Classification algorithm of patients with endometriosis: Proposal for tailored management

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Abstract

Endometriosis is a pseudoneoplastic disease that has a significant personal and social impact. Unlike other neoplastic diseases, its management is burdened by uncertainty and controversy. The aim of this article is to furnish clinicians with a simple, useful and updated tool to select an appropriate diagnostic-therapeutic care pathway for affected women. Guidelines and recommendations cite advances in diagnostics, novel medications and optimized assisted reproductive techniques; however, such advancements have not simplified the management of endometriosis, since they often lack an integrated, multidisciplinary view of diagnostic, therapeutic and reproductive scenarios that inevitably overlap in the management of the disease. We selected and compared major society guidelines on the diagnosis and treatment of endometriosis. Three international and 5 national guidelines were analyzed. The overlapping recommendations were extracted and mapped, developing a simplified diagnostic-therapeutic care pathway in the form of an algorithm. We subdivided the patient population attending our tertiary referral center according to 4 decision nodes: type (deep infiltrating endometriosis or isolated endometrioma); stage (I–IV according to the revised American Society for Reproductive Medicine classification); predominant health problem (pain or infertility); and fertility potential of the couple (normal/abnormal screening fertility). We identified 9 classes, each corresponding to a suggested mode of treatment (medical, surgical or assisted reproductive technique) according to the most recent evidence published. This simplified scheme is designed to standardize treatment and is intended for use as a tool in diagnostic and therapeutic planning with a view to reduce inappropriate treatment.

Key words: laparoscopy, infertility, endometrioma, deep endometriosis, endometriosis management

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Introduction

The care of patients with deep endometriosis requires treatment in a specialist referral center, where gynecologists collaborate in multidisciplinary teams and evaluate their work in a volume that is sufficient to maintain their high surgical skills. Such centers, designated in the literature as centers of excellence because they operate according to principles of evidence-based medicine, provide for cooperation between gynecologist (group coordinator); pelvic sonographer and radiologist; gynecologist from the assisted reproductive technologies (ART) services; gynecologic/colorectal/urologic laparoscopic surgeon; anesthetist for pain management; psychologist; professional nurse; and (ideally) a neurologist and a patient association representative.[1–3]

The complex nature of such a system leaves it prone to error. Diagnostic Therapeutic Care Pathways (DTCP) were developed to improve reproducibility and uniformity in the delivery of healthcare services and to minimize the occurrence of adverse events. They contextualize treatment guidelines for a disease within the reality of a hospital organization, while taking account of the resources available in order to achieve the best outcome (efficacy), with the best clinical practice (appropriateness), while optimizing resources and time (efficiency).

Endometriosis is estimated to affect 10% of women between the age of 20 and 40 years; about 20% of women are diagnosed with deep endometriosis. The social cost of the disease, in terms of illness and loss of work productivity, is over $ 9,911 per patient per year.[4] The reasons supporting the choice of disease for which a DTCP can be constructed rest on priority criteria: impact on the health of the individual and the community; presence of specific guidelines; variability and unevenness in the delivery of services; and economic impact. Endometriosis meets these criteria and represents an ideal candidate for establishing a DTCP.

This paper aims to present a simplified algorithm we developed and adopted as DTCP in our tertiary referral center for the management of patients with endometriosis. The scheme, based on published data and the latest major society international guidelines, may serve as a template for developing local care pathways.

Material and methods

A literature search was conducted for society guidelines for the clinical management of patients with endometriosis published in the last 5 years. Three international societies in the field of endometriosis, reproductive medicine and gynecology, and 5 national societies were included: the World Endometriosis Society (WES, 2017),[5] the European Society of Human Reproduction and Embryology (ESHRE, 2014),[6] the International Federation of Gynecology and Obstetrics (FIGO, 2016),[7] the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2010),[8] the American College of Obstetricians and Gynecologists (ACOG, 2010),[9] the National Institute for Health and Care Excellence (NICE, 2017),[1] the French College of Gynecologists and Obstetricians (CNGOF, 2018),[10] and the Italian Society of Gynecology and Obstetrics (SIGO, 2018).[11] The society recommendations were compared and presented systematically as an algorithm, along with the quality of evidence[6,8–11] and strength of recommendation.[6,8,10,11]

Results

Algorithm

The best way to illustrate a care pathway, essentially a series of decision nodes, is an algorithm, since it gives an overview of the entire course of decision-making. The algorithm (Fig. 1) shows how the clinician, following a course through 4 decision nodes (checkpoints), is able to subdivide the patient population into 9 classes (A–I), each requiring a specific care pathway. The diagnostic checkpoints and therapeutic classes are described below.

Diagnostic checkpoints

Check 1

On the basis of findings from accurate history taking,[1,6–8] self-report questionnaire (Endometriosis Health Profile EHP-30),[12] rectovaginal exam,[6,8] and transvaginal sonography,[1,6,9,13] the gynecologist will be able to discriminate between peritoneal (superficial or deep) endometriosis and isolated endometrioma(s). A transvaginal sonography exam should be performed by the coordinating gynecologist and include consultation, according to standard protocol.[14,15] Ovarian endometriomas are often markers of a more extensive disease.[8] When the 2 ovaries adhere posteriorly to the uterus in the cavity of Douglas, they appear as "kissing ovaries" on the sonogram. This necessitates ruling out deep pelvic endometriosis with bowel and tubal involvement (20% and 90%, respectively).[16] When ovarian and deep endometriosis are present, the latter is prioritized in the management pathway.

Check 1bis

When endometriosis has been found, the coordinating gynecologist stages the disease or orders further tests to stage it. If first-line investigations (history, consultation, transvaginal sonography) are inconclusive, second-line diagnostic tests should be ordered, e.g., pelvic magnetic resonance imaging (MRI) with contrast if organ involvement is suspected (bowel, bladder, ureters).[17] If bowel stenosis is suspected, double-contrast barium enema and/or computed axial tomography (CT) of the colon, eventually

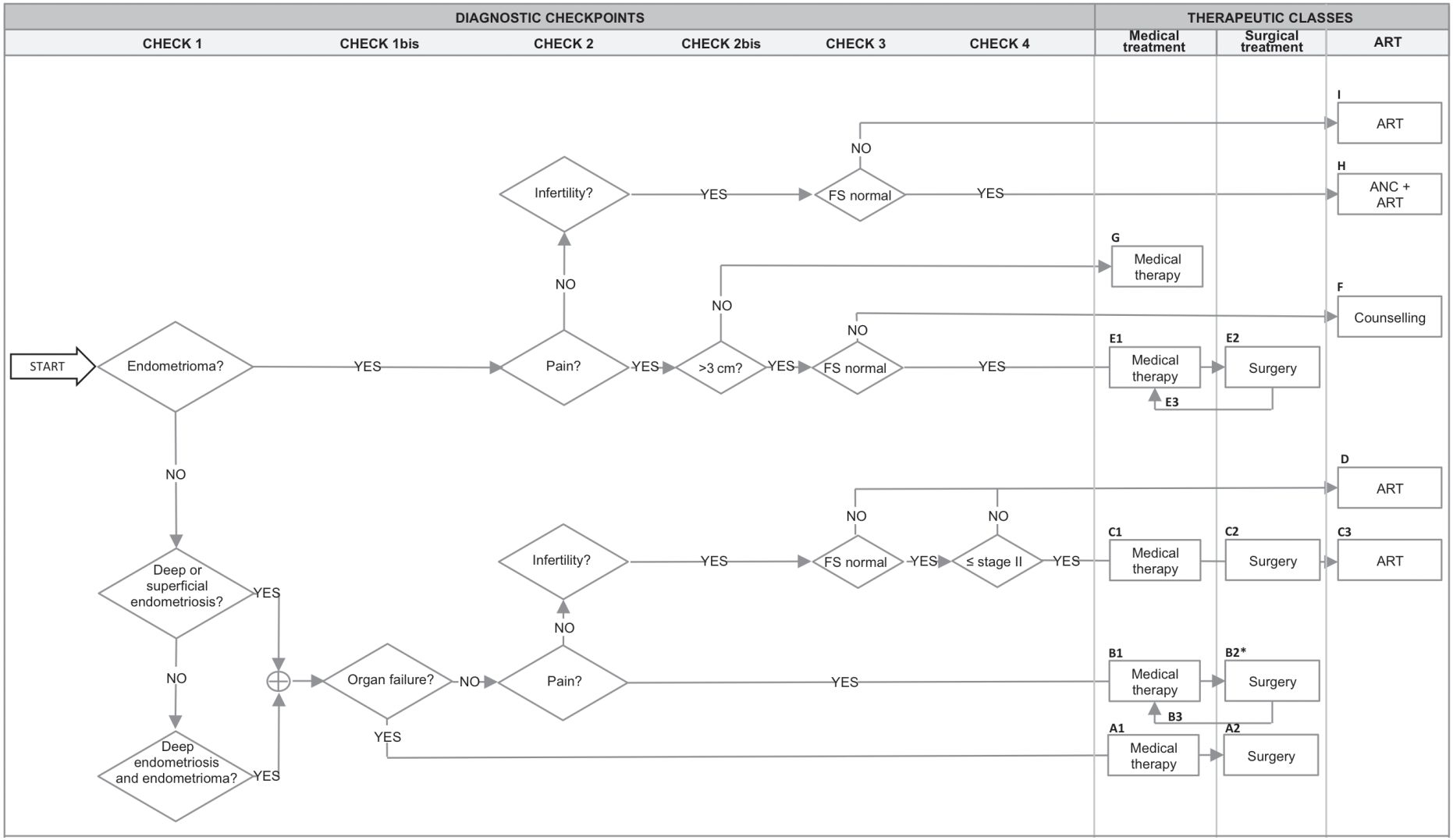

Fig. 1. Classification algorithm of patients with endometriosis (arrow: flowchart starting point)

FS – fertility screening; ANC – attempts of natural conception; ART – assisted reproductive technologies; * if medical treatment fails.

with virtual colonoscopy, can be ordered.[1,8] Cystoscopy can be useful to rule out bladder trigone involvement.[1,8] If hydronephrosis is suspected, renal scintigraphy will yield useful information on residual renal function. Imaging with 16α-[18F]-fluoroestradiol positron-emission tomography/CT has been shown useful in discriminating between scar tissue and endometriotic tissue in patients with a history of surgery and in the diagnosis of sites of extrapelvic disease. Its use is still limited to clinical studies, however.[18]

Check 2

Endometriosis causes pain and infertility. Pain manifests with dysmenorrhea in 80% of women and with dyspareunia in 30%. Between 30% and 50% of women will be affected by infertility, defined as the inability to conceive after 1 year of regular, unprotected intercourse. The monthly pregnancy rate is 2–10% compared to the 15–20% rate for the healthy population.[19] It is essential for the following decision node to understand the main reason why the patient sought consultation (pain or infertility) in order to meet her health needs.[1]

Check 2bis

Most guidelines set an endometrioma size of 3 cm as a cut-off value for clinical decision-making.[6,8,14]

Check 3

Since endometriosis affects women of reproductive age and ovarian surgery invariably leads to the depletion of oocytes, the reproductive state of the woman and her partner should be evaluated. Fertility tests include the level of anti-Müllerian hormone (AMH) in the blood, sonohysterosalpinography (SSG) and sperm test.[10] Fertility screening (FS) comprises these tests. We will use the term "subfertile" to identify women who are infertile but with normal fertility screening test results.

Check 4

The most widely used endometriosis classification is the revised American Society for Reproductive Medicine (r-ASRM) system issued in 1997 that uses 4 stages according to local spread of the disease (I – minimal, II – mild, III – moderate, IV – severe).[20] Other, more recent systems are the Enzian classification[21] and the Endometriosis Fertility Index (EFI).[22] All 3 have attracted criticism for the poor correlation between disease stage and symptoms and their inability to predict disease stage. Nonetheless, until new systems become available, it is recommended that patients undergoing surgery be evaluated according to the 4-stage r-ASRM classification and that those with deep endometriosis not yet treated surgically be evaluated according to the Enzian classification; finally, patients in whom fertility is a priority should be assessed according to the EFI.[5]

Therapeutic classes

Class A – patients with organ failure due to deep endometriosis

A1

In cases of deep endometriosis involving the bowel, bladder or ureters, 3-month therapy with gonadotropin-releasing hormone (GnRH) analogues can be considered before surgery.[1,23]

A2

Surgical treatment is indicated and necessary in cases of severe infiltrating or stenosing disease involving the bowel, bladder, ureters, or pelvic nerves.[8]

Class B – symptomatic patients with superficial or deep endometriosis

B1

Progestin or combined estrogen/progestin therapy can be considered as first-line treatment in patients with symptomatic endometriosis since it has been demonstrated effective in relieving dysmenorrhea (decrease from 3 to 9 points out of 10 on the visual analogue scale (VAS)), dyspareunia and chronic pelvic pain in patients with disease involving the rectum, vagina and rectovaginal septum (RVS). There is no evidence for recommending therapy only to reduce lesion volume in order to prevent surgical complications.[10]

Since there is no significant difference in efficacy between hormone therapies, the choice should be based on safety parameters (e.g., risk of venous or arterial thrombosis), tolerability and costs. There is consensus on first prescribing progestins, then combined estrogen/progestin therapy as first-line therapeutic options. The GnRH agonist therapy or Danazol, though equally effective, should be considered second-line treatment owing to their side effects.[11,24]

Progestins can be administered via oral, intrauterine, intramuscular (IM) or subcutaneous (SC) route. The 2 oral progestins most widely studied for their effect on deep endometriosis are norethindrone acetate (NETA) and dienogest. A recent observational study showed that the two have a substantially similar benefit and that dienogest has better tolerability. The NETA has androgenic activity, is partially metabolized into estrogen, which should protect against bone loss during prolonged therapy, and has greater progestin effects than dienogest,[25] which has mainly antiandrogenic effects. Although the lowest dose approved by the U.S. Food and Drug Administration (FDA) for NETA is 5 mg daily, excellent results have been obtained with half the dose (2.5 mg daily). Dienogest can provide an effective long-term therapeutic option.[26,27] A daily dose of 2 mg was found to be significantly superior

to placebo and equally effective as GnRH agonists in relieving pain.[8,28] Desogestrel[29] is another oral progestin that has been shown to reduce pain in patients with endometriosis of the RVS by 2 points on a VAS pain scale.[10]

Levonorgestrel-releasing intrauterine system (LNG-IUS) can be considered in patients with endometriosis of the RVS and adenomyosis, who no longer seek conception and do not tolerate systemic progestin administration.[30] The lower amount of progestin released in the bloodstream through the IUD reduces the risk of systemic side effects.

Depot medroxyprogesterone acetate (DMPA), IM or SC formulation is poorly manageable because its action can persist for more than 3 months after IM injection and the lack of androgenic properties increases the risk of bone mineral density loss and hypokalemia during prolonged use. Estrogen/progestins can be administered by oral, vaginal or transdermal route with equal efficacy.[1,4,17,24]

Preparations with a lower percentage of ethinylestradiol and containing second-generation progestins should be preferred. They can be administered cyclically or continuously. Continuous administration is preferable when the prevalent symptom is dysmenorrhea.

The GnRH agonists relieve endometriosis-related pain, although there is limited evidence regarding dosage and duration of treatment[31] (strength of recommendation A).[6] A GnRH agonist should never be used for prolonged periods without the addition of estrogen therapy (e.g., 1 mg of 17-alpha estradiol or equivalent).[8,9] The GnRH agonists do not cause flare-ups, have a rapid effect and suppress the pituitary gland in a dose-dependent manner. The FDA has recently approved their use (Elagolix) for the treatment of moderate-to-severe pain (dose 150 mg daily or 200 mg twice daily).[32]

In women with endometriosis of the RVS refractory to medical or surgical treatment, aromatase inhibitors with combined estrogen/progestin therapy or progestin therapy alone or with GnRH analogues can be considered as they have been shown to reduce endometriosis-related pain[33] (strength of recommendation B).[6]

B2

Between 1/4 and 1/3 of patients do not respond to medical therapy, probably because of progesterone resistance.[34,35] Surgical treatment of endometriosis is indicated in patients with pelvic pain who do not respond to, decline or have contraindications to medical therapy in order to relieve endometriosis-related pain and improve the patient's quality of life (evidence level IIIA)[6,9] (strength of recommendation B).[8]

The goal of conservative surgery is to remove endometriotic lesions, restore normal anatomy, and preserve visceral innervation and fertility.[8,11,36] Shaving, discoid and segmental resection are the most used techniques in the surgical management of intestinal endometriosis.[37] There is evidence for the superiority of the laparoscopic over the laparotomic approach in the treatment of pelvic endometriosis, independent of disease severity, as long as surgery is performed in a referral center highly specialized in endoscopic pelvic surgery and by surgeons expert in treatment of the disease[11] (evidence level IIIA).[8] Non-conservative surgical treatment (hysterectomy and adnexectomy) is reserved for cases with pain refractory to medical and surgical therapy and in women in perimenopause who do not desire future pregnancies. In such cases, visible endometriosis must be completely removed.[1,6,11]

B3

After excisional surgery, hormone therapy should be considered to prolong the benefits obtained with surgery and to prevent disease recurrence[38] (evidence level A).[6]

Class C – subfertile patients with early stage endometriosis

C1

Because adequate evidence is lacking in subfertile women with endometriosis, we recommend against prescribing hormone therapy before any intervention to improve spontaneous pregnancy rates. The only benefit of prescription is pain relief (strength of recommendation, good practice point (GPP)).[6]

C2

In subfertile women with r-ASRM stage I/II endometriosis, ablative or excision laparoscopy of endometriotic lesions raises the pregnancy rate as compared to diagnostic laparoscopy alone[39,40] (evidence level I)[8] (strength of recommendation A).[6] Eight patients need to be treated to achieve pregnancy in 1 of them. It would be more sensible to propose surgical treatment in young patients (<37 years) with a brief duration of infertility (<4 years), presence of ovulatory cycles, normal uterine anatomy, and partner's normal sperm function.[8]

C3

If spontaneous conception does not occur within 6 months after surgery, ART should be advised.[11] In infertile women with r-ASRM stage I/II endometriosis, it is reasonable to propose within 6 months after surgery a cycle of ovarian stimulation followed by intrauterine insemination (IUI) rather than further expectant management.[41] The pregnancy rate in such cases is similar to that reported for infertility of unknown origin[42] (strength of recommendation C).[6]

Class D – subfertile patients with advanced stage endometriosis and infertile patients with endometriosis

In subfertile women with r-ASRM stage III/IV endometriosis, there are no controlled studies comparing reproductive outcome after surgery and after expectant management. Prospective cohort studies showed a higher crude

spontaneous pregnancy rate after laparoscopic surgery than after expectant management.[43,44] However, the benefit of reproductive outcome obtained from surgical eradication of deep endometriosis compared to expectant management before ART has not yet been clearly established (strength of recommendation C).[6] The literature contains no randomized studies; there are only 2 prospective cohort studies that showed conflicting results. While some data suggests that surgical resection of endometriosis can improve the pregnancy rate, ovarian damage with decrease in the number of antral follicles can occur after the procedure.[45,46] The pregnancy rate after ART in women with deep endometriosis is the same as that after ART for other indications[47] (strength of recommendation C).[6] An improved outcome of ART after GnRH analogue therapy for 3–6 months before ART was mentioned in a single report and not confirmed to date.[23] Currently, there is weak evidence for the utility of this therapy (strength of recommendation B).[6]

Class E – symptomatic patients with endometrioma size >3 cm and normal FS

E1

Preoperative medical therapy should be understood as symptomatic and not cytoreductive since the lesions do not regress completely[48] and resume their metabolic activity when therapy is stopped.[11,49] Nonetheless, a recent study reported a marked reduction in cyst dimension after dienogest therapy.[26]

E2

It is reasonable to propose enucleation of endometriomas >3 cm in symptomatic women[6] with intact ovarian reserve, large unilateral cysts, or radiologically or clinically suspected cysts.[34] Compared with vaporization or coagulation of the cyst bed, excision of endometriotic cysts is better for reducing the number of recurrences, and the persistence/onset of pelvic pain.[9] It is also associated with a higher rate of spontaneous pregnancy in the short and long term[50,51] (evidence level I)[8] (strength of recommendation A and B).[6]

E3

In patients who do not desire future pregnancies, postoperative hormone therapy can be proposed, since it has demonstrated a lower recurrence rate (evidence level IA),[8] independent of the type of progestin used.[11]

Class F – symptomatic patients with endometrioma size >3 cm and abnormal fertility tests

Laparoscopic stripping is associated with a reduction in ovarian reserve, which is quantifiable with a mean postoperative decrease in AMH of 1.13 ng/mL.[52,53] Patients with endometrioma had significantly lower AMH levels than age-matched patients with no endometrioma, irrespective of the type of surgery, and reduced response to ovarian stimulation in the presence of large cysts.[34] Patients with symptomatic ovarian endometriosis, especially if bilateral, should be adequately counseled on the risks of reduced ovarian function or premature ovarian failure. The risks of surgery should be weighed against the benefits in women with a history of ovarian surgery[6] or low AMH levels (near 1 ng/mL). An option in selected cases is preservation of fertility via cryopreservation of ovarian cortical fragments or mature oocytes obtained with superovulatory induction and transvaginal ultrasound-guided oocyte retrieval.[11,55] Alcohol sclerosing therapy is an technique alternative to laparoscopic enucleation and may be considered in such circumstances, though it has not been tested in adequately sized patient samples in randomized prospective trials.[10]

Class G – symptomatic patients with endometrioma size <3 cm

In cases of endometrioma size <3 cm, watchful waiting and medical therapy for pain relief are recommended (evidence level IA).[8]

Class H – subfertile patients with endometrioma

Young women with regular menstrual cycles in whom endometrioma is incidentally discovered, without signs of malignancy, and with good ovarian reserve should be encouraged to conceive naturally for a limited amount of time.[34] If, however, natural conception fails and a course of ART is planned, excisional surgery can be considered to improve follicular access.[6,8]

Class I – infertile patients with endometrioma

In infertile patients with endometrioma size >3 cm, there is no evidence that cystectomy before ART improves the pregnancy rate[42,56] (strength of recommendation A).[6] The results of ART are similar for women with and those without endometrioma, even if the number of oocytes retrieved is smaller, indicating a reduced ovarian reserve.[11,57]

Atypical endometriomas or cysts with suspicious appearance absent, and asymptomatic women of advanced reproductive age with reduced ovarian reserve, bilateral endometriomas or a history of ovarian surgery may benefit from direct access to ART since surgery may further compromise ovarian function and delay the start of treatment.[34] Improved outcome after ART following GnRH analogue therapy for 3–6 months before starting ART therapy was reported in 1 study and never replicated[23]; further findings are awaited. Currently, there is weak evidence for the utility of this therapy (strength of recommendation B).[6] Outcome after ART is poorer for women with concomitant deep endometriosis.[58]

Discussion

Due to the poor correlation with disease symptoms as well as a lack of predictive prognosis and unclear pathways of treating pelvic pain and infertility, the current classification systems for endometriosis, which are based on disease extension, continue to attract criticism. Adamson stated that a good classification system is one that provides a simple description of the disease, correlates well with the pain and infertility experienced by women, and predicts response to pain relief, infertility and recurrence of post-treatment symptoms.[59]

As the primary goal is treating the patient rather than the disease, we developed a patient-based classification system concerning patients' health needs, identifying them as possible determinants of therapeutic choices. Personalized medicine emphasizes the customization of healthcare, where decisions and practices are tailored to individual patients whenever possible to improve tolerability and compliance.[60] However, unless details are provided on the parameters that lead to personalized choices, a generic appeal to personalized therapy risks turning into a justification for empiricism. Indeed, in clinical practice, physicians are more comfortable with pursuing these goals if pragmatic aids, such as predefined algorithms, are provided. Therefore, it is advisable to set up a clear decision-making process for complex situations in a complex environment.

In medicine, algorithm-based practice implies that the sequence is strictly followed and that the physician does not base primary decisions on individual patient characteristics. Conversely, a patient-tailored approach adopts a treatment strategy based on the individual patient's specific disease situation. Our algorithm was set up in an attempt to merge patient-related parameters (pain, pregnancy desire and fertility status) with disease-related parameters (superficial or deep endometriosis vs isolated endometrioma, disease staging), bearing in mind that a patient-tailored approach and an algorithm-based decision-making are not mutually exclusive but rather complementary.

For planning and analyzing the feasibility of DTCP in a referral center, the subdivision in patient groups is crucial to help clinicians to determine their own adherence to the management pathway and to monitor the quality of care through patient's outcomes. For instance, on the basis of the current literature on women with endometriosis, population A should be expected not to exceed 5% of the total[37]; population B2 to be about 25% of population B1[35]; ans populations C3, D and H/I to have pregnancy rates ≥35%, ≥30% and ≥30%, respectively.[57,60]

Though established in gynecological oncology, DTCP have not yet become part of clinical practice in the management of benign gynecological conditions. The algorithm presented in this article has the potential to help the clinician reduce interindividual variability and ensure patient-tailored treatment. We are confident that the dissemination and adoption of this management tool may, through consistent implementation, lead to the standardization of care.

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