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Endometriosis and adenomyosis: some aspects of medical (endocrine) treatment (part 1)

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Abstract. The article presents analysis of relevant literature on risk factors and pathogenesis of endometriosis and adenomyosis. Despite of numerous studies, it has not been possible so far to formulate a unified concept of the pathogenesis and etiology of endometriosis and adenomyosis. We discuss the role of cytokines, including chemokines, prostaglandins and matrix metalloproteinases, as well as disorders of steroid genesis in the pathogenesis of endometriosis. It has been shown that the main therapeutical approach for patients with endometriosis is the differentiated use of modern hormonal drugs, which depends on age and reproductive plans. According to the more recent European guidelines, progestogens are the drugs of the first line.

Key words: endometriosis, adenomyosis, hormonal drugs, cytokines, prostaglandins.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest associated with the publication of this article.

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Endometriosis is diagnosed in every tenth woman of reproductive age. Many obstetrician-gynecologists often encounter this disease in their clinical practice.However, endometriosis remains one of the most mysterious diseases in gynecology. Until now, the issues of etiology and pathogenesis, management tactics, especially for extra genital forms of endometriosis, have not been fully elucidated.

Over the past decades, scientists working in the field of pathomorphology, molecular biology, genetics, mass spectrometry, cellular technologies and many other specialties have been conducting research aimed to reveal the cause of endometriosis foci development, to determineways to influence them and prevent their occurrence. However, there are still many unresolved issues in the field of etiology and pathogenesis of endometriosis and endometriosis-associated diseases, as well as their relationship with the occurrence of malignant tumors of various localizations (Fig. 1) [1].

Endometrial tissue has a special receptor status that makes it resistant to progesterone. Endometrioid cells are resistant to progesterone since they contain a small number of progesterone receptors type B (PRB) and estrogen receptor α (ERα).

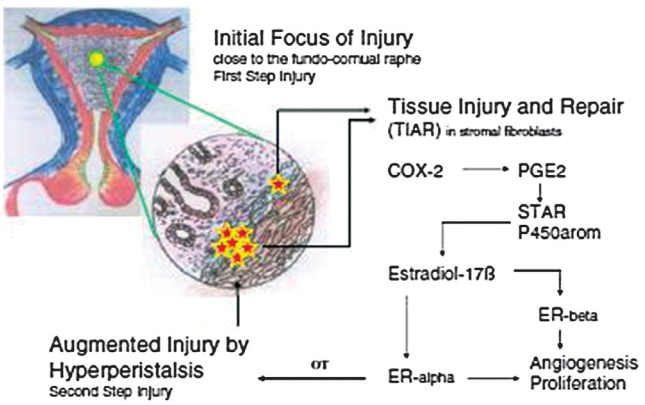

Figure 1. Pathogenesis of endometriosis.

PRB is a powerful progesterone target gene activator. Whereas progesterone receptor type A (PRA) is the dominant repressor of PRB that predominates in endometrial tissue. In general, endometriosis sites have a high ratio of ERβ/ERα and PRA/PRB, which causes progesterone resistance.

The inflammatory process is one of the mechanisms of infertility associated with endometriosis due to excessive production of inflammatory cytokines such as interleukins, in particular IL-6, tumor necrosis factor α and chemokines, as well as prostaglandins and matrix metalloproteinases. An increase in the concentration of these substances sufficiently increases the prevalence of atypical localization of the endometrium.

In the last two decades, more and more similarities have been found between the mechanisms of endometriosis development, autoimmune and oncological diseases. For this reason, many researchers focus on the role of cytokines, including chemokines, in the pathogenesis of the disease and associated infertility.

Cytokines are a kind of chemical signals by which cells interact with each other for the benefit of the overall survival of the body's tissue. The result is stimulation or suppression of proliferation, apoptosis and functional activity of immune competent cells.

Chemotoxic cytokines (chemokines) are molecules produced by cells to attract leukocytes, macrophages, T and B cells, eosinophils, basophils, and neutrophils to sites of inflammation or lymph nodes.

Chemokines can selectively influence cell reshaping, transiently increase the concentration of intracellular free calcium ions, granular exocytosis, integrin production, production of bioactive lipids (e.g. leukotrienes), and induce an "oxidative burst" that activates leukocytes. Chemokines act as early modulators of the inflammatory response, releasing inflammatory mediators, triggering chemo taxis and extravasations in the pathological focus.

The decisive role in the effect on the uterine mucosa is played not by the absolute amount of steroid hormones circulating in the peripheral bloodstream, but by the functional usefulness of their receptors [2].

Estradiol has an effect on the endometrium. It not only acts as a unique proliferative agent, but also contributes to the secretory celltransformation since it stimulates the synthesis of both its own receptors (the more estradiol, the more receptors), and receptors for progesterone and androgens. Progesterone, on the contrary, inhibits the production of both - its own receptors and estradiol receptors. Thus, a harmonious ratio and adequate dynamics of the concentrations of estradiol and progesterone have a full effect on the uterine mucosa.

Estradiol is simultaneously perceived by several types of receptors, the main ones being α- and β-estrogen receptors (ER-α and ER-β). The study of German specialists (2004) shows that in glandular epithelial cells, ER-α expression is associated with cell proliferation processes, while ER-β is associated with secretory function. ER-α expression occurs in the epithelial cells of the uterine mucosa during the periovulatory period, and the highest level of ER-β expression occurs in the periovulatory period. It is important to note that stromal cells and endotheliocytes of endometrial vessels also actively respond to estradiol. At the same time, both ER-β and ER-α are found in stroma perivascular cells, and only ER-β is found in vessel walls. It is interesting that progesterone stimulates the synthesis of ER-βby suppressing the expression of ER-α. Therefore, angiogenesis is dependent on ER-β that is influenced by both estradiol and progesterone.

The achievements of omics technologies in the diagnosis of endometriosis and malignant neoplasms deserve special attention. Conventionally, omics technologies include those based on the achievements of sciences that study how the genome is arranged and how the information encoded in it is realized (genomics, transcriptomics, proteomics, and metabolomics). It is thanks to the data obtained with their help that it became possible to develop panels for non-invasive diagnostics, the creation of a so-called molecular signature for the verification of the tumor process and endometriosis.[3,4]

There are many theories of the origin and development of endometriosis. Scientists from Yale University reported interesting results of studies during the 71st annual meeting of the American Societyof Reproductive Medicine (ASRM). They presented experimental data on the migration of endometrial cells to the brain and possibly other parts of the body, confirming the important role of stem cells in the development of this disease.Studying samples of various tissues of mice, 8 weeks after the surgically induced disease, the researchers found 100 % of them had ectopic endometrial cells in the brain tissue.In connection with the results, Dr. Samani noted, "Since cell migration to the brain occurred simultaneously in all mice with sensory-induced endometriosis, it indicates that the endometrial tissue secretes stem cells that can reach various organs outside the pelvis. These endometrial implants may not be clinically detectable, yet be biologically active and induce molecular changes that promote inflammatory responses."The authors of this study believe that the possibility that extra genital endometriosis is found more widespread than it was previously thought, but may not be clinically manifested, cannot be ruled out. The scientists agree that medical rather than surgical treatment is the most appropriate for endometriosis, including the extra genital one.At the same time, they do not exclude the need for surgical treatment.However, they emphasize that since medical professionals are dealing with various types of endometriosis and models of its development and, consequently, with different symptoms resulting from this disease, the treatment should not be the same in all cases, but should correspond to the type of disease and its manifestation in a particular woman[5].

The problem of endometriosis is gaining medical and social importance due to severe clinical manifestations and recurrent course of the disease as well as a negative impact on the quality of life and working capacity, and most importantly on reproductive potential.

Surgical treatment remains the only way to eliminate foci of endometriosis.However, even after a radically performed operation, relapses are possible. Given the above, it is necessary to develop a comprehensive interdisciplinary approach to the management of patients with endometriosis, especially in severe cases.

Surgery is not a definitive treatment for endometriosis; long-term supportive drug therapy is needed. Candidates for long-term drug treatment are women who do not plan pregnancy at the current time, but who would like to preserve fertility, which will be at risk if the disease progresses, as well as patients who have undergone surgery. It is necessary to select maintenance therapy taking into account the fact that endometriosis is an estrogen-dependent chronic inflammatory disease accompanied by resistance to progesterone[6].

By 2020, a stepwise approach to the treatment of patients with endometriosis has been consolidated in the world gynecological practice with strong recommendations for the early relief of endometriosis associated with pelvic pain. Progestin (dydrogesterone or dienogest) can be used as first-line hormone therapy for endometriosis. In a number of countries (Europe, USA, and Great Britain), combined hormonal contraceptives are included in the first line of hormonal therapy for patients with endometriosis, along with progestin-only drugs.However, the basic hormonal treatment for patients with endometriosis worldwide is the use of gonadotropin-releasing hormone (GnRH) agonists. At the same time, the treatment of patients with endometriosis with the help of GnRH agonists is considered as the "gold standard". On the one hand, this is because the official instructions formedical use of these drugs clearly state endometriosis as the indication for their useand because GnRH agonists are included in the protocol for the treatment of patients with endometriosis around the world. On the other hand, this results from the fact that the effect of other drugs (both used and under trial)on patients with endometriosis (progestins, aromatase inhibitors, progesterone receptor modulators (PRMs)) can be clinically and morphologically comparable tothe effect of GnRH agonists.

Non-steroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives, progestogens, and GnRH agonists are also recommended as drug therapy for endometriosis;levonorgestrel-releasing intrauterine system is recommendedas a second line therapy.For women with pain associated with endometriosis that is refractory to other medical or surgical treatments, aromatase inhibitors are recommended because they reduce pain associated with endometriosis. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, gonadotropin-releasing hormone agonists or antagonists. Danazol and antiprogestogens are no longer included in recommendations.

The ESHRE recommendations additionally include gonadotropin-releasing hormone antagonists for the reduction of pain associated with endometriosis, with the notation that data regarding dosage or duration of treatment are limited (see Fig. 2) [6, 7]

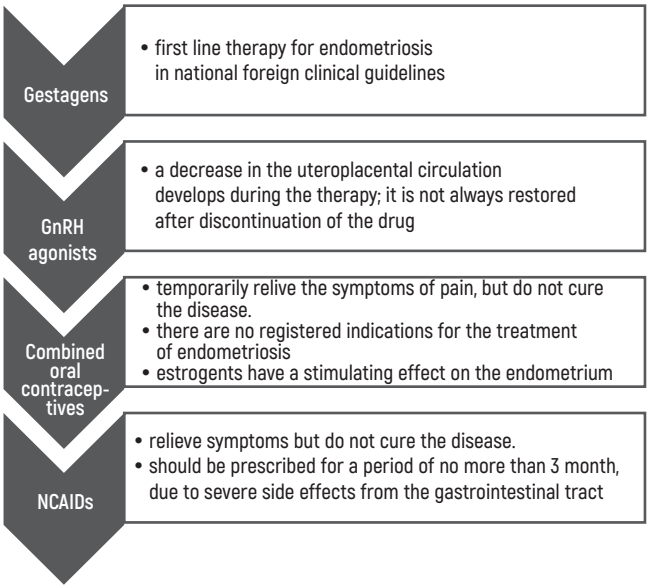

Figure 2. Medical treatment of endometriosis.

Gestagens are classified as first-line drugs (progesterone and a number of synthetic drugs) and second-line drugs (LNG-IUD and depot forms) for the treatment of endometriosis. In Russia, several progestogens are registered for the treatment of this disease[8,9].

Gestagens contribute to the regression of endometriotic lesions, reduce the severity of proliferation of eutopic and ectopic endometrium, suppress neoangiogenesis by inducing atrophy, and inhibit the expression of estradiol receptors. At high doses, progestins also inhibit folliculogenesis and ovulation. The drugs of this group contribute to the utilization of already synthesized estrogens by activating the enzyme 17 β-hydroxysteroid dehydrogenase (17β-HSD) type 2 (found in normal endometrium, while its expression is reduced in endometrioid heterotopias).[10]The main task of 17β-HSD is to convert active estradiol into inactive estrone. It has been shown that the expression of 17β-HSD type 1 prevails in the foci of endometriosis, which ensures a high concentration of estradiol at the local level[11-13].Another important effect of progestogens is the suppression of the synthesis of prostaglandins E2 that is involved in inflammatory reactions in endometriosis (stimulates the production of growth factors and enhances local estrogen synthesis). The result of this action is the activation of apoptosis, the suppression of cell proliferation and neovascularization.Currently, there are several gestagens with different routes of administration; oral use is the most common, but other applications are also possible (depot-forms for intramuscular injection, in the form of intrauterine systems). In clinical practice, most often prescribed drugs are dienogest, medroxyprogesterone, norethisterone, levonorgestrel, and dydrogesterone.

On average, about 9 % of patients do not respond to progestogen therapy, which is due to changes in the expression of different subtypes of progesterone receptors in endometriosis [14].Dienogest (fourth generation progestin), created in 2010 specifically for the treatment of endometriosis, combines the effects of progesterone and 19-nortestosterone. Due to the selective activity of derivatives, it binds exclusively to progesterone receptors and does not have an estrogenic or glucocorticoid effect, it has an antiandrogenic effect. It is distinguished by a powerful progestogenic activity as well as a pronounced antiestrogenic effect at the local level (see Fig. 3). Progestin does not have an ethynyl radical and is therefore metabolically neutral, which is important for long-term treatment [15].Withdienogest therapy, a reliable anovulatory effect occurs due to apoptosis of granulosa cells of the dominant follicle and is combined with a weak central effect (inhibition of FSH and LH) with a moderate decrease in the concentration of systemic estradiol.Dienogest reduces the synthesis of estradiol by the ovaries only within the therapeutic window, which prevents a number of symptoms of estrogen deficiency (hot flashes and vaginal atrophy) that are characteristics of GnRH agonists therapy [16].

Dienogest favorably affects the ratio of progesterone receptor isoforms α and β, which allows the drug to maintain clinical efficacy regardless of individual genetic differences in the expression of these receptors.

The effectiveness of hormone therapy in preventing recurrence of endometrioma in women undergoing surgery is still controversial. According to a meta-analysis and systematic review of postoperative hormonal treatment for the prevention of endometrioma recurrence after ovarian

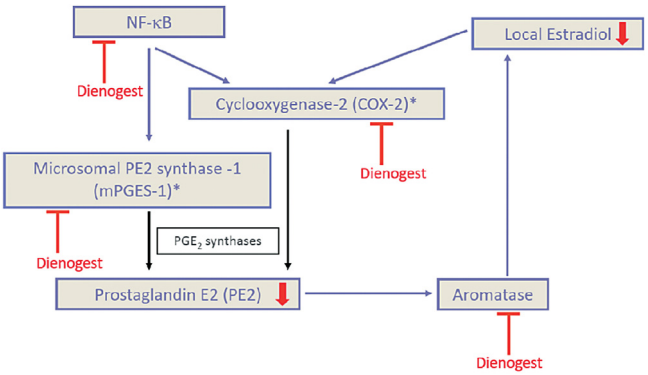

Figure 3, Effects caused by the intake of dienogest.

cystectomy,randomized controlled trials showed that all hormonal regimens had a slightly lower risk of endometrioma recurrence compared with expectant management. However, analysis of cohort studies found that LNG-IUD, dienogest, continuous hormonal contraceptives, GnRH agonists + combined hormonal contraceptives (CHC), and cyclic CHC therapy had a significantly lower risk of endometrioma recurrence than expectant management. When evaluating efficacy, LNG-IUD ranked first, followed by dienogest and GnRH agonists + LNG-IUD. Long-term use of hormone therapy (CHC) or progestin therapy had a significantly lower risk of endometrioma recurrence than expectant management[17].

However, when choosing a drug for the conservative treatment of endometriosis and the prevention of relapses, efficacy is not the only criterion that must be taken into consideration. With relatively equal effectiveness of different groups of drugs, medication compliance and acceptability for the patient as a long-term therapy, which directly depends on the severity of side effects, are important.

Certainly, GnRH agonists are effective in preventing recurrence after surgery and as a medical treatment for endometriosis without surgery, but have a number of side effects associated with estrogen deficiency (including a decrease in bone mineral density).The use of GnRH agonists is limited to 6 months unless "add-back" therapy is prescribed. At the same time, the optimal doses and duration of treatment with GnRH agonists have not been fully studied, and it is also not known whether "add-back" therapy affects the effectiveness of the treatment, and it has not been finally established, how GnRH agonists affect fertility,despite the large number of studies.

Dienogest 2mg/day has been shown in multiple clinical trials to be superior to placebo in the management of pain associated with endometriosis, including dysmenorrhea, dyspareunia, premenstrual pain, and diffuse pelvic pain. Dienogest also demonstrated similar efficacy in direct comparison with various GnRH agonists and, due to less pronounced side effects, dienogest is preferable for long-term conservative therapy, both as a prevention of relapse after surgical treatment, and as the main therapy (Fig. 4).

in 2016, Japanese researchers showed that dienogest, prescribed in the postoperative period, not only significantly reduces the intensity of pelvic pain, but also prevents the recurrence of endometrioma, which is important for maintaining the patient's fertility. According to the results of two randomized controlled trials, the safety and tolerability of the drug was higher than that of GnRH agonists[18,19].

There is also evidence of the effect of dienogest therapy on recurrence and size of ovarian endometrioma [20-22]. Korean researchers studied its use at a dose of 2 mg per day for at least 12 months in 188 women, in 90 % of whom the diagnosis was confirmed histologically during surgery.In 59 women with recurrent endometrioma, cyst diameter was significantly reduced at 12 months from baseline in both unilateral (on average 21 mm, with initial 31 mm) and bilateral (on average 37 mm, with initial 68 mm) ovarian cystic endometriosis. In the observed 35 patients, 18 months after the start of taking the drug the diameter of the cyst significantly decreased compared to the size of 6 months ago, both with unilateral localization (on average up to 14 mm, with initial 21 mm), and with bilateral (on average 41.5 mm, with initial 51mm).

The authors of the study published in 2018 focused their attention on a cohort of patients with relapses after surgical removal of endometrioma(121 participants) who received dienogest for more than 24 weeks (median 58 weeks). It was possible to relieve pain both in a subgroup of patients with recurrence of only symptoms of endometriosis, and in recurrence of endometrioma. The average diameter of recurrent endometrioma also decreased significantly. Specifically, the average size of 105 mass lesions in 88 participants was 38 mm, and it decreased to 27 mm after 4 weeks of treatment.

Another study (2020)of a small group of patients (32 participants) with unilateral endometrioma in combination with pelvic pain treated with dienogest for 6 months reports a decrease in the diameter of endometrioma by almost 2 times (the average cyst diameter was 4.0 ± 1.3 cm at the beginning of the study and 2.4 ± 1.2 cm at the end). A decrease in pelvic pain was revealed as well. Moreover, the number of antral follicles in the affected ovary improved significantly (by 105 % of the initial level), with a constant level of AMH. [23, 24]

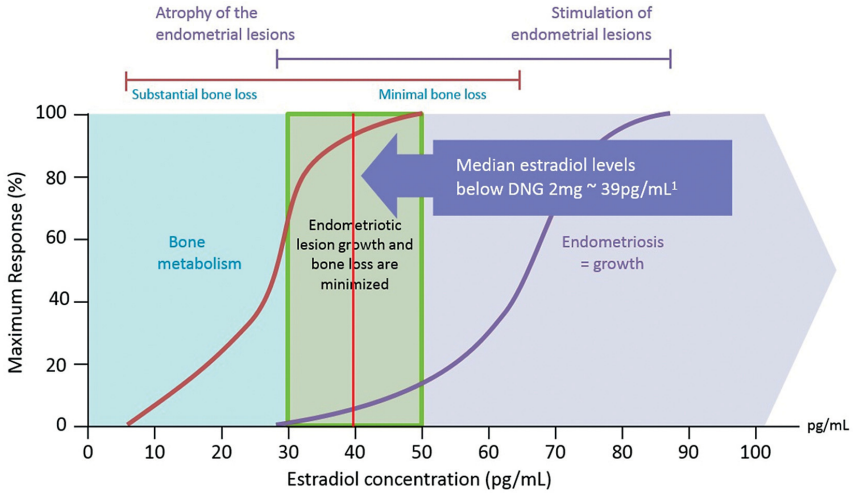

Figure 4. The use of dienogest at a dose of 2 mg/day and tissue mineral density.

Today, many authors are coming to the conclusion that endometrioma is not associated with an increased risk of infertility [25]. Therefore, the need for its removal is a debatable issue, especially if it is small and in the absence of any symptoms other than complaints of infertility. Indeed, in itself, surgery will do what the presence of endometrioma has not been proven to lead to. It will reduce the ovarian reserve, worsening the prognosis of a positive result of ART.According to data from French specialists, when a 5 cm endometrioma is removed, an average of 46 oocytes are lost from the remaining healthy ovarian tissue.

Retro cervical endometriosis occupies a special place among the various forms of endometriosis. It is characterized by the formation of deep infiltrative foci emanating from the rectovaginal septum, without a capsule or clear boundaries, spreading inward and along the length, passing to neighboring organs (rectum, sigmoid colon, bladder, etc.), with the formation of a cicatricial adhesive process.This form of endometriosis is characterized by severe clinical symptoms (pelvic pain, dyspareunia, dyschezia, etc.) and a decrease in the patient's quality of life. There are difficulties in diagnosing this form of endometriosis, which often occurs quite late, when a large amount of tissue is already affected.Surgical treatment, which is often very traumatic, requires a multidisciplinary approach (with the involvement of surgeons and urologists), and subsequently, often leads to the formation of adhesions. Of course, after radical surgical treatment, it is necessary to use medication in order to reduce the risk of recurrence and improve the quality of woman life.Noteworthy is the case of "off-label" use of dienogest 2 mg/day for 3 months with intravaginal administration of the drug. There was a decrease in clinical manifestations (in the posterior fornix of the vagina, see Fig. 5) a decrease in the severity of pelvic pain, while the patient reported better tolerability of the drug compared to oral administration.Vaginal administration of dienogest certainly requires further study regarding pharmacokinetics in clinical trials (see Fig. 5) [26].

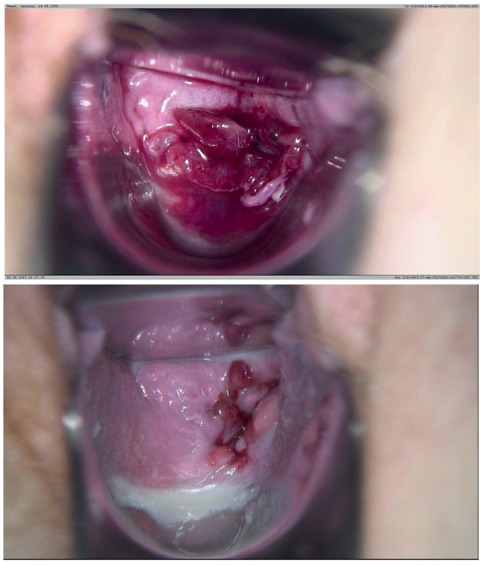

Figure 5. Retrocervical endometriosis before and after intravaginal administration of dienogest.

Conclusion

Endometriosis is a disease of a woman of predominantly reproductive age with a preserved two-phase menstrual cycle, ovulation, often burdened by a gynecological history (including artificial and spontaneous abortions). Therefore, a modern measure of pathogenetic prevention of endometriosis is the use of hormonal contraceptives from the onset of sexual activity in case of delayed reproductive plans, then in integrative intervals. The main strategy of therapy for patients with endometriosis is a differentiated use of modern hormonal drugs depending on patient's age (reproductive or approaching menopause) and on the immediate and long-term reproductive plans. In the absence of the effect of hormonal therapy, surgical treatment is recommended.

References

1. Koninckx PR, Ussia A, Adamyan L, Tahlak M, Keckstein J. Wattiez A. Martin DC. The epidemyology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear. Best Practice and Research. *Clinical Obstetrics and Gynaecology.* 2021;(71):14-26. DOI: 10/2016/j.bpobgyn.2020.08.005

2. ASRM (American Society for Reproductive Medicine). Practice Committee. Endometriosis and infertility: a committee opinion. Fertility and Sterility. 2012;(98):591-598.

3. Prašnikar E, Knez J, Kovačič B, Kunej T. Molecular signature of eutopic endometrium in endometriosis based on the multi-omics integrative synthesis. *Journal of Assisted Reproduction and Genetics.* 2020;37(7):1593-1611. DOI: 10.1007/s10815-020-01833-3

4. Stopiglia RM, Ferreira U, Faundes DG, Petta CA. Cystoscopy-assisted laparoscopy for bladder endometriosis: modified light-to-light technique for bladder preservation. *International Brazilian Journal of Urology.* 2017;43(1):87-94. DOI: 10.1590/S1677-5538.IBJU.2014.0362

5. Samani EN, Mamillapalli R, Li F, Mutlu L, Hufnagel D, Krikun G, Taylor HS. Micrometastasis of endometriosis to distant organs in a murine model. *Oncotarget.* 2017;10(23):2282-2291. DOI: 10.18632/oncotarget.16889

6. Members of the Endometriosis Guideline Core Group, Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group. ESHRE guideline: endometriosis. *Human Reproduction Open.* 2022;2022(2):hoac009. DOI: 10.1093/hropen/hoac009

7. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *The New England Journal of Medicine.* 2020;382(13):1244-1256. DOI: 10.1056/NEJMra1810764.

8. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E; ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group.

ESHRE guideline for the diagnosis and treatment of endometriosis. *Human Reproduction.* 2005;(20):2698-2704.

9. ACOG Education Pamphlet AP013:Endometriosis// The American Colege of Obstetricians and Gynecologists. September. – Washington,DC,2008. Schindler A., Dienogest in long-term treatment of Endometriosis. Intern. *Journal of Women's Health.* 2011;(3):175-184.

10. Leyland N, Casper R, Laberge P, Singh SS; SOGC. Endometriosis: diagnosis and management. *Journal of Obstetrics and Gynaecology Canada.* 2010;32(7):1-27.

11. ACOG Committee on Practice Bulletins--Gynecology. ACOG Practice Bulletin No. 51. Chronic pelvic pain. *Obstetrics & Gynecology.* 2004;(103):589-605.

12. Latthe P, Latthe M, Say L, Gülmezoglu M, Khan KS. WHO systematic review of prevalence of chronic pelvic pain: a neglected reproductive health morbidity. BMC Public Health.2006;(6):177-184.

13. Stones RW, Mountfield J. Interventions for treating chronic pelvic pain in women. *Cochrane Database of Systematic Reviews.* 2000;(4):CD000387.

14. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ.* 2011;(342):7086-7089.

15. Allen C, Hopewell S, Prentice A. Non-steroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database of Systematic Reviews.* 2005;19;(4):CD004753.

16. Grandi G, Mueller MD, Bersinger NA, Facchinetti F, McKinnon BD. The association between progestins, nuclear receptors expression and inflammation in endometrial stromal cells from women with endometriosis. *Gynecological Endocrinology.* 2017;33(9):712-715. DOI: 10.1080/09513590.2017.1314458

17. Wattanayingcharoenchai R, Rattanasiri S, Charakorn C, Attia J, Thakkinstian A. Postoperative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: a systematic review and network meta-analysis. *BJOG.* 2021;128(1):25-35. DOI: 10.1111/1471-0528.16366.

18. Ozaki R, Kumakiri J, Jinushi M, Ikuma S, Murakami K, Kawasaki Y, Kitade M. Comparison of effect of preoperative dienogest and gonadotropin-releasing hormone agonist administration on laparoscopic cystectomy for ovarian endometriomas. *Archives of Gynecology and Obstetrics.* 2020;302(4):969-976. DOI: 10.1007/s00404-020-05691-3

19. Zakhari A, Edwards D, Ryu M, Matelski JJ, Bougie O, Murji A. Dienogest and the Risk of Endometriosis Recurrence Following Surgery: A Systematic Review and Meta-analysis. *Journal of Minimally Invasive Gynecology.*2020;27(7):1503-1510. DOI: 10.1016/j.jmig.2020.05.007

20. Angioni S, Pontis A, Malune ME, Cela V, Luisi S, Litta P, Vignali M, Nappi L. Is dienogest the best medical treatment for ovarian endometriomas? Results of a multicentric case control study. *Gynecological Endocrinology.* 2020;36(1):84-86. DOI: 10.1080/09513590.2019.1640674

21. Vignali M, Belloni GM, Pietropaolo G, Barbasetti Di Prun A, Barbera V, Angioni S, Pino I. Effect of Dienogest therapy on the size of the endometrioma. *Gynecological Endocrinology.* 2020;36(8):723-727. DOI: 10.1080/09513590.2020.1725965

22. Wattanayingcharoenchai R, Rattanasiri S, Charakorn C, Attia J, Thakkinstian A. Postoperative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: a systematic review and network meta-analysis. *BJOG.* 2021;128(1):25-35. DOI: 10.1111/1471-0528.16366

23. Muzii L, Galati G, Di Tucci C, Di Felicianotonio M, Perniola G, Di Donato V, Benedetti Panici P, Vignali M. Medical treatment of ovarian endometriomas: a prospective evaluation of the effect of dienogest on ovarian reserve, cyst diameter, and associated pain. *Gynecological Endocrinology.* 2020;36(1):81-83. DOI: 10.1080/09513590.2019.1640199

24. Vignali M, Belloni GM, Pietropaolo G, Barbasetti Di Prun A, Barbera V, Angioni S, Pino I. Effect of Dienogest therapy on the size of the endometrioma. *Gynecological Endocrinology.* 2020;36(8):723-727. DOI: 10.1080/09513590.2020.1725965

25. Doyle JO, Missmer SA, Laufer MR. The effect of combined surgical-medical intervention on the progression of endometriosis in an adolescent and young adult population. *Journal of Pediatric and Adolescent Gynecology.* 2009;22(4):257-263.

26. Ebert AD. Daily Vaginal Application of Dienogest (Visanne©) for 3 Months in Symptomatic Deeply Infiltrating Rectovaginal Endometriosis: A Possible New Treatment Approach? *Case Reports in Obstetrics and Gynecology.* 2018;(2018):8175870. DOI: 10.1155/2018/8175870

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