorbidities.

Patients with endometriosis are more likely to present with concomitant autoimmune disorders such as:

— lupus;
— Sjögren's syndrome;

— multiple sclerosis;
— rheumatoid arthritis;
— inflammatory bowel diseases (ulcerative colitis, Crohn's disease) and celiac disease [45–48].

Allergic conditions such as:
— atopic dermatitis;
— asthma;
— food and drug allergies [49–53].

Dysmenorrhea and dyspareunia are common occurrences also in the general population and are not necessarily caused by endometriosis, but cyclic nature of the pain is the key feature of the disease [54].

Patients who only report dysmenorrhea and have no reproductive plans need not be diagnosed for endometriosis if their complaints may be alleviated with hormonal contraceptive therapy, on condition they respond well to treatment [24, 28, 55].

Targeted clinical evaluation is recommended if the patient presents with symptoms which are predictive for endometriosis [55].

Recommendation

At the initial stages of the diagnostic process for endometriosis, it is advisable to use the endometriosis questionnaire.

Patients with dysmenorrhea as a sole symptom and without reproductive plans do not need be diagnosed for endometriosis if their complaints may be alleviated with well-tolerated hormonal contraceptive therapy.

Targeted clinical evaluation is recommended if the patient presents with symptoms indicative of endometriosis.

Clinical evaluation

Routine pelvic evaluation is not always sufficient to diagnose pelvic endometriosis. Targeted clinical evaluation for endometriosis should include:
— pelvic inspection and palpation;
— a double-bladed speculum test;
— a bimanual pelvic examination.

Symptoms predictive for endometriosis include:
— bluish implants in the posterior vaginal fornix in speculum exam;
— nodules on the uterosacral ligaments or the Douglas pouch palpable on bimanual exam;
— tense and tender uterosacral ligaments;
— fixed and retroverted uterus and adnexa;
— tender adnexal masses;
— intestinal wall thickening or unnatural intestinal twist;
— palpable masses in the intestinal wall;
— pelvic pain during the exam.

The detection rate for endometriosis might be higher if the clinical evaluation was performed during menstruation [56, 57].

Imaging tests should always be performed in case of suspected endometriosis based on the questionnaire score, even if the clinical evaluation revealed no abnormalities [28].

Recommendation

Targeted clinical evaluation should include:
— **pelvic inspection and palpation;**
— **double-bladed speculum test;**
— **bimanual examination.**

In women with suspected endometriosis based on the questionnaire score, algorithm-based imaging tests should always be performed, even if the clinical evaluation revealed no abnormalities.

Imaging tests

Imaging tests which are especially useful when attempting to visualize endometriotic lesions include:
— transabdominal ultrasound;
— transvaginal ultrasound;
— transrectal ultrasound;
— contrast MRI [58–61],

although these imaging techniques remain ineffective in case of peritoneal endometriosis [62].

Standard transvaginal ultrasound should be the first-choice imaging method in patients with suspected endometriosis [28, 55, 58]. It is an effective technique of diagnosing endometriomas and differentiating between them and other types of ovarian masses [63], but it is not useful for detecting small foci of endometrial implants [64]. According to the International Ovarian Tumor Analysis (IOTA) Group, a unilocular cyst with ground glass echogenicity represents a typical image of an endometrial cyst on ultrasound [65].

In some cases, to improve the diagnostic effectiveness, modified ultrasound techniques are used, including transvaginal ultrasound and colon preparation for imaging tests to visualize deep endometriosis within the recto-vaginal space [66], rectal water contrast transvaginal ultrasonography and sonovaginography [67], and three-dimensional (3D) ultrasound [68].

According to the diagnostic protocol designed by the International Deep Endometriosis Analysis (IDEA) Group, transvaginal ultrasound — performed within the so-called endometriosis algorithm (expert ultrasound imaging) — allows to identify with high probability not only the adhesions located in the pelvis, but also the endometrial lesions located within the bladder wall, infiltrating the rectum or the pelvic ureter [58].

Magnetic resonance imaging plays a vital role in the diagnostic process for extrapelvic DE lesions, which infiltrate

the intestinal loops on many levels, but — due to excessive costs and limited availability — it is not often used in routine clinical practice [60, 69]. Several modifications to MRI testing have been made to ensure a more thorough diagnostic process for endometriosis, chief among them T1/T2-weighted images, fat-suppressed images (performed with or without contrast), 3D MRI or high-field 3T MRI [70–72].

The implications for clinical practice are that — combined with medical history and pelvic exam — it is highly likely to make the diagnosis of endometriosis (endometrial cysts, deep endometriosis) using algorithm-based ultrasound imaging and/or MRI (Fig. 4).

Nevertheless, neither ultrasound nor MRI tests are suitable diagnostic tools for superficial foci, therefore endometriosis cannot be excluded even if clinical and algorithm-based ultrasound evaluation revealed no abnormalities.

In cases when endometriosis is suspected based on medical history but the imaging tests did not confirm the diagnosis, and the patient has no immediate reproductive plans, continuous administration of combination pill or progestogens as a kind of clinical test should be the management of choice [24]. Symptom resolution or reduction after pharmacotherapy will allow to confirm or exclude the diagnosis of endometriosis with high probability.

Recommendation

Transvaginal ultrasound should be performed in women with suspected endometriosis.

In certain cases, when deep endometriosis is suspected based on patient-reported symptoms and ultrasound findings, patient-dedicated algorithm-based ultrasound or pelvic MRI might be recommended to determine the advancement of the disease before elective surgical treatment.

Of note, negative imaging test does not exclude the presence of superficial endometriotic foci.

Diagnostic challenges

Non-invasive/minimally-invasive diagnostic tests

Misdiagnosis or delayed diagnosis of endometriosis is also associated with the lack of a specific biological marker detected in body fluids, which would reliably exclude or confirm the disease [73–76]. Serum CA-125 concentration test should not be used to detect endometriosis because low (< 30 IU/mL) CA-125 concentration does not rule out endometriosis, while elevated CA-125 level (> 30 IU/mL but below the levels found in ovarian cancer patients) may be indicative of the disease, but it may also be caused by other conditions, which might lead to therapy without the causal factor [77].

While this guideline was being prepared for publication, new tests emerged and they used:

— brain-derived neurotrophic factor (BDNF) in serum using ELISA [78];
— saliva-based microRNA (miRNA) signature for endometriosis [79];
— fucosyltransferase 4 (FUT4) expression in the endometrium [80].

In preliminary clinical trials, a statistically significant positive correlation was found between all of the above-mentioned biomarkers and endometriosis, with BDNF demonstrating the highest specificity.

Nevertheless, at present, the literature offers insufficient evidence of the efficacy of these tests in representative populations, particularly when differentiating the causes of chronic pelvic pain, which precludes recommending their widespread use as independent methods in the diagnosis of endometriosis.

Different phenotypes of endometriosis

The diagnosis of endometriosis remains challenging due to the heterogenous nature of the disease, the presence of three (four, if adenomyosis is also included) different phenotypes, possible concomitant non- and gynecological comorbidities, and/or asymptomatic presentation [81–83].

Symptom differentiation

Clinical presentation of endometriosis varies in individual cases. Pain, manifesting as dysmenorrhea, dyspareunia, dyschezia, dysuria or chronic pelvic pain, is frequently the main symptom of the disease, not to mention that the symptoms may overlap. Chronic pain is the key feature of endometriosis [83], but pain itself is not pathognomonic or synonymic with endometriosis. Furthermore, pain may also be caused by non-gynecological causes, mainly diseases of the urinary, gastrointestinal, and vascular (pelvic congestion syndrome, May-Thurner Syndrome, Nutcracker Syndrome) systems [85].

Comorbidities

It is vital to establish whether pain is caused by endometriosis or other gynecologic conditions such as:

— ovarian cyst;
— myoma;
— pelvic inflammatory diseases;

or conditions associated with chronic pain:

— adhesions;
— irritable bowel syndrome;
— interstitial cystitis;
— pelvic congestion syndrome;
— fibromyalgia;
— depression [86].

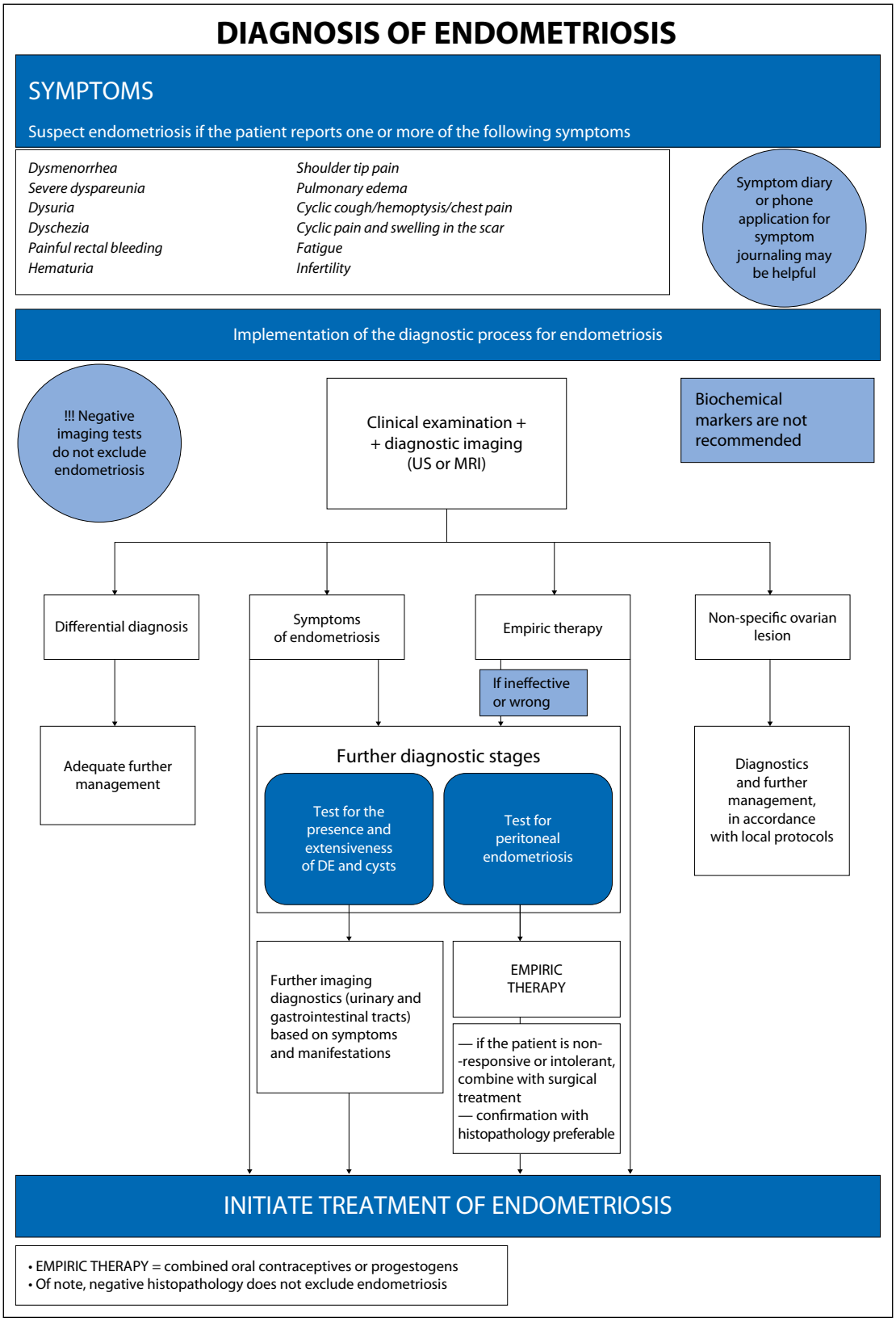

Figure 4. Diagnostic management of patients with suspected endometriosis; US — ultrasonography; MRI — magnetic resonance imagining

Recommendation

CA-125 and other blood-, endometrium-, urine- and uterine fluid-based markers should not be used as independent diagnostic markers for endometriosis. CA--125 and other, new biomarkers may be helpful in the diagnostic process but only as an element of the overall clinical picture.

When in doubt, pharmacological suppression of the ovulation should be the test of choice and other than endometriosis-related causes need to be considered if the pain persists.

PHARMACOTHERAPY FOR ENDOMETRIOSIS

Treatment for endometriosis should be based on a long-term plan, with optimal pharmacotherapy and minimal number of surgical interventions [27].

The following groups of medications are used in the pharmacological management of endometriosis, depending on the therapy goal:

— NSAIDs;
— COC pills;
— progestogens;
— anti-progestogens;
— GnRH agonists;
— aromatase inhibitors;
— levonorgestrel-releasing intrauterine devices;
— GnRH antagonists;
— danazol [28].

None of the pharmacotherapies proved to be superior over others [24, 28]. The choice of pharmacological treatment should be tailored to the needs of the patient, individual response to therapy, adverse effects, cost, and other factors (*e.g.* reproductive plans) [24, 28, 87].

Goals and limitations of pharmacotherapy

The main goal of the treatment is to reduce or eliminate chronic pain caused by endometriotic lesions [88]. The therapy may also lower the risk of recurrent postoperative pain, endometrial cysts, or formation of new adhesions [89]. Pharmacotherapy for endometriosis does not affect the pre-existing lesions such as adhesions or endometrial cysts [90]. Its goal is not to improve fertility [91], as hormonal therapy for endometriosis prevents simultaneous conception [28]. The effectiveness of pharmacotherapy usually decreases over time, at which point symptom recurrence is observed, not unlike after therapy cessation [92].

Context-based treatment

Despite the fact that efficacy of pain reduction is comparable for the abovementioned groups of medicines, the choice of therapy may depend on other features of endometriosis, patient response to treatment, or patient wishes. The literature lacks conclusive evidence to support the choice of a given treatment [28]. Patients with mild to moderate intensity pelvic pain (pain which does not interfere with daily functioning) and without endometrial cysts on ultrasound should receive a combination therapy of NSAIDs + COC [90]. Patients with contraindications to COC may benefit from the combination of NSAIDs and progestogen only pill [90]. Nonsteroidal anti-inflammatory drugs may be used as monotherapy to reduce chronic pain in patients with reproductive plans [90]. In that context, it is advisable to avoid cyclooxygenase 2 (COX-2) selective inhibitors, as they may disrupt ovulation and impair conception [91].

Pharmacotherapy as complementary therapy to surgical treatment

Pharmacological treatment of endometrial cysts before elective surgery to improve the surgical outcome is not recommended [28]. Such therapy may be attempted to control pain during the preoperative period, but it does not impact the outcome of the surgical intervention [28].

Postoperative pharmacotherapy in patients with pain should always be used after the diagnosis was confirmed perioperatively, as it lowers the risk for recurrent pain and lesions over the course of 12 months [93–96]. Furthermore, the literature offers reports of higher pregnancy rates after postoperative pharmacotherapy [92]. Continuous therapy using combined oral contraceptives and levonorgestrel-releasing intrauterine devices were proven to be the most effective as far as prevention of disease recurrence is concerned [93]. However, another study confirmed the effectiveness of a postoperative course of dydrogesterone, between day 5 and 25 of the cycle, to control pain in patients after laparoscopic intervention due to endometriosis [94].

Recommended stages of treatment

At present, there are no treatment algorithms for endometriosis which would be based on compelling evidence from randomized clinical trials. Treatment protocols are based on expert opinions. The following stages of treatment have been suggested [88]:

1. COC (continuous regimen) + NSAIDs;
2. follow-up evaluation of therapy effectiveness after 3 months:
   a) if the therapy proves to be ineffective or poorly-tolerated, the treatment should not be discontinued but a different combination of COC + NSAIDs should be attempted,
   b) effective and well-tolerated medicines need to be continued until the patient reports reproductive plans or reaches mean age for menopause. The treatment should not be discontinued.
   After the period of breastfeeding, the pre-pregnancy therapy needs to be resumed;

3. if a different combination of COC + NSAIDs also proves ineffective or in case of high-intensity pain (preventing normal daily functioning), GnRH analogue + low-dose *add-back* estrogen therapy or surgical intervention may be considered. Postoperatively, continuous oral contraceptive pill regimen should be recommended to lower the risk for adhesions and recurrence;
4. if the patient remains unresponsive to the abovementioned regimens, other medicines which proved to be effective in clinical trials (aromatase inhibitors, levonorgestrel-releasing intrauterine device) may be used to alleviate the pain and menorrhagia and/or dysmenorrhea. For some patients, it may be beneficial to participate in clinical trials for new treatments;
5. a primary-level care center should refer the patient to a higher-level of care center if the first-line treatment, *i.e.* attempts to treat the patient using two different types of basic hormonal preparations (a single-component pill and a combined oral contraceptive) proved ineffective.

Therapeutic management of a patient with endometriosis is presented in Figure 5.

Groups of medicines

Combined oral contraceptive pills

Combined oral contraceptive pills are the first-line choice to treat chronic pain in endometriosis [24, 97, 98]. However, the evidence supporting COC efficiency leaves much to be desired due to frequent lack of blinding or placebo groups. Combined oral contraceptive pills reduce perimenstrual pain, chronic pelvic pain, discomfort during intercourse, and improve patient quality of life [98–100]. Continuous COC regimen, which results in menstrual suppression, is more effective than a cyclic regimen (21 + 7 days), as was demonstrated for the pill containing dienogest (2 mg) and ethinylestradiol (30 μg) [28, 98, 101]. The literature lacks conclusive evidence for the superiority of one hormonal therapy over others for treating chronic pain of endometriosis [28]. Some studies reported the highest efficacy of the combination therapy of ethinylestradiol with norethindrone acetate as well as ethinylestradiol with drospirenone [100], as such postoperative regimen reduces the risk for disease recurrence [100]. The extent of pain reduction remains comparable for COC pills, oral progestogens, and GnRH analogues [98, 99]. At present, there is no evidence to suggest that combined hormonal vaginal rings or transdermal patches are as effective as COC or oral progestogens. So far, the vaginal rings have proven to be less effective than desogestrel [101].

Nonsteroidal anti-inflammatory drugs

Data about NSAIDs are obtained from studies on perimenstrual pain [102]. Nonsteroidal anti-inflammatory drugs are more effective in treating perimenstrual pain as compared to placebo, but they are associated with more adverse effects [103]. The literature lacks evidence for higher analgesic efficacy of one specific NSAID as compared to others. No benefits of using COX-2 selective inhibitors to reduce endometriosis-related pain as compared to other NSAIDs have been found. Nonsteroidal anti-inflammatory drugs have been demonstrated to be more effective than paracetamol. Despite being widely used in clinical practice, there is no indisputable evidence to support the analgesic efficacy of NSAIDs in chronic pain management for endometriosis [104]. They are most often used in combination with COC, although a monotherapy with NSAIDs may also be used in patients with reproductive plans. COX-2 selective inhibitors should be avoided in that group of patients, as they may inhibit ovulation [105] and conception [92, 106].

Progestogens and anti-progestogens

The most commonly used progestogens to treat endometriosis include:

— norethindrone acetate;
— medroxyprogesterone acetate (MPA);
— dienogest, desogestrel [28, 90].

Gestrinone, an anti-progestogen which is not available in Poland, and whose efficacy is comparable to danazol and leuprolide, may also be used in treating endometriosis [106, 107]. The route of administration for medroxyprogesterone acetate may be oral, intramuscular, and transdermal (depot). Progestogen therapy offers an alternative to patients who cannot receive estrogens contained in the COC pills. In comparison to GnRH agonists, progestogens do not reduce bone mineral density (except for long-term use of MPA). In the absence of reliable data about differences in efficacy between various progestogens, the choice of the preparation is often based on the adverse effect profile and the cost of therapy [28, 108, 109] (Tab. 1). Endometriosis-related pain may also be reduced using a transdermal patch with etonogestrel and a levonorgestrel-releasing intrauterine device [109–111].

The efficacy of levonorgestrel-releasing device is comparable to GnRH analogues, with a lower risk for dyslipidemia [109].

The main adverse effects of progestogen include:

— irregular bleeding;
— amenorrhea;
— weight gain;
— mood disorders;
— dyslipidemia;
— androgenization;
— edema;
— headache;
— constipation [28, 99, 112].

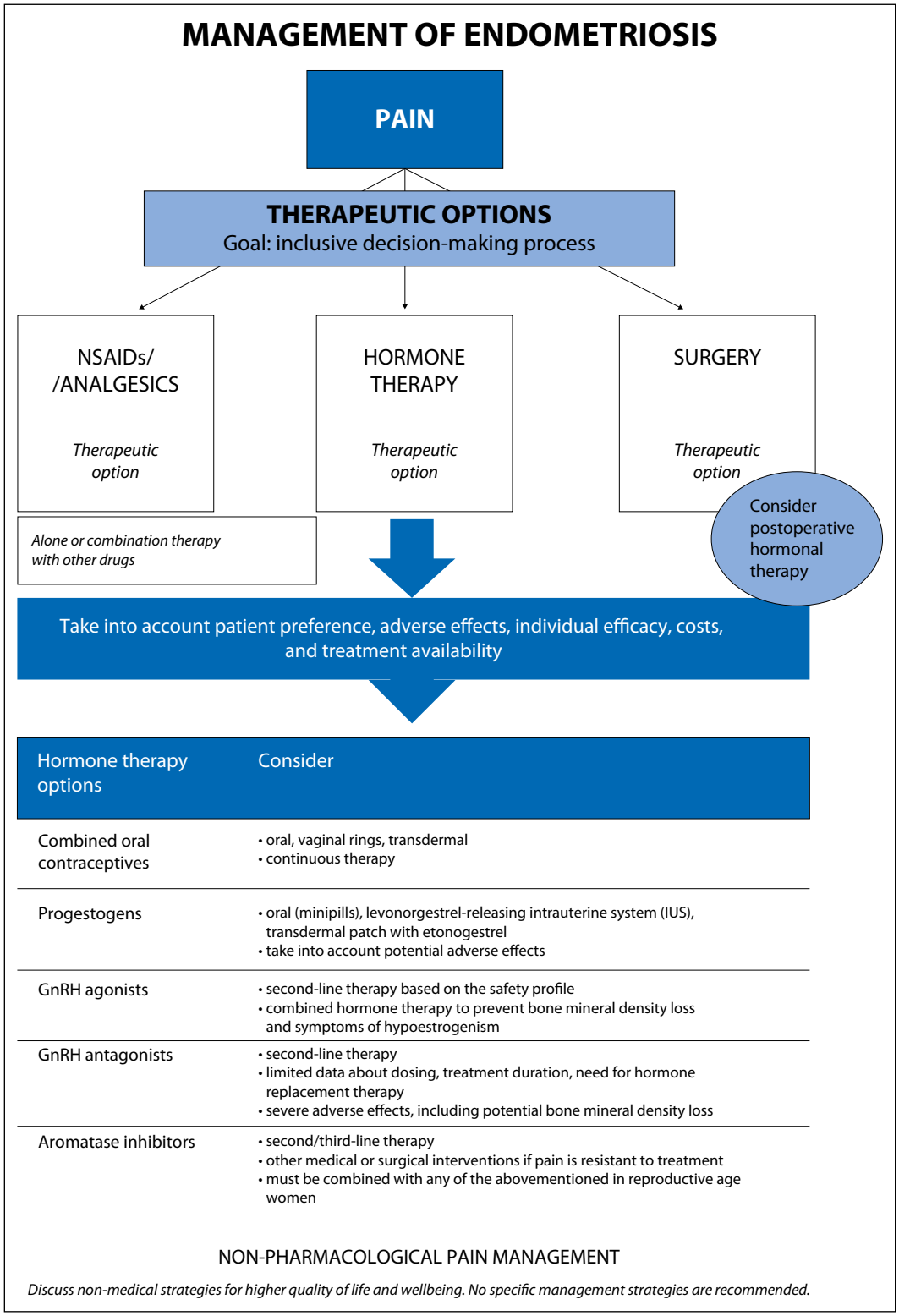

Figure 5. Therapeutic management of patients with endometriosis; NSAIDs — nonsteroidal anti-inflammatory drugs; GnRH — gonadotropin-releasing hormone

The lipid profile needs to be monitored during progestogen therapy (especially norethindrone). Long-term use of progestogens is possible. The safety profile for dienogest over the course of 52 weeks was verified [111]. Due to possible adverse effects, the use of danazol to treat endometriosis-related pain is not recommended for longer than 6 months [28].

Table 1. Dosing and adverse effects of some progestogens for endometriosis therapy

Agent	Dosing	Adverse effects
Norethindrone acetate	5 mg, orally, once/day, maximum dose — 15 mg, continuous regimen (uninterrupted)	Irregular bleeding, abnormal lipid profile
Medroxyprogesterone acetate (MPA) depot	150 mg, intramuscularly, every 3 months	Bone density loss, acne, edema, irregular bleeding
Dienogest	2 mg, orally, once/day, continuous regimen (uninterrupted)	Irregular bleeding, headache, constipation
Levonorgestrel (IUD)	Once every 5 years	Irregular bleeding, ovarian cysts

GnRH agonists and antagonists

Preparations from the gonadoliberin analogue group alleviate pain in endometriosis more efficiently than placebo [113], by leading to endometrial atrophy, including in the ectopic-endometriotic foci. The route of administration does not effect GnRH agonist efficacy [113]. GnRH agonist therapy is associated with numerous adverse effects such as vaginal dryness, hot flashes, weight gain, acne, and headaches. The risk for decreased bone mineral density is higher, directly proportional to the dose [114]. In this respect, higher safety was found for the 1.88 mg to 3.75 mg dose, with similar analgesic efficacy [113, 114]. The route of administration does not affect the intensity of adverse effects.

The *add-back* therapy is used simultaneously to alleviate the effect of GnRH agonist on bone mineral density. The therapy may include:

— progestogens (norethindrone acetate);
— combination of estrogen with progesterone;
— SERMs;
— bisphosphonates or testosterone [115].

Such management decreases bone density loss within the lumbar region of the spine, while maintaining the analgesic efficacy for endometriosis [114]. Due to possible adverse effects, GnRH agonists are a second-line choice for patients with endometriosis, used if the COC therapy proved ineffective [28]. Caution is advised in teenage patients due to the risk for bone mineral density loss during adolescence.

Clinical trials confirmed the efficacy of GnRH antagonists such as elagolix, relugolix and linzagolix for pain management in patients with endometriosis [115, 116]. Elagolix was approved in the US to treat endometriosis-related pain in two therapeutic doses: 150 and 200 mg. Higher doses of GnRH antagonists alleviate pain more effectively but are associated with more frequent adverse effects, comparable to GnRH agonists [116]. Relugolix administered orally at the dose of 10, 20 and 40 mg alleviates endometriosis-related pain in a dose-dependent manner. Oral relugolix (40 mg GnRH antagonist + 1 mg estradiol + 0.5 mg norethindrone acetate) used for 24 weeks proved to be more effective than placebo, with low rate of adverse effects [116, 117].

Aromatase inhibitors

Aromatase inhibitors such as letrozole or anastrozole alleviate pelvic pain and improve the quality of life in patients with endometriosis [118]. They are used in combination therapy together with other ovulation suppressors: progestogens (norethindrone acetate) or oral contraceptive pills, but they should not be used separately to alleviate pain [118, 119]. Also, aromatase inhibitors have been demonstrated to decrease the size of the endometrial cysts after 3 months [119]. Adverse effects include hot flushes, vaginal dryness, and lower bone mineral density. Data on aromatase inhibitor therapy are limited, at best. Long-term effects remain to be fully elucidated. Therefore, aromatase inhibitors are recommended only after all pharmacological and surgical options have failed, and only in combination with COC or progestogens [28].

Recommendation

Management for endometriosis should be based on a long-term plan, with focus on pharmacotherapy and minimal number of surgical interventions.

Pharmacotherapy should be tailored to the needs of the patient, individual response to therapy, adverse effects, cost, or patient wishes.

Combined oral contraceptives should be the first-line choice to treat chronic pain in endometriosis, preferably COC with dienogest.

Progestogen therapy is advised if the use of COC which contain estrogens is contraindicated.

Pharmacological treatment of endometrial cysts before elective surgery to improve the surgical outcome is not recommended.

Long-term hormonal therapy (COC, progestogens) is advised postoperatively to lower the risk for disease recurrence, if it is not contraindicated and well-tolerated by the patient.

Hormonal therapy for endometriosis is not recommended after surgical intervention in patients with reproductive plans. Monotherapy with NSAIDs may be used in those patients to reduce chronic pain.

ADJUNCTIVE TREATMENT IN ENDOMETRIOSIS

Endometriosis, which causes localized as well as systemic inflammation, often requires a more holistic approach than

pharmacotherapy alone - which is merely symptomatic in the first place. Therefore, a dietary consultation is recommended to introduce a proper diet, which modifies the gut microbiome, that will primarily serve as an adjunctive treatment to pharmacotherapy [120]. Similarly, there is a need to implement physiotherapy and psychological counseling at the very beginning of the therapeutic process. These elements of an adjunctive treatment play a crucial role in improving the outcomes of pharmacotherapy. In cases where conservative management fails to yield satisfactory results, they serve as vital components of preoperative prehabilitation.

SURGICAL TREATMENT OF ENDOMETRIOSIS

The choice between the pharmacological versus surgical treatment of endometriosis should always be tailored to the individual needs of every patient, patient-reported complaints, response to therapy and adverse effects, reproductive plans, as well as disease advancement. Pelvic pain is an indication for surgical intervention if it is resistant to empiric hormonal therapy or if the treatment was poorly tolerated. Surgical therapy in endometriosis is laparoscopic, except for the rare cases which require laparotomy, *i.e.*, history of numerous surgical interventions, multifocal advanced deep endometriosis, or symptoms causing the so-called 'acute abdomen' [121, 122]. Hormonal therapy is not recommended before surgical management to improve visualization.

However, hormonal therapy should be implemented after surgical intervention due to pain or endometrial cysts in patients with no immediate reproductive plans. It is recommended to implement physiotherapy and proper diet before making the final decision about surgery, as this approach allows to defer the decision in some cases, and serves as a prehabilitation measure in all other cases. If the therapy is well-tolerated, it should be continued either short-term, until the patient reports reproductive plans, or long-term, if the patient has no reproductive plans, to prevent disease and pain recurrence [123].

In patients with reproductive plans, surgical treatment of endometriosis is predominantly conservative, *i.e.*, radical excision of the endometriotic foci but preservation of the uterus and the ovaries. Due to the nature of the disease, that course of treatment is often incomplete. Radical excision of all endometriotic foci and hysterectomy, with or without oophorectomy, is the recommended therapeutic option in women beyond the childbearing period. Surgical techniques allow to reduce the symptoms in 50–80% of the patients with endometriosis. Unfortunately, disease recurrence is observed in 5–15% of the women, even after hysterectomy with bilateral salpingo-oophorectomy [123].

Recommendation

Laparoscopy remains the method of choice in surgical treatment of endometriosis.

Preoperative hormonal therapy to improve the conditions during surgery is not recommended.

Postoperative hormonal therapy should be implemented in patients with no immediate reproductive plans if the surgery was performed due to pelvic pain or endometrial cysts.

It is recommended to implement physiotherapy and proper diet before making the final decision about surgery, as this approach allows to defer the decision in some cases, and serves as a prehabilitation measure in all other cases.

Surgical treatment of the ovarian endometrial cysts in patients with reproductive plans should preserve the ovarian cortex, while the obstructed Fallopian tubes or the hydrosalpinx should be excised.

Peritoneal endometriosis

Laparoscopy should be recommended in patients with suspicion of peritoneal endometriosis whose pain persists even after pharmacotherapy for endometriosis. At present, visualization of the endometriotic foci in the peritoneal cavity during laparoscopy, with or without histopathology to confirm the presence of endometriotic tissue, remains the only available method for diagnosing peritoneal endometriosis [124]. During diagnostic laparoscopy, it is recommended to biopsy the endometriotic foci for histopathology. It is not advised to take samples from a normal peritoneum [55]. After laparoscopy, detailed macroscopic description of the lesions, their size, location and presence of adhesions is required to establish the link between patient-reported complaints and the implemented treatment [55]. Diagnostic laparoscopy is only indicated if the patient has difficulty conceiving or there is a need to confirm the diagnosis.

Diagnostic laparoscopy to confirm the diagnosis of endometriosis is not advised before first attempting pharmacotherapy [125]. Excision/coagulation of the peritoneal endometriotic foci in infertile patients results in higher pregnancy rates [126, 127]. The literature offers no compelling evidence which surgical method — excision or ablation of the peritoneal endometriotic foci — is more efficient in alleviating endometriosis-related pain [127]. Both methods seem to have comparable outcomes [127, 128].

Recommendation

It is recommended to biopsy the endometriotic foci during a diagnostic laparoscopy to confirm the diagnosis on histopathology.

It is not advised to take samples from a normal peritoneum.

Due to comparable efficacy, both surgical excision and ablation of the peritoneal endometriotic foci are recommended to alleviate endometriosis-related pain.

Diagnostic-therapeutic laparoscopy is recommended in infertile women with suspicion of endometriosis if pharmacotherapy proves ineffective or is poorly tolerated.

In patients with no immediate reproductive plans, diagnostic laparoscopy to confirm the diagnosis of endometriosis is not advised before first attempting pharmacotherapy.

Endometrial cysts

Isolated endometrial cysts are extremely rare. They are most often accompanied by peritoneal endometriotic foci or deep endometriosis. Therefore, during the diagnostic or therapeutic process for endometrial cysts, thorough pelvic evaluation and treatment of all lesions is advised. Laparoscopic cystectomy is the recommended method of intervention [130]. The technique is associated with lower rates of recurrent dysmenorrhea, dyspareunia, cysts, as well as the need for reoperation as compared to drainage and coagulation [130]. Histopathology of the excised endometrial cyst or its fragment is necessary to confirm or exclude malignancy [131]. Ablation of the cyst wall or electrocoagulation make it impossible to obtain samples for histopathology. Laser vaporization is associated with a higher recurrence rate in the course of 12 months as compared to cystectomy, although the 5-year recurrence rates are comparable for both approaches [129]. Regardless of the surgical method, minimal impact on the healthy ovarian tissue, and consequently on the ovarian reserve, needs to be prioritized [130]. In case of surgical intervention for an endometrial cyst, the patient should be informed about the diminished ovarian reserve, which might lead to decreased fertility, especially if the cyst is large, bilateral, or has a tendency for recurrence. In patients with reproductive plans, surgical treatment of the endometrial cysts should preserve the ovarian cortex, while the obstructed Fallopian tube or the hydrosalpinx should be excised.

The patient should also be made aware of the risk for the loss of one or both ovaries, and the associated consequences, which should be included in the consent form. The Anti-Mullerian Hormone (AMH) test to evaluate the ovarian reserve and the possibility of preoperative harvesting and freezing of the oocytes should be considered, especially in case of bilateral endometrial cysts [124, 132]. Out of all benign ovarian tumors, endometrial cysts play the most significant role in decreasing the ovarian reserve [132].

Recommendation

During a laparoscopic intervention for endometrial cysts, thorough pelvic evaluation to check for concomitant types of endometriosis and treatment of all lesions is advised.

Excision/coagulation of the endometriotic foci is the recommended surgical treatment in patients with infertility and DE as it increases the pregnancy and birth rates.

Laparoscopic cystectomy is the recommended technique for surgical excision of an endometrial cyst.

Regardless of the surgical method of treating endometrial cysts, minimal impact on the ovarian reserve needs to be prioritized.

Histopathology of the excised endometrial cyst or its fragment is necessary to confirm or exclude malignancy.

Before cystectomy, especially in case of bilateral and recurrent endometrial cysts, the ovarian reserve and the possibility of preoperative harvesting and freezing of the oocytes should be considered in patients with reproductive plans. Surgical treatment of endometrial ovarian cysts in patients with reproductive plans should preserve the ovarian cortex, while the blocked Fallopian tubes or the hydrosalpinx should be excised.

DEEP ENDOMETRIOSIS

The most up-to-date description of DE defines the condition as the presence of endometrial lesions, penetrating at least 5mm into the peritoneal surface, resulting in fibromuscular growth which surrounds the endometriotic foci [133]. The diagnosis of DE is significantly more challenging than in case of the other two phenotypes of endometriosis. Detailed medical history (with the use of the endometriosis questionnaire), bimanual test (including palpation of the abdomen), and imaging tests [which were mentioned in the previous chapters] are vital to make the diagnosis. The extent of lesion infiltration should also be evaluated. The latest, modified #ENZIAN classification seems to be the optimal system to address the issues associated with adequate description of the location of DE lesions, demonstrate correlation with the symptoms, plan the scope of the surgical intervention, as well as make prognosis about the treatment outcome [134]. There is insufficient amount of data to confirm the efficacy of empiric pharmacotherapy in patients with suspicion of DE.

Typical images of endometrioid foci on ultrasound or MRI might be taken into consideration without the need to perform a laparoscopy with histopathology. In the past, laparoscopic identification of DE implants on histopathology was considered to be the gold standard. However, the availability and advances in imaging techniques, periopera-

tive risk, limited number of highly specialized centers, and the financial constraints have led to the modification of the earlier management protocols and algorithms [135, 136].

Disease characteristics

Pain in patients with deep endometriosis is non-specific and its intensity is not necessarily correlated with disease advancement, determined on the basis of the size and number of endometriotic foci, which may delay diagnosis and treatment [137]. The presentation of deep endometriosis is typically multifocal, and if the involvement is isolated to the intestinal wall then the lesions are also multifocal in 40% of the cases [137]. Multifocal presentation is defined as the presence of another implant at least 2 cm from the previous one [138].

Deep endometriosis may be found in the following:
— colon;
— bladder;
— ureters;
— uterosacral ligaments;
— rectovaginal space;
— neural and vascular structures.

The uterosacral ligaments are the most common locations for DE, followed by the rectovaginal space, and the colon [137, 138]. In 90% of the cases, intestinal endometriosis is found in the sigmoid colon and the rectum, significantly less often in the ileum, appendix and cecum [138, 139]. Intestinal endometriosis may manifest as deep infiltrating foci in the muscular, less often mucosal, layer or as a superficial condition of the serous or subserous layer of the intestine. Deep endometriosis has been estimated to affect 3.8–37% of the women with undiagnosed [140, 141], and 5–12% of the women with diagnosed endometriosis. A significant percentage of women with intestinal endometriosis are preliminarily diagnosed due to other conditions of the gastrointestinal system, *e.g.*, irritable bowel syndrome (IBS) [142].

Medical history, clinical exam, diagnostic tests

The pathogenesis of pelvic pain in endometriosis is a complex issue, with a significant contribution of the autonomic system, which explains why the pain might be mistakenly taken for a symptom of IBS [142]. Deep endometriosis as a possible diagnosis should always be considered in infertile women with dysmenorrhea. Early detection of DE might allow to implement proper treatment and positively affect the quality of life in patients with endometriosis [143, 144].

Pelvic exam is useful when diagnosing DE, especially if it is conducted during menstruation. The endometriotic lesions, which are most often located in the uterosacral ligaments, the vagina, and the rectovaginal space, are particularly enlarged and palpable at that time. A double-bladed speculum exam should be performed alongside the vaginal and the rectal exam, which will allow to visualize the bluish grey endometrial implants in the vagina and help to identify the presence of the lesions in the rectovaginal space and the rectum [145].

CA-125 concentration is not recommended as a diagnostic marker for endometriosis [146]. Vasoactive Intestinal Peptide (VIP), Substance P (SP), and Neuropeptide Y (NPY) are potential diagnostic markers for DE, and miRNA and long noncoding RNA (lncRNA) assays have also attracted the attention of researchers in recent years [146–148]. Nevertheless, clinically verified, non-invasive tests are not available at present.

Diagnostic imaging

Preoperative diagnostic imaging should play a key role when devising a management plan to treat deep endometriosis. Ultrasound and MRI are the two imaging techniques which are characterized by the highest sensitivity and accuracy in the diagnostic process. Location of the endometriotic implants should be described with great accuracy before the procedure. One of the most commonly used scales should be used to assess the disease advancement. The #ENZIAN system, unlike other scales, may be used to describe ultrasound and MRI findings, which — combined with a clinical evaluation — allows for a comprehensive preoperative diagnosis [135]. In consequence, it allows not only to plan the extent of the surgical intervention with great precision, but also to compare treatment outcomes.

Apart from DE, the scale also includes description and classification of peritoneal, ovarian, and Fallopian endometriosis. Transvaginal ultrasound, ideally combined with a pelvic exam, remains the diagnostic method of choice for DE. In order to make preoperative therapeutic decisions, it is vital to determine the size of the lesions, their location, depth of infiltration, the extent of the narrowing of the sigmoid lumen, and the number of the endometriotic implants.

In a large multicenter study, undertaken to design a diagnostic model for endometriosis among symptomatic premenopausal women, high sensitivity and specificity of ultrasound testing was confirmed in patients with endometriosis (rASRM grades III and IV), especially ovarian endometriosis [149]. Numerous studies have already confirmed the correlation between ultrasound testing and correct diagnosis [149, 150]. The IDEA group published the effective methods of obtaining precise ultrasound evaluation of the endometriotic lesions [56].

According to the IDEA algorithm, the first stage of transvaginal ultrasound should focus on uterine assessment (mobility: normal, decreased, or absent), ultrasound features of adenomyosis and the adnexa (presence of endometrial cysts). The search for the so-called 'soft markers', *i.e.*, pain in the infiltrated places and ovarian immobility should constitute the second stage. Next, it is important to check for the negative sliding sign, which allows to detect adhesions

between the peritoneum and the anterior and posterior uterine wall, rendering uterine movement impossible. In the next stage, the anterior and the posterior compartments should be checked for DE nodules. The anterior compartment includes the bladder, and vesical area, and the ureters. The most common sites of DE lesions in the posterior compartment include the uterosacral ligaments, posterior vaginal vault, anterior part of the rectum, and the sigmoid colon. Ultrasound imaging of the posterior compartment should aim to determine the number, size, and location of DE lesions which infiltrated these structures [150].

Some reports in the literature claim comparable sensitivity and specificity of algorithm-based MRI and transvaginal ultrasound for the diagnosis of DE, especially using the so-called 'tenderness-guided sonography,' and higher sensitivity (75–98%) as compared to computed tomography (CT), transrectal ultrasound and clinical evaluation [151–153].

Kido et al. [154], reviewed the literature on MRI-assisted diagnostic process for endometriotic foci in various locations. MRI evaluation of pelvic endometriosis, especially deep endometriosis, should be performed in accordance with the European Society of Urogenital Radiology (ESUR) guidelines [155]. The diagnostic possibilities of MRI in endometriosis increase if the abovementioned protocols and guidelines are followed. As far as patient preparation for MRI is concerned, the following criteria should be met: fasting 3–6 hours before the test, bladder emptied 1 hour before the exam, current test results for CBC (complete blood count), urea, and creatinine levels.

Other diagnostic techniques which might increase the sensitivity of diagnosing DE include 3D ultrasound and sonovaginography, especially rectal water contrast transvaginal sonography (RWC–TVS). Rectal water contrast transvaginal sonography is based on the administration of 250–500 mL 0.9% NaCl per rectum through a Foley catheter to assess disease advancement and the extent of the intestinal stenosis. The test allows to assess not only intestinal stenosis, but also the distance between the endometrial lesion and the external anal sphincter [156]. Despite high-precision ultrasound, lesions on the colon remain a problem as they are typically not visible during imaging. The diagnostic process for DE uses computed tomography based on the modified three-dimensional colonoscopy, which allows to predict the level of the advancement of intestinal endometriosis. It is a novel approach, during which the rectum is insufflated with 25 mmHg CO_2 to obtain 3D visualization of the intestinal model [157].

Transvaginal ultrasound and cystoscopy, with biopsy and histology, remain the main diagnostic techniques for bladder endometriosis. It is essential to bear in mind that the diagnostic value of such samples is limited, as is the case with colonoscopy for suspected intestinal endometriosis. In case when ureteral endometriosis is suspected, renal ultrasound with evaluation of the severity of hydronephrosis is required. Renal scintigraphy should be considered if hydronephrosis is severe.

Surgical treatment

Precise identification of the location of DE implants is necessary to select the adequate range of surgical therapy. The optimal model of surgical treatment depends on the skill of the operators, access to the diagnostic and operating tools, and whether the operators are experienced in surgical treatment of endometriosis.

Surgical intervention should be the method of choice in women with severe pelvic pain which is resistant to pharmacotherapy. During the surgery, all endometrial implants within the pelvis (nodules on the uterosacral ligaments, endometriotic foci on and in the ureters, colon, and bladder, intraperitoneal adhesions, as well as all peritoneal foci) should be removed. Complete excision will result in total symptom resolution (in 85% of the women) and low rate of disease recurrence (< 5%) [123].

The presence of estrogen and progesterone receptors has been confirmed in all DE implants, as well as in the surrounding tissues. Therefore, all lesions should be excised with a healthy tissue margin to prevent disease recurrence [158].

The methods of surgical treatment of intestinal endometriosis are classified into three main categories: conservative shaving, discoid resection, and radical segmental bowel resection [159–164]. According to numerous sources, segmental resection is the most efficient method in case of DE [159–163]. The decision to surgically treat patients with intestinal endometriotic lesions should be based on pain intensity [from 0 to 10 points], using the visual analogue scale (VAS).

Surgical intervention needs to be considered in women with the score of > 7, *i.e.*, severe pain, because it notably deteriorates the quality of their life. In cases with less severe pain, chronic constipation, caused by significant (> 50%) intestinal stenosis due to DE lesions, is yet another eligibility criterion for surgery [160–164]. Intestinal stenosis of > 80% on RWC–TVS should also be an indication for surgical treatment, regardless of patient-reported or non-reported complaints. Asymptomatic patients, whose intestinal DE foci were accidently detected during a pelvic exam or on ultrasound, do not require surgical treatment if the following conditions are met: intestinal stenosis of < 80%, no rectal bleeding, no disease progression.

The most common complications associated with surgical interventions due to the presence of DE include:

— leakage after conservative resections or anastomoses;
— fistula formation, especially colovaginal fistula after concurrent low bowel anastomosis and opening of the vaginal lumen;

— formation of abscess;
— necrotizing colitis or ureteral necrosis in case of segmental resections.

Secondary postoperative complications may affect the neurovascular structures located below the rectum [163]. Aggressive resection below the rectum requires complete and wide excision of the peri-rectal area, where the vessels and nerves of the sympathetic and parasympathetic systems, including pelvic splanchnic nerves and superior hypogastric plexus, are located. Distant consequences of damage to these structures, known as low anterior resection syndrome (LARS), include intestinal stenosis, fistulas, ischemia, severe constipation, and hydronephrosis [164]. If the endometriotic lesions are located above the colon, including on the small intestine, close to the ileocecal valve, radical excision (segmental or discoid resection) of the lesions is advised, which is safer than in case of the large intestine.

Recommendation

Patients with DE should be diagnosed and treated at high-level care specialized centers for endometriosis — multidisciplinary hospitals which offer specialist, multidisciplinary care.

Each patient undergoing surgery for DE should receive comprehensive information about the potential benefits (*i.e.*, improved quality of life), as well as the possible serious complications associated with the surgery. These factors determine the choice of the optimal treatment strategy.

Indications for surgical intervention in patients with DE include severe pain resistant to pharmacotherapy, hydronephrosis, and symptomatic and/or critical (> 80%) intestinal stenosis.

ENDOMETRIOSIS AND INFERTILITY

Epidemiology of endometriosis in infertile women

In infertile patients, the prevalence of endometriosis has been estimated at 20–35%, although some sources claim the rate to be as high as 50%. In controlled clinical trials among women with endometriosis, medical history of infertility was confirmed 6-fold more often [35]. According to other studies, 30–50% of women with endometriosis were infertile. Fertility in patients with endometriosis is significantly decreased and the pregnancy rate for a natural menstrual cycle is only 2–10% [165].

The effect of endometriosis on infertility — pathogenic mechanisms

In advanced endometriosis, the resulting anatomical abnormalities (numerous adhesions and obstructed Fallopian tubes) may constitute an obvious, mechanical cause of infertility [165]. Various prospective and retrospective clinical trials demonstrated impaired insemination and defective implantation during *in vitro* fertilization procedures in patients with endometriosis. According to different studies, endometriosis may have a detrimental effect on the following: the quality of the oocytes, efficacy of the insemination, embryo quality, follicular and peritoneal fluid environment, and normal embryogenesis. Data about the relationship between endometriosis and the receptiveness of the uterine mucosa remain inconclusive [166].

Pharmacotherapy for endometriosis and fertility

Pharmacotherapy remains an efficient way of treating pelvic pain in women with endometriosis, but there is no hard evidence to support the beneficial effect of pharmacological treatment on fertility in that group of patients. Most of the available medicines (danazol, GnRH agonists and antagonists, progestogens, and combined pills) suppress ovulation so, in consequence, fertility during therapy is inhibited. In a meta-analysis of 12 randomized studies, which compared the therapy with the placebo, no beneficial effect of the pharmacotherapy on pregnancy rates in women with endometriosis was observed [90]. Also, none of the pharmacotherapies was found to be superior over others as far as pregnancy rates are concerned [90]. However, in case of laparoscopic removal of the endometriotic lesions and GnRH analogues, both these therapies proved to be more effective than placebo in terms of pregnancy rates [166].

In another randomized trial, no beneficial effects of preoperative pharmacotherapy on the pregnancy rates were observed. Despite these findings, due to heterogeneity of the analyzed studies and lack of data about time elapsed until pregnancy, in their latest guidelines, the ESHRE, advised caution when interpreting these observations [28]. The ESHRE experts believe that these findings should be interpreted as lack of detrimental effect of postoperative pharmacotherapy on the pregnancy rates, *i.e.*, pharmacotherapy to alleviate the pain may be recommended to women who at present cannot or have no desire to conceive. In randomized trials in women with endometriosis, no beneficial effect of anti-inflammatory treatment (pentoxifylline) and anti-estrogen therapy (aromatase inhibitors — letrozole) on fertility in natural cycles was demonstrated [167–169].

Recommendation

In infertile women with endometriosis, pharmacotherapy which suppresses ovulation does not improve the chances for conception. Postoperative hormone therapy should not be recommended merely to improve fertility. In case of patients who have no immediate

reproductive plans after surgery, hormone therapy does not lower the chances for pregnancy later on and may significantly alleviate endometriosis-related pain.

Surgical treatment of endometriosis and fertility

In minimal and mild endometriosis (rASRM grades I and II; mainly peritoneal endometriosis), operative laparoscopy and removal (excision/ablation) of the endometrial implants improves the chances of conception as compared to diagnostic laparoscopy [170].

One large, well-designed multicenter randomized trial, conducted in Canada (Endocan Study) among 341 women, demonstrated a two-fold higher probability of conception in women after surgical removal of the endometrial implants [odds ratio (OR) = 2.03; 95% confidence interval (CI): 1.28–3.24] [169]. In turn, Garcia-Velasco et al. [172], found no positive relationship between surgical removal of the endometrial cysts and the number of pregnancies in the population of patients after IVF treatment and after cystectomy, as compared to conservative treatment. In advanced stages of endometriosis, surgical treatment may restore the organs to their original position within the pelvis, but there is no reliable data to evaluate the efficacy of such management. According to a 2020 meta-analysis of 19 studies, a significant AMH decrease is observed at 3 and 6 months of follow-up after surgical intervention for ovarian endometriosis, either for one or both ovaries [173]. In another meta-analysis, the authors suggested that surgical removal of the endometrial cysts before assisted reproductive techniques may lower the number of the retrieved oocytes [174].

The effect of endometrial ovarian cysts on fertility remains to be fully elucidated because it is a rare occurrence for the disease process to be located only in the gonad. However, there are reports that the presence of endometrioma leads to lower follicular density, fibrosis, and loss of normal ovarian stroma and, in consequence, decreased ovarian reserve. According to a 2019 meta-analysis, the pregnancy rate after surgical treatment of an endometrioma was 43.8% (95% CI: 22.5–66.4) and cystectomy did not improve fertility as compared to IVF-ET, surgery and IVF-ET as well as aspiration/sclerotherapy of the cystic lesion and IVF-ET [175].

Due to the fact that it is possible to remove healthy ovarian cortex with the follicles simultaneously, and to diminish the ovarian reserve, current guidelines advise caution when making decisions about surgery for an endometrial cyst [28]. The surgical plan should take into account patient age, history of surgical interventions, ovarian reserve, pain, dynamics of the lesion growth and the prognosis, based on *e.g.*, EFI. Endometriosis Fertility Index is a validated index which describes the probability of spontaneous conception after endometriosis-related surgery (over the course of 3 years postoperatively) in infertile women.

This multi-dimensional index (0–10 points), described in 2010, is comprised of elements from patient history (age, duration of infertility, previous pregnancy — 0–5 points) and intraoperative description of the lesions (disease advancement and total scoring according to the modified classification of the American Society for Reproductive Medicine — rASRM; 0–2 points), as well as qualitative visual inspection of the adnexal function during surgery (functional postoperative score — Least Function Score; 0–3 points) [16]. A systematic review and a meta-analysis from 2020 demonstrated that the probability of spontaneous conception after endometriosis-related surgery was higher in women with higher EFI. Over 3 years, the chance for conception was 10% for EFI 0–2 points, and 69% for the highest EFI score of EFI 9–10 points [18]. The EFI index is a good predictor of chances to conceive postoperatively and may be used as a tool to plan further treatment [176, 177]. There is no evidence that removal of an endometrial cyst improves IVF-ET outcomes so surgery should be considered only in case of high-intensity pain and difficulty accessing the ovary for puncture during the IVF-ET procedure. As far as spontaneous conception is concerned, it was demonstrated that the excision of the cyst and stripping generated better outcomes than aspiration of the content of the cyst with subsequent ablation [176]. Laparoscopic cystectomy and removal of the cyst wall are associated with an almost 2-fold higher chance of spontaneous pregnancy as compared to coagulation with CO_2 laser of the lesion bed [178].

There are no well-designed studies which would compare pre- and postoperative pregnancy rates in the population of women with DE [179, 180]. The available systemic reviews, of moderate quality, demonstrated a possibility of improving natural fertility with surgical treatment [178]. Also, there are no guidelines on the optimal surgical management of infertile women with DE [179]. Due to the extent of the surgical intervention and potential complications, surgical treatment in infertile women with DE should be considered only in patients with high-intensity symptoms [28, 179, 180].

Recommendation

In infertile women with minimal and mild endometriosis (rASRM grades I and II), the laparoscopic excision of the endometriotic foci may increase the probability of conception.

Surgical treatment of endometrial cysts may be considered in case of severe pain and difficulty in accessing the gonad during IVF-ET puncture, however surgery for endometrial cysts most probably does not increase the chances for pregnancy in IVF-ET programs.

Before surgery, the patient should be made aware of the risks and benefits during a consultation. Patient

age, wishes, surgical history, ovarian reserve, and pain need to be taken into consideration.

Surgical intervention in infertile women with deep endometriosis should only be considered in case of high-intensity pain.

Endometriosis Fertility Index should be used to assess the probability of spontaneous conception after surgical treatment.

Assisted reproductive techniques in women with infertility concomitant with endometriosis

In infertile women with minimal and mild endometriosis (rASRM grades I and II), ovulation induction and IUI increase fertility and pregnancy rates [182, 183]. Such management is more effective than IUI without induction of the ovulation or conservative management. In case of moderate and severe endometriosis (rASRM grades III and IV), the use of IUI seems to be limited. However, certain retrospective studies demonstrated that ovulation induction and IUI may be considered in some women (< 35 years of age) with grade III or IV endometriosis, if at least one Fallopian tube remains patent [28, 184]. Intrauterine insemination in a stimulated cycle may be recommended in women with favorable prognosis for pregnancy (age up to 35 years, normal ovarian reserve, patent Fallopian tubes, normal semen parameters in the partner). Still, such option should only be recommended in max. 3 cycles, as the subsequent insemination cycles have significantly lower therapeutic efficacy [185].

IVF treatment should be considered in infertile patients with concomitant endometriosis resistant to treatment, especially in women aged > 35 years, with unfavorable prognosis (low EFI) and poor ovarian reserve, impaired Fallopian tube function, and male factor infertility [28, 186]. The first meta-analyses from the 90s reported that women with endometriosis had a 50% lower chance of conceiving using IVF-ET programs [187]. A 2021 metanalysis of 8 studies in women with endometrial cysts and concomitant endometriosis demonstrated a significantly lower number of the obtained oocytes, which did not affect the rates of pregnancy and live births [188]. The latest systemic reviews and meta-analyses demonstrated lower rates of conception and clinical pregnancy in women with endometriosis undergoing IVF-ET, which did not result in lower rates of live births in that group of patients [189, 190]. Further analysis of the subpopulation of women with endometriosis revealed that significantly decreased rates of successful implantation, clinical pregnancy and live births were found only in patients with rASRM grades III and IV [189, 190]. The choice of the ovarian stimulation protocol in women with endometriosis (with GnRH agonist or antagonist) does not affect the efficacy of the IVF-ET programs [191]. Earlier reports, indicating that prolonged desensitization (3–6 months) with GnRH analogues before an IVF-ET program brings beneficial effects in women with moderate and severe endometriosis, have not been confirmed [192]. At present, routine use of GnRH analogues, COC pills and progestogens to prepare women with endometriosis for ovarian stimulation in an IVF-ET program is not recommended [193]. The available literature also shows no evidence of increased risk for disease recurrence in women with endometriosis who underwent assisted reproduction treatment [194]. Also, routine laparoscopy is not advised in patients with suspicion of grade I/II endometriosis before IVF-ET treatment because it does not improve its efficacy [190]. Routine excision of an endometrial cyst before IVF-ET remains both, controversial and not recommended, as surgery may result in decreased ovarian reserve, lower number of oocytes and the need to use higher doses of gonadotropin in IVF-ET programs [190, 195] (Fig. 6). Surgical treatment may be considered in case of large cysts and concomitant pain, as well as to improve access to the ovary for IVF-ET procedures [28]. If a woman with endometriosis wishes to undergo surgical treatment, one radical surgery is recommended, as any subsequent surgical intervention may diminish her chances of conceiving [181].

Recommendation

Ovulation induction and IUI increase fertility and pregnancy rates in women with minimal and mild endometriosis (rASRM grades I and II). If the treatment proves to be ineffective, especially in patients > 35 years of age and/or with unfavorable prognosis, *in vitro* fertilization (IVF-ET) is recommended. In women with endometriosis, the choice of ovulation induction protocol does not affect the efficacy of the IVF-ET programs. Prolonged desensitization with GnRH analogues before IVF-ET to improve the outcome is no longer recommended, as there is no compelling evidence to confirm its benefits.

Deep endometriosis and fertility

The presence of DE foci has a negative effect on fertility. The underlying causes of problems with conception in patients with deep endometriosis are complex. Among other things, infertility is caused by the formation of intraperitoneal adhesions, which complicates oocyte transport [196]. Anatomic distortion (formation of endometrial cysts or adenomyosis) in the course of the disease leads to infertility [197]. Surgical treatment in infertile patients with DE does not always improve prognosis. There is no evidence to support the claim that infertility rate is higher for intestinal endometriosis as compared to other locations.

The decision to implement surgical treatment in women with DE with concomitant infertility should be tailored to the individual needs of the patient. These women should be informed about the potential benefits and complications,

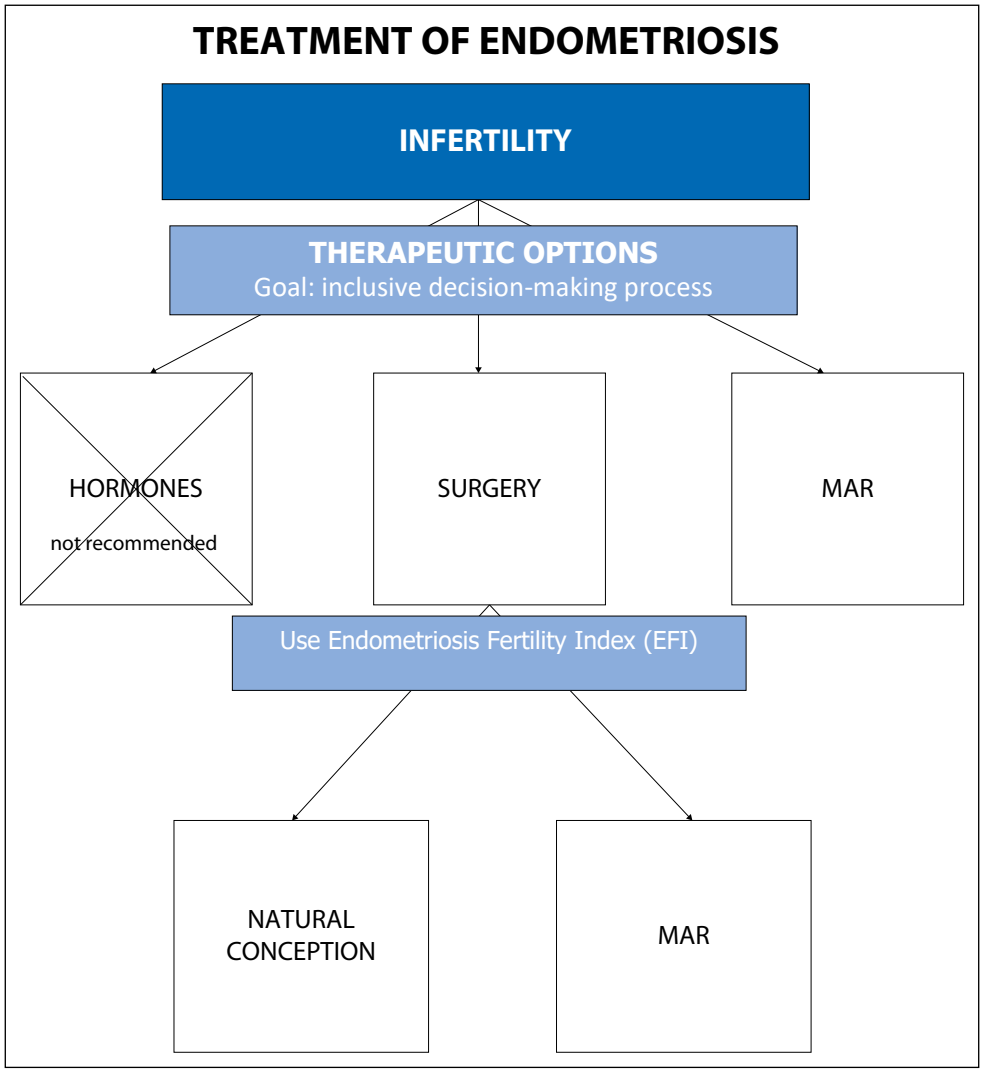

Figure 6. Management of endometriosis-related infertility; MAR — medically assisted reproduction

as well as the consequences of selecting an alternative method of treatment. According to the latest guidelines, there is limited evidence to recommend surgical therapy only to improve reproductive outcomes [198].

Several other factors are considered before implementing surgical treatment, chief among them pelvic pain, age, location of the foci, history of DE therapy, and obstetric history. Laparoscopy with complete excision of all endometriotic implants is the method of choice, aiming not only to restore the organs to their original position but also to alleviate pain, improve sexual function, mend or strengthen the bond between partners, and improve the quality of life.

Surgical treatment, which was extensively discussed in the Deep Endometriosis chapter, should be recommended to patients who report high-intensity pain, manifesting as dyspareunia and dyschezia (VAS score of > 7), as well as to patients with intestinal stenosis and those with history of IVF failure [197]. Surgery has been proven to improve fertility after at least two IVF failures [199].

ADENOMYOSIS

Adenomyosis is a benign condition, characterized by the invasion of the endometrial glands and stroma into the myometrium [200]. The pathogenesis of this pelvic disease remains to be fully elucidated but there are several hypotheses, with invagination of the endometrial basalis layer into the myometrium through the damaged junctional zone (JZ) among them [201].

According to that hypothesis, changes in the following areas might be involved in this process:

— apoptosis;
— response to sex steroid hormones;
— extracellular matrix-induced signaling pathways.

Another theory proposes the role of the 'tissue injury and repair' (TIAR) processes in the pathogenesis of adeno-

myosis. The basis for these processes includes cyclic injuries, resulting from:

— multiparity;
— history of uterine interventions, including cesarean sections [202].

Yet another theory claims that adenomyosis develops *de novo* from metaplasia of embryonic or adult stem cells in the myometrium. That theory, also known as the 'from outside to inside theory,' postulates migration of the endometrial ectopic cells from the external endometriotic foci into the myometrium [203]. It is supported by a considerable number of cases with focal adenomyosis of the outer myometrium (FOAM) among women with DE foci of the posterior compartment [204].

The most common symptoms of adenomyosis include:

— painful and heavy periods;
— dyspareunia;
— infertility.

Importantly, approximately one-third of all women with adenomyosis remain asymptomatic [205]. Until recently, adenomyosis was diagnosed accidentally, usually in a hysterectomy specimen. However, recent advancements in imaging techniques, especially MRI and ultrasound, allow to diagnose adenomyosis based on correlated clinical symptoms and imaging tests [206]. The prevalence of adenomyosis is most probably underestimated due to the lack of adequate diagnosis. Based on the findings from the uterine tissue samples removed due to abnormal bleeding, heavy menstrual pain, and other benign pelvic diseases, adenomyosis was detected in almost 60% of symptomatic and 40% of all women who underwent hysterectomy. Adenomyosis concomitant with uterine myomas was detected in 58.9% of cases. Also, adenomyosis was found in 23.8% of the postmenopausal patients [207].

Based on the imaging diagnostic criteria, a high number of adenomyosis cases (20–25%) was found among women undergoing assisted reproduction techniques [208]. Traditionally, adenomyosis has been perceived as a health problem of perimenopausal women and those in their 40s, but some sources report high incidence of adenomyosis among younger (14–24 years) women with chronic pelvic pain, reaching up to 46% [209].

Concomitance of adenomyosis and endometriosis is perhaps the most significant issue. Despite a growing number of suggestions that adenomyosis should be treated as an entirely separate disease entity, concurrent diagnosis of both these conditions has been estimated at 80% of all cases [210]. At present, the available classification systems are based on the histopathology findings, *e.g.*, classification into diffuse, focal, and cystic adenomyosis [211], but also on the imaging findings, *e.g.*, external and internal adenomyosis, as well as visualized on MRI [212].

Magnetic resonance imaging has a high predictive value if adenomyosis is suspected. The most typical indicators of adenomyosis on MRI include:

— irregularities in the junctional zone following its focal or diffused thickening;
— junctional zone thickness to myometrium thickness ratio > 40%;
— alternating areas of high and low myometrial signal intensity on T2-weighted images [213].

Nevertheless, a combination of ultrasound, whose accuracy is on a par with MRI if performed by an expert, with clinical data and pelvic exam remains the most basic and current algorithm for diagnosing adenomyosis [212].

In 2015, a consensus opinion from the MUSA group was released, in the hope that it will help physicians make more accurate diagnosis of adenomyosis [214].

When in doubt, diagnostic hysteroscopy is advised, as it often allows to detect endometrial changes that are typical for adenomyosis:

— small openings on the endometrial surface;
— irregular endometrium layer;
— fibrous-cystic lesions and hemorrhaging cysts, often with a strawberry-like appearance.

Such hysteroscopy image, with the possibility of obtaining a histopathology specimen, frequently allows to achieve a more thorough diagnosis [215].

Adenomyosis may be treated using surgery and pharmacotherapy. The choice of treatment should be determined at the discretion of the physician and the patient, depending on patient wishes and reproductive plans. If the patient has no desire to conceive, the most effective methods include total laparoscopic hysterectomy or supracervical laparoscopic hysterectomy, if the glands and stroma are disease-free and there are no signs of endometriosis in the rectovaginal septum [216]. As far as pharmacotherapy is concerned, progestogen therapy to suppress hormone secretion (preferably dienogest and norethindrone acetate or medroxyprogesterone acetate), GnRH agonists and antagonists, SERMs may be used [217]. Levonorgestrel-releasing intrauterine device is among the most effective methods of treatment [218]. If the patient has reproductive plans but presents with concomitant infertility, the treatment should be individually tailored to the patient needs. In such cases, uterus-sparing surgery is often associated with elevated risk for hysterectomy, requires experienced and skilled operators, and advanced surgical techniques [219]. In such cases, it is always advised to refer the patient to a high-level care center [220].

Recommendation

Up-to-date algorithm for the diagnosis of adenomyosis should be based on the clinical data, pelvic exam, and ultrasound test, performed in accordance with the

consensus opinion from the MUSA group. When in doubt, the MRI test — which has high predictive value — should also be included in the diagnostic process.

If the patient has no reproductive plans, the most effective methods include total laparoscopic hysterectomy or supracervical laparoscopic hysterectomy, if the glands and stroma of the cervix are disease-free and there are no signs of endometriosis in the rectovaginal space.

If pharmacotherapy is considered, progestogen therapy to suppress hormone secretion (preferably dienogest and norethindrone acetate or medroxyprogesterone acetate), GnRH agonists and antagonists, SERMs, as well as levonorgestrel-releasing intrauterine device are used.

If the patient has reproductive plans but presents with concomitant infertility, the treatment should be individually tailored to the patient needs and conducted at a high-level care center.

ENDOMETRIOSIS AND THE RISK OF MALIGNANCY

Significantly elevated risk for malignant transformation to endometrioid and clear-cell ovarian carcinoma has been observed in patients with endometrioid cysts [221–223]. A meta-analysis of 75 studies from the last 52 years, published in 2021, demonstrated that the risk for developing cancer in postmenopausal women with endometriosis is significantly associated with prior hysterectomy, bilateral salpingo-oophorectomy, and long-term estrogen-only hormonal replacement therapy without progestogens [223], although the authors also noticed the effect of the changing attitudes and disease management protocols.

Despite being a benign disease, endometriosis shares features with cancer-like transformation, including:

— development of distant foci;
— dysregulated mechanism of apoptosis;
— invasion into tissues and surfaces, with subsequent organ damage.

Endometriosis is also responsible for the development of localized and generalized inflammation, which is also associated with an elevated risk for developing cancer [224]. Moreover, a significant amount of new data about the possibility of gene sequencing appeared recently. These reports demonstrated that somatic mutations, which might cause cancer, are detected in approximately 20% of endometriomas and DE lesions [225]. The last decade witnessed a growing interest in the relationship between endometriosis and malignant transformation, especially since population studies about a possible elevated risk for certain types of cancer in women with endometriosis emerged at the same time [226].

The abovementioned findings and concerns were the reason Marina Kvaskoff et al. [227], conducted a meta-analysis of the available literature about endometriosis. A total of 17,878 publications were selected, out of which 49 cohort studies and clinical-control trials (both retro- and prospective), published until October 2019, were analyzed. The results of this meta-analysis confirmed 93% (SRR — Summary Relative Rik — 1.9) higher risk for developing ovarian cancer for women with endometriosis, especially the clear-cell (3.4×) and endometrioid (2.3×) carcinoma subtypes. Additionally, 39% (SRRs 1.39) higher risk for developing thyroid cancer and 4% (SRRs 1.04) higher risk — low but still statistically significant — for developing breast cancer, regardless of the menopausal status of the woman and breast cancer subtype, were also confirmed. These authors found no statistically significant higher risk for developing endometrial cancer, colorectal cancer, and melanoma in women with endometriosis. Their analysis revealed 32% (SRRs 0.68) lower risk for developing cervical cancer among these women [227]. These findings are a cause for concern both, for patients with endometriosis and their physicians. In light of these reports, the questions whether to update cancer prevention guidelines for women with endometriosis seems valid. The findings of that meta-analysis have been juxtaposed against the actual increase rate and the risk for developing cancer among women with endometriosis compared to the general population has been calculated as follows: absolute risk for developing ovarian cancer is 1.3% in the general population [228], and 1.8% in women with endometriosis, *i.e.*, mean increase in the risk is in fact slight — 0.5%. The risk for developing thyroid cancer is 1.3% in the general population [228], and 1.8% among women with endometriosis, *i.e.*, 0.5% increase. Absolute risk for developing breast cancer is 12.8% in the general population and 13.3% among women with endometriosis, which again amounts to 0.5% increase. Therefore, it needs to be emphasized that, despite statistically documented higher risk for developing ovarian, thyroid, and breast cancers in women with endometriosis, the percentage increase in risk does not indicate the need to modify and update the guidelines for cancer prevention in women with endometriosis. The authors of the analysis of postmenopausal women with endometriosis who underwent preventive, bilateral salpingo-oophorectomy to lower the risk for developing ovarian cancer also found no reason to modify the guidelines due to no statistically significant differences in the incidence of ovarian cancer and survival rates between patients with endometriosis and the general population [229].

Recommendation

Endometriosis, despite being a benign disease, shares numerous features with malignant transformation.

Despite statistically documented higher risk for developing ovarian, thyroid, and breast cancers in women with endometriosis, the percentage increase in risk does not indicate the need to modify and update the guidelines for cancer prevention in women with endometriosis.

The analysis of postmenopausal women with endometriosis who underwent preventive, bilateral salpingo-oophorectomy to lower the risk for developing ovarian cancer also found no reason to modify the guidelines due to lack of statistically significant differences in the incidence of ovarian cancer and survival rates between patients with endometriosis and the general population.

Article information and declarations

Funding

None.

Acknowledgments

The authors wish to express their gratitude to Harald Krentel, M.D., Ph.D., the President of the European Endometriosis League, for his invaluable help, insightful and critical review of the manuscript.

Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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