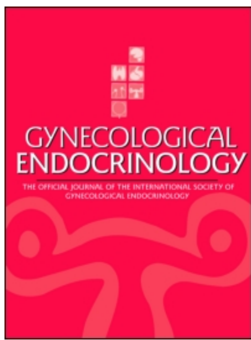

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ORIGINAL ARTICLE

Conservative treatment of deep infiltrating endometriosis: review of existing options

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ABSTRACT
Endometriosis with its estimated incidence rate of ~7–10% of women of reproductive age is a disease with the wide spectrum of symptoms depending on form and localization of endometrial foci. One clinical form of endometriosis is deep infiltrating endometriosis (DIE), most difficult to manage and generating a lot of direct and indirect treatment costs. We search the literature from PubMed database to establish the role of conservative treatment of DIE. Randomised controlled trials are lacking but in experts opinion hormonal treatment should be the first-line treatment in DIE. After evaluation of pain or other symptoms, second-line therapy with GnRH analogs or danazol should be offered or minimally invasive surgery. Consensus is not made whether surgery is the best therapeutic treatment for affected patients. Strong depending on surgeon's experience conservative surgery should be offered if the total excision of DIE foci is possible, which is essential for a successful outcome. If available treatment options do not release pain associated with DIE, experimental treatment in clinical trials should be discussed with patients.

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Introduction

Endometriosis is a common gynecological disease (it affects 7–10% of women of reproductive age) in which tissue from the uterine cavity becomes implanted outside this organ (95% is located in pelvic minor). Endometriosis tissue is biologically the same as basal endometrial tissue but there are some changes in genes expressions. Foci of endometriosis consist of glands, stroma cells, and smooth muscle. They are supplied by nerves (neurogenesis), lymphatic vessels, and blood vessels (angiogenesis) [1,2]. Clinically, we are able to distinguish three forms of endometriosis: superficial peritoneal lesions, ovarian cyst (i.e. endometrioma) and deep infiltrating endometriosis (DIE). DIE is the most debilitating form of this disease and it affects several anatomical locations: the urinary bladder, torus uterinum, uterosacral ligament, rectovaginal septum and bowel. Symptoms of DIE include: severe pain that increases during menstruation, pelvic tenderness, digestive and urinary symptoms (painful defecation, chronic pain in the abdomen, bloating, diarrhea, dysuria), and infertility [3]. The available evidence suggests the same pathogenesis for deep infiltrating vesical and rectovaginal endometriosis. Moreover according to anatomic, surgical, and pathologic findings, deep endometriotic lesions seem to originate intraperitoneally rather than extraperitoneally. Furthermore, the lateral asymmetry in the occurrence of ureteral endometriosis is compatible with the menstrual reflux theory and with the anatomic differences of the left and right hemipelvis [4]. Examination of patient with DIE requires precision because subtle changes in the vaginal wall, nodules in rectovaginal septum and uterosacral ligament can be easily overlooked during a routine colonoscopy or palpation. Occasionally, endometriosis implants may be visible in the vagina or the cervix. Moreover, during palpation it is important to detect painful infiltration in the sacral–uterine ligaments, vesicocervical septum and cul-de-sac [5]. Beside clinical examination ultrasound, so called 'tenderness-guided ultrasound' [like TRUS (transrectal ultrasonography) and TVUS (transvaginal ultrasonography)] or magnetic resonance imaging (MRI) should be implemented. MRI has a high accuracy in the diagnosis of endometriosis and can visualize most endometrioid implants, including those that are located under adhesions and in the subperitoneal regions [6]. Furthermore, it can provide useful information for planning surgery in patients with suspected DIE. MRI yields morphological information by using mainly T_1- and T_2-weighted sequences, but can also provide functional information by means of intravenous gadolinium, diffusion-weighted imaging or cine-MRI [7]. TVUS could be used clinically to identify additional anatomical sites of DIE compared with MRI during preoperative planning. TVUS and TRUS have similar degrees of accuracy for predicting intestinal involvement but TVUS must be the first-line imaging process to perform for patients presenting with clinically suspected DIE [8–11]. However, TRUS is valuable in identifying bowel endometriosis (MRI has low informative capabilities in this case). Moreover, if there is suspicion that endometriosis is in urinary bladder, cystoscopy should be performed [6,12,13]. It has to be highlighted that choosing the most effective treatment method is a challenge and should be based on patient history and clinical signs/symptoms [14]. On the photo, we show a typical DIE foci on rectovaginal septum (Figure 1)

Methods of conservative treatment

Conservative therapy which include pharmacological or/and modern surgical conservative treatment is used in young women

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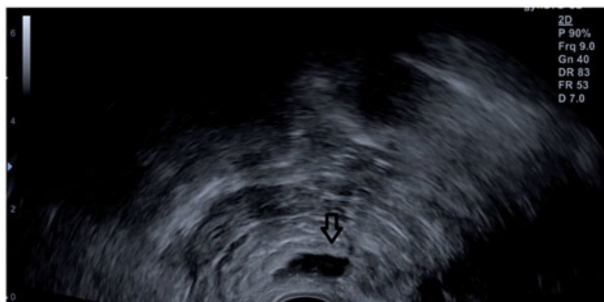

Figure 1. DIE foci on rectovaginal septum.

in reproductive age who are planning to become pregnant. Furthermore, complementary treatment plays an important role in whole therapy and it consists of proper lifestyle, diet rich in vegetables, omega-3 polyunsaturated fatty acids with less consumption of red meat, coffee, alcohol and trans fats [15]. It is proved that dairy foods and some nutrients can modulate inflammatory and immune factors, which are altered in women with endometriosis. Moreover, Harris et al. [16] showed in their study that proper lifestyle, intakes of magnesium phosphorus, calcium and vitamin D lower the risk of occurrence and strengthen the effectiveness of treatment of endometriosis [16].

Conservative surgical treatment

Laparoscopic approach is considered as gold standard in diagnostic and therapeutic methods and include: adhesiolysis, laser/diathermy ablation of endometriotic implants, resection of endometriosis nodules and excision of focals in neighboring organs. Remarkably to the aims of such procedures, we can enter restoration of fertility and reduction of chronic pain [17,18]. Furthermore, endometriosis due to its inflammatory nature, is an adhesiogenic disease and it can have directly negative impact on the tubo-ovarian unit by distorting the anatomy, indirectly by invoking inflammation which leads to further adhesion formation. For these reasons, adhesions and endometriosis are two connected entities and adhesion prevention or removal in endometriosis treatment should be considered [19]. What is more the ESGE Adhesions Research Working Group and the European Society of Human Reproduction and Embryology ESHRE recommend the consistent use of an anti-adhesion standard and eventually adhesion prophylactic agents during endometriosis surgery [19,20].

According to Shervin et al. [21] in advanced endometriosis with DIE and infertility, fine excision and stripping of the endometrioma along with radical resection of DIE improves fecundity without any significant adverse effect in comparison with patients with intact ovaries [21]. Moreover, it is proved that laparoscopic surgery for bladder endometriosis is favorable for spontaneous pregnancy and conception after *in vitro* fertilization (IVF) treatment and it seems warranted to offer laparoscopic surgical management to symptomatic infertile patients diagnosed with bladder endometriosis, even after IVF failure [22]. Additionally, it is confirmed that laparoscopic surgeries can be safely performed in cases of deep rectovaginal endometriosis and more patients may benefit from rectal sparing procedures [23,24].

Pharmacological treatment

Pharmacotherapy is used to induce regression and inhibition of endometrial implants, restoration of fertility and reduction of pain, and it is widely implemented in patients in reproductive period. The choice of treatment depends mainly on the tolerance of the patient to frequent adverse reactions and monthly expenditure on medicines [25]. Pharmacological treatment can be implemented as part of the preparation for the surgery, as well as a suplement in the postoperative period. It has been proved that the best therapeutic effects are achieved by the combination of surgical treatment with pharmacological therapy. Medical treatment for endometriosis include combined oral contraceptive pills, danazol, gestrinone, medroxyprogesterone acetate, and gonadotropin-releasing hormone agonists (GnRH-a) [26,27]. Typical dosage is shown in Table 1. In this article, the role of them as well as current evidences in DIE will be disussed.

Combination oral contraceptives

Combination birth control pills, also known as the pill, are oral contraceptives that contain estrogen and a progestin. Combination oral contraceptives (COCs) showed a positive effect on patients with endometriosis by down-regulating cell proliferation and enhancing apoptosis in the eutopic endometrium [25]. Furthermore use of hormonal therapy can be associated with significantly reduced nerve fiber density in DIE lesions and this may be an important mechanism of action of hormonal therapy for controlling pain symptoms. The results of Tarjanne et al. [28] showed that the expression of estrogen-regulated nerve growth factor and its receptor was only partially suppressed during the use of hormonal therapy, suggesting that local estrogen action is often maintained during conventional hormonal therapy in cases of DIE [28]. On the other side, the relationship between the use of oral contraception and endometriosis remains controversial. It is speculated that the past use contraception for primary dysmenorrhea may serve as a marker for women with endometriosis and DIE. It is associated with surgical diagnosis of this disease especially when it was implemented because of painful menses [29].

Gnadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists (GnRH-a) have an important place in the treatment of endometriosis. Their effect can be described as entering woman in a state of 'artificial menopause'. Inhibiting the secretion of pituitary luteinizing hormone lead to a decline in estradiol concentrations (characteristic phenomenon for women in menopausal period) [30]. During treatment, menstrual periods should be lost as well because it is the determinant of hypoestrogenism and thinning of the endometrium. During therapy can appear side effects characteristic for the reduced level of estrogen, which include: hot flashes, vaginal dryness, loss of bone density, and mood fluctuation [31]. Moreover, Angioni et al. [32] performed study in which they evaluated the role of post-surgical medical treatment with GnRH-a in patients with DIE that received complete or incomplete surgery laparoscopic excision. The results of the research showed that GnRH-a administration was followed by a temporary improvement of pain in patients with incomplete surgical treatment but it had no role on post-surgical pain when the surgeon was able to completely excise DIE implants [32].

Dienogest

Dienogest is a progestogen dedicated for the treatment of endometriosis. It works by suppressing estradiol production and preventing the growth of the endometrium. The advantage of this

Table 1. Typical dosage of drugs used in endometriosis treatment (according to manufacturers' drugs leaflets).

The name of drug	Dose	Route of administration	Duration of treatment	Registration for treatment of endometriosis (YES/of label)
Triptorelinum	0.1 mg/1 ml	s.c.	0.5 mg QD/7 days, 0.1 mg QD next 6 months	YES
Triptorelinum (Depot)	3.75 mg	i.m.	1×/28 dni; first injection in the first 5 days of menstrual cycle	YES
Goserelinum	3.6 mg	s.c.	1×/28 dni; first injection in the first 5 days of menstrual cycle	YES
Dienogest	2 mg	p.o.	1 tablet QD; 6 months, up to 15 months	YES
Danazol	200–800 mg/day	p.o.	Maximum 6 months	YES
EE + progestins	Continuous use 1 tablet QD	p.o.	6 months	of label
EE + progestins	Used according to drug leaflet (21 + 8; 24 + 4)	p.o.	6 months	of label

EE: ethinyloestradiol; sc: subcutaneous; im: intramuscular; po: per os = orally; dni: days.

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drug is reduction of pain associated with endometriosis and this reduction is comparable to GnRH-a. Moreover, dienogest can be started on any day of the menstrual cycle but it should be taken every day without interruption (if a tablet is missed, the next one should be taken as soon as possible and dosing continued as normal the next day). However, dienogest should not be given to patients with hypertension, an active thrombo-embolic disorder and history of cardiovascular disease. Furthermore, diabetes and severe hepatic disease, a history of liver tumors or sex hormone-dependent malignancies are contraindications to dienogest [33]. It demonstrated clinical efficacy comparable to GnRH-a in reducing chronic pelvic pain, menstrual pain and dyspareunia [34]. Furthermore, Agarwal et al. [35] presented a case of 38-year-old woman in post-delivery period with DIE in urinary bladder and primary symptoms like mild dysmenorrhea, catamenial dysuria and hematuria and in which dienogest treatment was implemented because of declined surgery. After 16 months, >50% reduction in the size of the bladder nodule was seen. As a result, it can be concluded that it may be one of the options for medical management of deep endometriosis in young women especially when surgical intervention is for some reasons delayed [35].

The levonorgestrel-releasing intrauterine system

The levonorgestrel-releasing intrauterine system (LNG-IUS) has been reported to improve the pain symptoms associated with endometriosis and adenomyosis, to reduce menstrual blood loss and increase hemoglobin levels [36]. Lan et al. [37] showed a comparable effect in the treatment of endometriosis-associated symptoms of LNG-IUS to GnRH-a but LNG-IUS may have some clinical advantages over GnRH-a. According to the results of their study, the level of CA125 decreased significantly at 6 months after insertion of the LNG-IUS, suggesting that the LNG-IUS may have an effect on endometriosis lesions. Furthermore, LNG-IUS releases high levels of LNG directly to the circumambient endometrium, depleting estrogen and progesterone receptors, thereby reducing endometrial cell proliferation, which is subsequently followed by decidualization of the stroma and atrophy of endometrial glands. The LNG-IUS is generally well-tolerated when used as a contraceptive device in women. Any adverse effects are often transient and do not have any detrimental influence on patient satisfaction [37,38]. Moreover, studies show that use of LNG-IUS in the treatment of rectovaginal endometriosis has strong effectiveness [39]. Efe et al. published a case of 29-year-old female presented to the emergency department with massive red-colored solid endometrial lesion extending into the bladder on the left ureter orifice on the left side wall of the bladder accompanied by hydronephrosis in the left kidney. In the medical history of the patient, it was recorded that the patient had complaints of hematuria and severe pelvic pain which had been ongoing for 4–5 menstrual cycles. After application of LNG-IUS, at the end of 12 months, the mass had completely recovered and the symptoms had disappeared. Therefore, this treatment method had a positive effect on the patient's quality of life [40].

Danazol

Danazol is a synthetic steroid (17α-ethinyltestosterone derivative) that acts by inhibiting steroidogenesis and by increasing free testosterone levels. It has antigonadotrophic effects on the pituitary. It has efficacy in suppressing normal endometrial growth and in causing atrophy of deposits of endometrium [41]. Danazol competitively inhibits aromatase activity in endometriosis-derived stromal cells without affecting either the mRNA or protein levels of aromatase. Danazol has been shown to be effective in treating endometriosis, leading to remission [42,43]. Therapy is generally well-tolerated by the patients, however, there are reported side effects like: acne, oily skin, seborrhea, water retention, hirsutism, hot flushes, and atrophic vaginitis which often led to discontinuation of treatment [44]. Nowadays, it is most common to use vaginal danazol which can be administered by ring, gel and capsule. This therapy has effectiveness in DIE resulting in a cure of dysmenorrhea and tenderness in cul-de-sac within 3 months and induration or nodularity in the cul-de-sac within 7 months. Positive aspects of this treatment are: undetectable serum danazol concentrations (which implies with possibility of ovulation and conception occurrence in infertility women), no endometrial atrophy, absorption of danazol through the vaginal mucosa and reaching the DIE via diffusion [45].

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line treatment for pain caused by endometriosis. Treatment of pain associated with endometriosis is intended to reduce symptoms enough to allow women every day work. There is no evidence whether any individual NSAID is more effective than another [25,46].

New treatment of DIE

Statins are proposed as possible and effective tools for controlling this disease due to its antiproliferative, antiangiogenic, antioxidant and anti-inflammatory properties [47]. Scientists emphasize the utility of statin administration because of their ability to

reduce cell viability and migration, and the inhibition of angiogenesis [48]. New options could be selective steroidal aldo-keto reductase 1C3 (AKR1C3) inhibitors or selective progestin receptors modulators but clinical data has been still lacking [49,50]. Promising are aromatase inhibitors, successfully used by Ferrero et al. [51] in bladder endometriosis or GnRH-a [52]. Each of mentioned new agents requires clinical trials before being implemented to routine use.

Conclusions

Managing patients with DIE is a challenge for a gynecologist. Patient should be informed about appropriate dairy products and vitamin D intake. Hormonal treatment should be the first-line treatment in DIE. After evaluation of pain or other symptoms, second-line therapy with GnRH analogs or danazol should be offered or minimally invasive surgery. Consensus is not made whether surgery is the best therapeutic treatment for affected patients. Strong depending on surgeon's experience conservative surgery should be offered if the total excision of DIE foci is possible. Concluding, side effects of treatment and expected improvement in quality of life should be always keep in mind.

Disclosure statement

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