The Efficacy of Synthetic Oral Progestin Pills in Patients with Severe Endometriosis

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Endometriosis is an important public health issues concerning women of reproductive age due to its debilitating painful symptoms. Deep infiltrating endometriosis is the severe form, involving uterosacral ligaments, rectum, bowel and bladder. There is no optimal treatment for this disease, but there are 3 main therapeutic options: medical, surgical and a combination of both. A modern approach for the treatment of endometriosis pain uses dienogest, a progestin, as a long-term solution for women who do not wish to procreate or to whom surgery is not an option. Dienogest 2mg daily has a positive effect on the reduction of pain and endometrial lesions when used perioperatively or as a long-term postoperative treatment. This article focuses on the literature evidence on the efficacy of newly approved oral synthetic progestins in the treatment of severe endometriosis.

Keywords: severe endometriosis, dienogest, pharmacological treatment

Endometriosis is a chronic benign estrogen-dependent disease affecting women of reproductive age. The European Society of Human Reproduction and Embryology (ESHRE) reports a prevalence of more than 6-10% among women between 25-30 years old [1]. The disorder is characterized by the presence of endometrial stroma and glands at ectopic sites. The ectopic endometrial tissue reacts to cyclic hormonal changes similarly to the one situated inside the uterus. The main symptoms are chronic pelvic pain, dysmenorrhea, irregular menses, dyspareunia and infertility. Many women are asymptomatic or with a variable clinical presentation. Studies found that endometriosis also affects mental health and reduces the patient's quality of life [2]. A relationship between the extent of the endometrial lesions, which sometimes extend in the pelvic-sub peritoneal space, and the intensity of symptoms could not be found [2,3].

A classification of endometriosis is difficult to establish, due to the complexity of the disease. There are a few systems used by clinicians, some of them considered insufficient and put under review. The most frequently used is the revised classification of the American Society of Reproductive Medicine, which classifies the disease into 4 stages, according to intraoperative findings: minimal, mild, moderate and severe. In the severe form of the disease, the ectopic endometrial tissue involves the posterior compartment, uterosacral ligaments, cul-de-sac, the posterior vaginal wall, the rectum, the bowel, the ureters and the urinary bladder. Patients usually experience severe pain, deep dyspareunia, dysmenorrhea and also signs and symptoms of lesions infiltrating into certain organs: menstrual diarrhea, dyschezia, menstrual hematochezia, catamenial mictalgia, frequency, vesical tenesmus, hematuria [3,4].

Treatment of endometriosis can be either surgical, in order to remove all visible lesions and to restore normal anatomy by removing adhesions, or pharmacological, aiming to alleviate pain and to reduce endometrial lesions. A combination of both is also used [5].

Pharmacological agents used in daily practice are: non-steroid anti-inflammatory drugs, oral contraceptives and progestins as first line treatment, and gonadoliberin (GnRH) agonists, danazol or aromatase inhibitors as second line treatment.

Unfortunately, there is no ideal treatment for endometriosis-related pain and there is no overwhelming evidence in favor of particular treatments over others among hormonal contraceptives, progestins, gonadotropin-releasing hormone agonists and antagonists and aromatase inhibitors. Interestingly, some authors found connections between certain genitourinary infections (e.g. candidiasis) and the development of endometriosis [6,7]. Therefore, new treatments with proven in vitro antimicrobial

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activity against C. albicans could also be useful [8]. A modern approach uses new synthetic oral progestins, such as dienogest, as a long-term option in single therapy or combined with surgery [9,10]. The aim of this article is to review literature and asses the efficacy of dienogest in patients with severe forms of endometriosis.

Experimental part

This systematic review is based on material searched on Pubmed from 2010 until present, English-language articles examining the efficacy of newly approved synthetic progestins in the long-term treatment of severe endometriosis. Search terms included: *deep infiltrating endometriosis, severe endometriosis, progestin, dienogest, efficacy, long-term treatment.*

Results and discussions

Diagnosis of endometriosis

Endometriosis is a chronic benign, but progressive disease, characterized by the worsening of symptoms in the absence of treatment. Due to the variable presentation of the disease and to the fact that many patients are asymptomatic, there is a delay in diagnosis up to even 7 years, as stated in some literature studies and there are plenty of differential diagnostics which can be misleading [11-13]. A complete diagnosis is based on clinical presentation, imaging aspects (transvaginal sonography, transrectal sonography, MRI), laparoscopy and is ideally confirmed by histology [14,15] in order to exclude other diagnosis [16-18].

Treatment of endometriosis

Endometriosis is a chronic disease, with no permanent cure, that requires long-term management in order to reduce symptoms and size of lesions, without excessive repetitive surgical interventions. The modern desiderate is to maximize the use of medical treatment and to improve quality of life [19] by coupling the pain at first [20]. The treatment of choice should be adapted to the individual needs of each patient and to the associated pathologies, to avoid further complications [21-24]. Efficacy, tolerability and safety in the long term are also very important. In severe endometriosis, debilitating pain and the risk of recurrence are one of the biggest concerns [25].

Surgical

Conservative surgery improves pain and enhances fertility, but since recurrence rate of endometriosis is 21.5% at 2 years and 50% at 5 years, repetitive surgery is shown to further have a negative impact on pain and fertility [26,27]. There are two possible mechanisms leading to recurrence: regrowth of residual lesions and *de novo* lesions through retrograde menstruation. Moreover, cases of endometriosis after hysterectomy have been described in the literature, suggesting that ovulation may also be a cause for this disease. Surgical excision of deep endometriotic nodules is necessary when they cause subocclusive symptoms, bowel stenosis, ureteral stenosis, hydronephrosis [28-33]. Surgery is also needed in 1 out of 3 women in whom the hormonal treatment fails or is not applicable [34].

Medical

Medical treatment options depend on the severity of symptoms, the extension of lesions, localization of disease, patient's age and the patient's desire to conceive. Pharmacological agents used are non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal agents: combined oral contraceptives (COCs), progestins, androgens, GnRH agonists, aromatase inhibitors. The side effects of these drugs reduce the possibility of using them in the long-term. NSAIDs are used for analgesia but they cannot be used long-term due to the increased risk of gastric ulceration, the antiovulatory effect, cardio-vascular disease, renal dysfunction and cerebrovascular events [35-37]. In the severe forms of endometriosis, they are inefficient to treat severe pain [38,39]. COCs can be safely used for the long-term treatment but they often cause breakthrough bleeding. GnRH agonists produce accelerated bone mineral density loss and their use is limited to 6 months in the absence of "add-back" therapy [39]. Bone mineral density loss can lead to pain, bone fracture which sometimes requires surgical intervention and various methods of osteosynthesis and can also mask the existence of other concomitant diseases [40-44]. Progestins, either oral, intrauterine or parenteral, have been used for many years in the treatment of endometriosis, but there are a few comparative data about the benefits of one over another and also about the right dose to use. The ESHRE Guidelines 2013 recommend the use of progestins for the treatment of pain in endometriosis [1]. The World Endometriosis Society Consensus 2013 also recommends progestins as first line therapy for endometriosis [14].

Dienogest in the treatment of severe endometriosis

Dienogest is a synthetic oral progestin which has been recently approved for the treatment of endometriosis. It was first used in 2007 in Japan and now is also available in Europe, Australia and Singapore. In Romania, dienogest 2mg is authorized on the market since 2010 [45]. It has a special chemical structure and a unique pharmacological profile. It combines the benefits of the 19-norprogestin derivatives, such as an important progestative effect on the endometrium, and the properties of other progesterone derivative classes: good tolerability, antiadrogenic effect, moderate inhibition of gonadotropins, favorable safety profile and causes no metabolic dysbalances.

The chemical structure of dienogest

Dienogests's chemical structure offers an explanation for the unique pharmacological properties of this substance. It combines both the properties of 19-nor-progestins and the properties of progesterone derivatives. As shown in the chemical formula below (fig. 1), the substance has a supplementary double bond with a strong affinity for progesterone receptors and a cyanomethyl instead of ethinyl group in 17a position, which allows a lower interaction with liver proteins such as Cytochrome P450. The molecular formula is $C_{20}H_{25}NO_2$ [39,46].

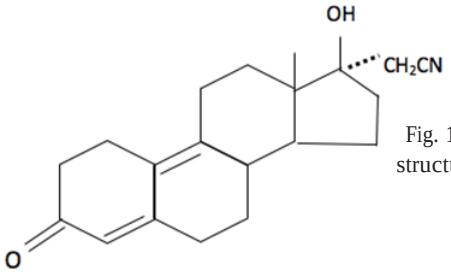

Fig. 1. The chemical structure of dienogest

The effective recommended dose was tested in different control studies, using 1mg, 2mg or 4 mg of dienogest in a 3-month, 6-month or 1-year period, comprising more than 600 women [47]. The reduction of the endometrial lesions is done by two main mechanisms, as shown in table 1 [48].

A number of comparative studies between different progestins or between progestins and estroprogestins are

described in the literature. Among progestins, dienogest was compared to norethindrone acetate (NETA) concerning efficacy and side effects. NETA 2.5mg daily was compared to a COC and has proven to alleviate pelvic pain and dyspareunia in 92% of cases after 12 months therapy in women with rectovaginal endometriosis. It also improved bowel symptoms in patients still symptomatic following non-radical surgery. Recent studies found that dienogest is as effective as NETA in improving pain symptoms in women with rectovaginal endometriosis [4,14]. It also has fewer adverse effects and a better tolerability. Dienogest has also proven effective in improving urinary symptoms in women with bladder endometriosis [50].

Another recent systematic review of nine randomized clinical trials including stage I-IV endometriosis, confirmed that Dienogest 2mg/day has similar results with GnRH agonists (buserelin, leuprolide acetate and triptorelin) in controlling endometriosis associated symptoms. The disadvantages mentioned were the higher cost of dienogest as compared to other drugs and the fact that dienogest should not be used as a contraceptive method [45].

Recurrence of endometriosis is frequent even after successful surgical removal of lesions. In the cases with deep infiltrating endometriosis, data about postoperative recurrence and prevention is still sparse. In a recent review, recurrence rate varied between 5% to 25%, most studies reporting 10% after a 2 years follow-up. Interestingly, a prospective study of 500 women managed for deep infiltrative rectovaginal endometriosis, showed that recurrence rate was lower in those who received continuous postoperative progestin or had immediately interrupted treatment and rapidly got pregnant than in those who abandoned medical treatment but did not become pregnant [8,50].

Central action	Local action
Inhibition of gonadotropin secretion: - produces a moderate inhibition of FSH and LH. - keeps estradiol levels in the lower physiological range, avoiding adverse outcomes of a hipoestrogenic state (flushes and bone density loss). - anovulation is induced with 2mg and is restored immediately after cessation of treatment.	Inhibits proliferation of ectopic endometrial tissue.
By moderately decreasing endogen estradiol production, it inhibits the growth of the endometrial tissue.	Has antiproliferative, anti-inflammatory and antiangiogenic effects (studied on animal models) [49].
	It reduces the volume of ovarian endometriomas.

Table 1
DIENOGEST'S MECHANISMS OF REDUCTION OF THE ENDOMETRIAL LESIONS [48]

Author	Year	Study design	Treatment and duration	No. of patients	Follow-up period (months)	Recurrence rate
Cucinella et al. [53]	2013	Randomized control study	Oral contraceptive (OC)with desogestrel/ OC with dienogest/ Expectative management (EM)	43/44/43/38	24	Desogestrel (26.5%)/ Gestodene (31.8%)/ Dienogest (20.5%)/ EM (74.7%)
Ouchi et al. [54]	2014	Cohort	OC (always)/ OC (ever)/Dienogest/ GnRHa 6 months/EM	25/9/7/16/110	38.3	OC always (0%)/ OC ever (56%)/ Dienogest (0%)/ GnRHa(25%) EM (23%)
Ota et al. [55]	2015	Cohort	Dienogest/EM	151/417	60	Dienogest (4%)/ EM (69%)

Table 2
RECENT STUDIES REPORTING THE EFFICACY OF POSTOPERATIVE MEDICATIONS ADMINISTERED FOR MORE THAN 6 MONTHS ON ENDOMETRIOMA RECURRENCE

Another review article by Roman et al. stated that the two treatment options, surgical and medical, should be combined for an effective prevention of recurrent severe endometriosis [51,52]. Other recent studies reported the efficacy of postoperative medications administered for more than 6 months on endometrioma recurrence. The volume of endometrioma was measured by transvaginal ultrasound. Recurrence was defined as > 20 mm (table 2).

Dienogest was investigated as a long-term treatment option in two large studies performed in Japan and Europe, establishing efficacy, improvement of quality of life, safety and tolerability. The Japanese study included 168 women on a 65 weeks-therapy. The European study included 135 women on a 52-week therapy. Both showed long-term improvement of painful symptoms, reduction of endometriotic lesions, no metabolic biochemical disturbances and no accelerated bone density loss. The main adverse outcome was metrorrhagia, but most patients expressed their desire to continue therapy [50].

Conclusions

The above studies indicate that dienogest is a promising and effective treatment for endometriosis related pain and for suppressing recurrence of endometriosis in a long term. The treatment of severe endometriosis requires complex surgical procedures, chronic hormonal medication, psychological support and assisted human reproduction techniques. The modern approach requires long-term effective hormonal medication with fewer adverse outcomes and less invasive surgical procedures. Newly approved synthetic progestins, such as dienogest, have proved to be an effective reliable choice and are recommended as both first-line therapy and as postoperative therapy in the long-term for women who do not wish to conceive. Dienogest also seems a promising option for the treatment of bladder endometriosis symptoms in patients who refuse surgery.

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Manuscript received: 22.02.2018