УДК 618.14

Clinical aspects of long-term care of endometriosis by progestogen dienogest

V.I. Pyrohova[1], S.O. Shurpyak[1], B.J. Kryvko[2]
[1]Lviv National M edical University named after Danylo Halytskyy
[2]Lviv Municipal Emergency Hospital

The article reviews clinical aspects of long-term treatment of endometriosis with the use of dienogest in patients with gynaecological proliferative syndrome.
Key words: *endometrios, dienogest, gynaecological proliferative syndrome.*

Endometriosis is considered as a benign hormone-dependent condition in which the outside lining of the uterus is proliferation of tissue morphological and functional properties identical endometrium («endometriosis lesion», «Endometrial heterotopy»), which leads to the onset of clinical symptoms that can affect the physical condition psychological status and social well-being of patients [1].

According to epidemiological studies suffe from endometriosis 5–10% of the female population – worldwide about 176 million mainly women of reproductive age (one in ten). Endometriosis is found in 50% of women with dysmenorrhoea, including half of the adolescents who suffer from severe dysmenorrhoea, 75% of patients with chronic pelvic pain in 25–40% of women with infertility, and in the structure of gynaecological disease endometriosis are in third place after inflammation and uterine fibroids [2, 7, 8].

Although the causes of the disease so far not fully elucidated, but studied many aspects of pathogenesis. According to one popular theory today, endometriosis occurs with atypical arrangement is prone to hyperplasia, endometrial modified, based on what is a violation of apoptosis [7]. In endometriosis in eutopic endometrium and endometrial heterotopias dominated defective receptors for progesterone related enzyme 17th dehydrogenase (type 2) and 17-β-hydroksylsteroid that lead to relative deficiency of progesterone at target organs of reproductive system [2, 8]. In this regard, more prevalent term «proliferative syndrome in gynaecology», which involves a combination of fibroids, endometriosis, endometrial hyperplasia, dysplastic changes in cervical tumours and tumour-like formations of ovaries, dishormonal breast diseases [3, 7].

There is no universal drug that can completely cures endometriosis, and obviously wouldn't be in the foreseeable future. Therefore, the major clinical challenge is to ensure achieving the goals of treatment is important for a particular patient, determining priorities cocks' therapy: elimination of the main complaints (pain, infertility), optimization of the profiles of efficacy, safety and tolerability, improving compliance [8]. That variety of different purposes treatment of patients is currently no universal cause of endometriosis treatment method [3]. Moreover, so far not fully clarified the reasons for the frequent recurrence of the disease, different clinical activity of endometriosis, lack of effectiveness of drug therapy, including hormonal [3].

Currently «endometriosis should be considered as a long-term disease that requires treatment during the planned life, which - to achieve the most efficient use of drug therapy and avoid repeated operations» [1, 8].

Variability and nonspecific symptoms of endometriosis complicates clinical diagnostics disease that, according to different authors verified the diagnosis determines an average of 7–8 years after the first treatment of patients with corresponding complaints in connection with what is called endometriosis «lost» disease [3, 8]. Early verification of diagnosis determines the appointment of adequate therapy of endometriosis, which is critical for preventing further progression, reproductive health and quality of life patients in general.

The systemic nature of endometriosis on the background of proliferative gynaecological syndrome necessitates a comprehensive approach to the treatment of these patients, taking into account the individual characteristics of the organism. The overall concept of the treatment of endometriosis is a combination of surgery and drug therapy. Operative treatment of patients with endometriosis, despite the improvement of technology, does not always provide the complete elimination of endometriosis lesions and relapse does not prevent the disease.

Drug monotherapy for pain management and other symptoms of endometriosis possible and appropriate in the presence of adenomyosis, accompanied by corresponding symptoms (heavy menstruation or other irregular menstruation, dysmenorrhoea); predictable superficial peritoneal endometriosis; deep infiltrative endometriosis confirmed by biopsy and histology, or in patients who have lesions of endometriosis radical removal was not done in the interest of preserving reproductive potential; persistence or recurrence of symptoms after surgery) [1, 7, 8].

The main criteria for the effectiveness of the combined treatment are relief of clinical symptoms, absence of relapses and restore fertility in women of reproductive age. Hormonal drugs long used in drug therapy of endometriosis – danazol, progestin's, COCs and aGnRH though they have comparable efficacy, but the cost and availability care side effects are different (level of evidence Ia). A number of side effects limit the long-term use of these drugs and often lead to violations of the reception.

Resistance to progesterone is seen as a key pathogenic mechanism of endometriosis, since no antagonistic estrogens' effect, which determines the need to choose progestogen, which has not only a strong antiproliferative activity but also impact on other pathogenic link disease and metabolic neutrality, which enables long holding treatment [6].

According to the recommendations of leading gynaecological societies monotherapy with varying progestin through the introduction should be considered as first-line therapy (level of evidence Ia) [1, 7, 8].

Dienogest belongs to the fourth generation of progestogens, combining the properties of both 19-nortestosterone derivatives, and derivatives of progesterone. As a derivative of 19-nortestosterone it is characterized by high selectivity to the progesterone receptor, progestogen powerful influence on the endometrium, a relatively short half-life (approximately 9-11 hours) and high bioavailability (approximately 90%), which reduces the risk of cumulating with daily admission. As dienogest derived progesterone inherent good tolerability, the absence of adverse metabolic and vascular affects that is the basis for long-term treatment [6].

Numerous experimental and clinical studies revealed the many mechanisms of action of dienogest and evaluate its effectiveness and safety for the treatment of endometriosis, which exceeds that using other progestogens [15]. Proved that dienogest, like the efficiency of aGnRH may long used to treat pain and prevent a recurrence of endometriosis without causing adverse side effects of estrogens' deficiency [4, 12, 13]. Dienogest inhibits ovulation during treatment; it does not adversely affect the return to fertility after discontinuation of treatment [5, 9].

Dienogest shows antiproliferative, antiangiogenic, anti-inflammatory, immunomodulatory effects caused by endometrial implants normalize intracellular signalling disorders and immune system cycles causes direct inhibition of intranuclear factor NFkB, which plays a key role in the inflammation and neoanhiohenezis [6]. The advantages of it belonging to a particular mechanism of blockade of ovulation, aims to apoptosis of granulose cells of growing follicles, weak central effect (inhibition of FSH and LH) and a moderate decrease in production of estradiol, the level of which is within the therapeutic window, avoiding the development of symptoms of estrogens' deficiency, while maintaining pronounced antiproliferative effects [4, 13].

Another of the features of dienogest is its anti-androgenic activity, which is implemented due to lack of communication with a protein that binds cortisol and with binding globulin sex hormone (SHBG) and accordingly does not displace testosterone or with dehydrotestosteron bound to SHBG state and therefore does not increase the concentration of free testosterone and dienogest does acceptable for long-term therapy [6, 12, 13

Several placebo control trials found that dienogest 2 mg / day buys associated with endometriosis pain significantly reduces the incidence of endometrial lesions that define according rAFS at repeated laparoscopy, and not inferior in efficacy of gonadotropin releasing hormone agonists (level of evidence Ib) [11]. The drug suitable for long-term treatment of endometriosis because it is well tolerated patients and it has no negative impact on the metabolic profile and liver function [7]. The incidence of breakthrough bleeding comparable to treatment with other progetagens and decreases with increasing duration of therapy. Currently results of long-term (65 weeks) studies demonstrated not only high performance, of dienogest but also safety in the treatment of endometriosis (level of evidence Ib) [10, 14, 15].

Purpose: to assess the efficiency and safety of long-term treatment of endometriosis by dienogest in women with gynaecological proliferative syndrome.

MATERIALS AND METHODS

Under supervision there were 30 patients of reproductive age verified on the basis of a comprehensive survey of external genital endometriosis diagnoses on the background of proliferative gynaecological syndrome who were treated for 6 months by dienogest. All patients diagnosed with endometriosis were established on the basis of the results confirmed by laparoscopy and histology. It is generally accepted survey included the study of family and personal history, pelvic examination, cytology, transvaginal ultrasound, breast ultrasound, the study of protein, carbohydrate, lipid profiles, levels of tumour markers CA-125 in blood serum.

RESULTS AND DISCUSSION

According to the revised classification of the American Society of Fertility (R-AFS), I extent of endometriosis occurred in 12 (40.0%), II – 14 (46.7%), III – in 4 (13.3%) women. Endometrioma was diagnosed in 13 (43.3%) patients.

First endometriosis was diagnosed in 8 (26.7%) patients; recurrent nature of the disease was of 22 (73.3%) women.

Among patients with recurrent endometriosis course of GnRH agonist therapy for 8–12 months prior to inclusion in the study received 10 (33.3%) patients, treatment micronized progesterone, didrohesteron from 3 to 6 months – 5 (16.7%) patients, systematically taking COCs, combined with NSAIDs – 7 (23.3%) women.

Prior dienogest treatment of dysmenorrhoea was observed in 22 (66.7%) patients, complaints of pelvic pain not related to menstrual cycle, presenting 11 (36.7%) patients. Violation of the menstrual cycle (MC) as long baldly bleeding to/or after menstruation, presenting 13 (43.3%) patients.

Comprehensive survey, which to stage laparoscopic intervention involved a transvaginal ultrasound dynamics, clinical and ultrasound breast screening, hysterosalpingography, hysteroscopy, diagnostic fractional scraping the walls of the uterus with their future pathomorphological investigation material obtained showed that endometriosis in most cases combined with other hyperplastic processes of the reproductive system. Adenomyosis occurred in 16 (20.0%) cases, simple endometrial hyperplasia without atypical – in 10 (33.3%), complex endometrial hyperplasia without atypical – in 4 (13.3%), uterine fibroids – 7 (23.3%) patients. In 17 (56.7%) patients diagnosed with diffuse breast with a predominance of glandular component.

Evaluation of dienogest therapy at a dose of 2 mg/day in continuous mode at 6 months showed that patients with endometrial hyperplasia during pelvic ultrasound thickness M-echo on average 3.8±0.54 mm.

Particular attention was paid to the observation of patients with uterine myoma, as growth nodes can affect not only estrogen, but progestogen. During the treatment period there was no cases of recurrence or progression of the growth of myoma nodes. Similar results (assessment of uterine size) have been obtained by observation of patients with adenomyosis. Assessment of the severity of pain as the main complain of patients showed a significant decrease, and the severity of dysmenorrhoea decreased by 3.5 times, and pelvic pain – in 2,8 times.

One of the most common side effects of progestogen therapy are irregular, vary in duration and intensity of bleeding. Changes in menstrual function analysis showed that of 17 patients with regular MC before treatment, while taking dienogest regular MC retained in 9 (52.9%) cases, and menstruation became baldly and short-lived. In 7 (23.3%) of all patients receiving dienogest, has evolved amenorrhea. Menstrual disorders of the type «intermenstrual» bleeding recorded in 12 (40.0%) women, «breakthrough bleeding» – only 2 (6.7%).

Among the side effects reported in patients studied in the treatment of the most frequent mood changes took place – 2 (6.7%), mastodynia – 1 (3.3%), weight gain – in 2 (6.7%), but in all cases, the complaints have not led to the refusal to continue treatment.

Clinical and laboratory studies did not reveal the dynamics of changes of protein, carbohydrate, lipid metabolism, in any case, indicating that the metabolic safety of long-term treatment of endometriosis in patients with proliferative combined processes of reproductive organs.

CONCLUSIONS

Dienogest 2 mg significantly reduced the severity of pain, can be used long and should be considered as the drug of choice in patients with recurrent disease.

Therapy by dienogest in case of endometriosis that runs in the background of combined benign proliferative processes of reproductive organs does not lead to a deterioration of their course.

The results obtained on high performance dienogest therapy with little frequency of side effects, lack of progression of combined proliferative processes of reproductive organs confirm the possibility of using dienogest as a promising method of long-term treatment.

Клінічні аспекти довгострокової терапії ендометріозу дієногестом

В.І. Пирогова, С.О. Шурпяк, Б.Я. Кривко

У статті розглядаються клінічні аспекти довгостроковій терапії генітального ендометріозу із застосуванням дієногесту у пацієнток з гінекологічним проліферативним синдромом.

Ключові слова: *ендометріоз, дієногест, гінекологічний проліферативний синдром.*

Клинические аспекты долгосрочной терапии эндометриоза диеногестом

В.И. Пирогова, С.А. Шурпяк, Б.Я. Кривко

В статье рассматриваются клинические аспекты долгосрочной терапии генитального эндометриоза с применением диеногеста у пациенток с гинекологическим пролиферативным синдромом.

Ключевые слова: *эндометриоз, диеногест, гинекологический пролиферативный синдром.*

Сведения об авторах

Пирогова Вера Ивановна – Львовский национальный медицинский университет имени Данила Галицкого, 79010, г. Львов, ул. Пекарская, 69; тел.: (050) 581-94-48. E-mail: pyroh@mail.lviv.ua

Шурпяк Сергей Александрович – Львовский национальный медицинский университет имени Данила Галицкого, 79010, Львов, ул.Пекарская, 69

Кривко Борис Ярославович – Львовская коммунальная клиническая больница скорой медицинской помощи, 79059, Львов, ул. Миколайчука, 9

REFERENCES

1. ESRHE guideline. http://guidelines.endometriosis. org/pain.html. 2007.
2. Giudice LC. Endometriosis. N Engl J Med 2010;362:2389–98.
3. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Updare 2009;15:441–61.
4. Harada T, Momoeda M, Taketani Y, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis – a randomized, double-blind, multicenter,controlled trial. Fertil Steril. 2009;91(3):675–681.
5. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2007 Jul18;(3):CD000155.
6. Klipping C, Duijkers I, Faustmann TA, et al. Pharmacodynamic study of four oral dosages of dienogest. Fertil Steril 2010: 94 (suppl): S181.
7. Leyland N, Casper R, Laberge Ph, Singh SS et al. Endometriosis: diagnosis and management. SOGC Clinical and practical guideline. Journal of Obstetrics and Gynaecology Canada 2010;32(7):1–28.
8. Management of endometriosis. Practical Bulletin No.114. The American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;116: 223–36.
9. McCormack PL. Dienogest: a review of its use in the treatment of endometriosis. Drugs 2010;70(16): 2073–88.
10. Momoeda M, Harada T, Terakawa N, et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009;35(6):1069–1076.
11. Momoeda M, Taketani Y. Randomized double-blind, multicentre, parallel-group dose–response study of dienogest in patients with endometriosis. Jpn Pharmacol Ther. 2007;35:769–783.
12. Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2011;285(1): 167–173.
13. Sasagawa S, Shimizu Y, Kami H, Takeuchi T, Mita S, Imada K, et al. Dienogest is a selective progesterone receptor agonist in transactivation analysis with potent oral endometrial activity due to its efficient pharmacokinetic profile. Steroids 2008;73: 222–231.
14. Strowitzki T, Faustmann T, Gerlinger C, et al. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010;151:193–198.
15. Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: A 24-week, randomized, multicentre, open-label trial. Hum Reprod. 2010;25(3):633–641.

Статья поступила в редакцию 22.11.2015

РАЗВИТИЕ ПРЕЭКЛАМСПИИ МОЖНО ПРЕДСКАЗАТЬ ЗА НЕДЕЛЮ

Исследовательская группа из немецкого Университета Шарите (Charite University) разработала способ определения вероятности развития преэклампсии.

Преэклампсия - осложнение беременности, развивающееся у 2-5% женщин в последнем триместре. Она может стать причиной развития серьезных проблем со здоровьем как у будущей матери, так и у ребенка, а в некоторых случаях привести к летальному исходу.

Штефан Верлорен (Stefan Verlohren) и его коллеги разработали специальный тест, позволяющий предсказать возникновение преэклампсии в течение недели после его проведения. Он основан на определении соотношения концентраций белка sLIt-1 и плацентарного фактора роста (PlGF) в сыворотке крови. Каждый из этих белков участвует в развитии преэклампсии, отмечают авторы, а изменение их концентраций указывает на вероятность возникновения этого осложнения беременности еще до появления первых симптомов.

Авторы уже протестировали новый тест на 1000 женщинах, риск развития преэклампсии у которых был повышен. В том случае, если соотношение концентраций sLIt-1 к PlGF было меньше 38, риск развития преэклампсии в течение недели был минимален. Если же этот показатель превышал 38, то вероятность возникновения этого осложнения беременности существенно возрастала.

Ученые объясняют, что новый тест позволит своевременно выявить риск развития заболевания и предотвратить возникновение нежелательных осложнений как для матери, так и для ребенка.

Источник: http://medportal.ru