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Operation, hormone therapy and recovery of the patients with severe forms of adenomyosis

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ABSTRACT

Endometriosis is among the prevalent gynecological diseases and diagnosed in 10% of women of reproductive age. Endometriosis/adenomyosis is becoming increasingly a health-social problem, which is associated with severe clinical manifestations and recurrent disease which has a negative effect on quality of life, women ability to work and her reproductive function. This article presents modern approaches of drug therapy to treat severe forms of adenomyosis. We have reviewed recent major studies in the field of surgical treatment of this disease, analyzed the main stages of disease progress and the results of our surgeries. Here, we are presenting our own results of long-term post-operative hormonal therapy and complex medical treatment.

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Introduction

Adenomyosis is a benign uterine disorder characterized by the presence of heterotopic endometrial glands and stroma in the myometrium and reactive fibrosis of the surrounding smooth muscles cells of the myometrium, that results into such clinical disorders like dysmenorrhea, hypermenorrhea, anemia, dyspareunia, and infertility [1–4].

More women are delaying their first pregnancy until later in their thirties or forties, and consequently adenomyosis encountered more frequently in the fertility clinic during diagnostic work-up [5]. Adenomyosis is decreasing the potential of fertility in this age-group [6–9].

In most cases, drug therapy of adenomyosis, including hormonal, are ineffective or inefficient. To increase the effectiveness of operative treatment of adenomyosis and ensure long-term remission are of primary importance. Subsequent suppressive hormonal therapy should be applied [3]. The modern trend toward organ preservation treatment has immediate implications regarding adenomyosis [10,11].

The standard treatment of adenomyosis is hysterectomy. Thus, there is no proper medical therapy to treat the symptoms of adenomyosis. Medical therapies with suppressive hormonal treatments, such as continuous use of oral contraceptive pills, high-dose progestins, selective estrogen receptor modulators, the levonorgestrel-releasing intrauterine device, aromatase inhibitors, danazol and gonadotropin receptor hormone agonists can temporarily induce regression of adenomyosis and relief some symptoms [9].

A lack of randomized, controlled trials exploring the impact of GnRH-a treatment on fertility makes the understanding of adenomyosis unclear [4]. There is only one case study reported that treatment of severe adenomyosis with GnRH for 16 weeks resulted in the birth of a healthy male infant [12].

Progestogens

The role of progesterone in the development or persistence of adenomyosis is not clear for the following reasons: (1) the protective role of progesterone in endometrial cancer, epithelial proliferation but rather increased inflammation and cell survival due to diminished apoptosis or differentiation; (2) progesterone induces a transient proliferation of stromal cells in normal endometrium; (3) only half of patients with adenomyosis benefit from progesterone therapy; (4) antiprogestins with mixed agonist and antagonist properties (SPRM) reduce adenomyosis-associated pelvic pain, possibly more effectively than progestins; although the reason is not clear, it may be secondary to progesterone resistance in adenomyosis; and (5) adenomyotic lesions produce significant quantities of progesterone and contain strikingly lower levels of progesterone receptor (PR) with endometrium [13,14]. Women with adenomyosis are characterized by a lower expression of PRs (A and B) in endometrial lesions, but also in the outer and inner layers of the myometrium. The treatment of adenomyosis with progesterone may be restricted due to the abnormal expression of PRs [6,15].

Dienogest (progestin)

Dienogest (progestin) has been used to treat adenomyosis pharmacologically. Dienogest – a selective PR agonist is widely used to treat endometriosis and efficiently relieves the symptoms [16]. Dienogest directly inhibits cellular proliferation and induces apoptosis in human adenomyotic stromal cells [17]. Apart from that, Dienogest exerts comprehensive inhibition of abnormal estrogen production through inhibition of aromatase and 17 β -hydroxysteroid dehydrogenase (HSD17 β 1), contributing to a therapeutic effect of Dienogest on endometriosis [16]. Two non-

randomized studies on a small number of patients have been published, but neither refers to the patients' fertility [6].

Levonorgestrel intrauterine system

The use of Levonorgestrel intrauterine system treatment is accompanied by a decreased pain and lowering of heavy uterine bleeding [18]. During the treatment of LNG-IUS for symptomatic adenomyosis, there are changes of the menstruation pattern such as gradual increase of amenorrhea and shortened menstruation as the most common manifestations, while adverse effects decrease significantly [19]. The LNG-IUS is a suitable alternative treatment option for the management of dysmenorrheal and heavy menstrual bleeding prior to hysterectomy for patients with large adenomyosis [20]. LNG-IUS is approved for treating women with adenomyosis, who have completed their childbearing [6].

Patients with severe pain, hypermenorrhea and, as a consequence, severe anemia, belong to the group of 'active adenomyosis'. Active adenomyosis is usually an indication for surgical treatment. Very recently, hysterectomy was mostly a choice of surgical treatment for severe forms of adenomyosis [21,22]. However, many women suffering from adenomyosis, wish not only to preserve the uterus, but to have children in the future. Thus, the trend of modern gynecology is aimed at the use in practice of treatment with conservative surgery methods [23–26].

Tsui et al. think that conservative surgical technique is controversial, but still some data prove its efficiency. Conservative treatment is still needed in the group of patients that requires preservation of fertility and improvement of life quality [27].

In our opinion, very promising in solving the problem of organ-preserving surgical treatment of patients with adenomyosis is a method of radical resection of adenomyomatous tissue, proposed by the Japanese surgeon Osada, who in 2011 published his own experience of performing such operations in 104 patients with this disease by his technique. All patients felt immediate relief of symptoms of hypermenorrhea and dysmenorrhea [28].

This laparotomy technique involves: (1) extraperitonealization of the uterus and rubber tourniquet placement for hemostasis; (2) bisection of the uterus in the midline and in the sagittal plane with a scalpel until the uterine cavity is reached; (3) opening of the endometrial cavity to permit the introduction of the index finger to guide during excision of adenomyotic tissues; (4) use of Martin forceps to grasp adenomyotic tissues and to excise it from surrounding myometrium, leaving a myometrial thickness of 1 cm from serosa above and endometrium below; (5) closure of the endometrium with 3–0 Vicryl; and (6) closure of the flaps of the uterine wall approximating the myometrium and serosa of the one side of the bisected uterus in the anteroposterior plane with interrupted 2–0 Vicryl, while the contralateral side of the uterine wall is brought over the reconstructed first side in such a way as to cover it [23,28].

The advantages of this method – first, allows to resect the affected tissues more widely and thoroughly than the wedge resection. Second, the massive tissue defects after wide excision of the affected area can be transformed by using three layers of myometrium in the reconstructed wall of sufficient thickness to sustain a normal pregnancy without the risk of uterine rupture. This operation has shown its high efficiency in the elimination of symptoms and restoration of reproductive function, as well as only a small number of relapses of the disease [28–30].

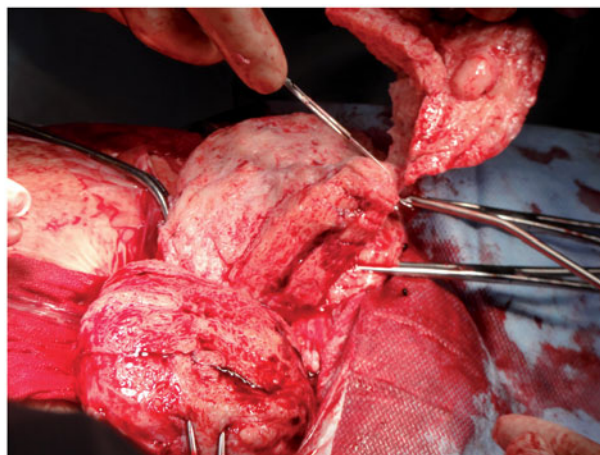


Figure 1. Adenomyomectomy with the reconstruction of the uterine wall by the replacement method after Osada.

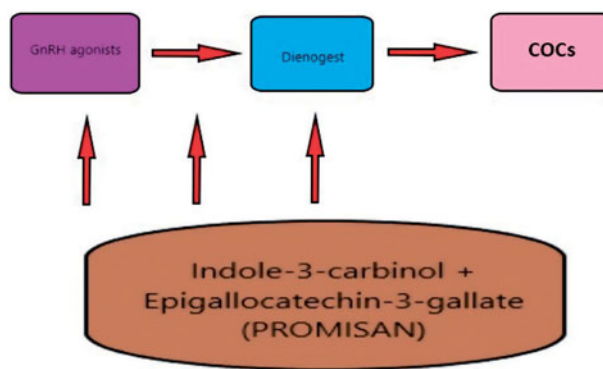


Figure 2. PROMISAN.

Materials and methods

Twenty one patients with adenomyosis were operated by the method of Osada from 2012 to 2016 by the staff of the Department of obstetrics and gynecology of Krasnoyarsk State Medical University affiliated with the Regional Perinatal Center.

The results of the study

The average age of patients amounted to 35.3 ± 7.2 (22–47) years. All patients (100%) complained about chronic abnormal uterine bleeding, 19 (90.4%) – algomenorrhea, 12 (57.1%) – dyspareunia, 15 (83.3%) patients had chronic hemorrhagic anemia of varying severity. Fourteen (66.7%) patients had history of infertility. However, four patients were not interested in reproductive functions, but insisted on having conservative surgery. In all patients' records, there were repeated but unsuccessful courses of adenomyosis treatment with hormonal therapy (progestin, agonists of gonadoliberin, combined hormonal contraceptives).

All patients with adenomyosis were operated with the following technique: laparotomy by Pfannenstiel, adenomyomectomy with the reconstruction of the uterine wall by the replacement method after Osada (Figure 1). During the operation, it was seen that in 10 patients the size of the uterus fitted 12–14 weeks of pregnancy, in eight women – 15–16 weeks, in two patients – 18 weeks and in one patient – up to 20 weeks. The average duration of surgery was $156, 8 \pm 52.2$ min. The average amount of blood loss during the operation amounted to 512 ± 219.4 ml.

Tissue removed during surgery of the uterus affected by adenomyosis, averaged 416.6 ± 254.1 g.

According to the results of histological examination of removed tissue in almost all fields of view in identified areas of the inner glandular-stroma endometriosis; every third patient (28.5%; $n=6$) by the results of histological examination, had a combination of endometriosis and massive myomatosis of the myometrium.

The results of immune histochemical examination of postoperative material: in all researched patterns Vimentin and E-cadherin are intensively expressed with a high level of expression of Bcl-2 (from 70 to 100%); identified high levels of Ki-67 in all samples due to the epithelial cells of the glands; the expression of a larger number of TGF- β 1 (60–100% of cells in the studied samples) was identified.

With the purpose to increase the efficiency of surgical treatment and prevent disease recurrence in the postoperative period, all the patients received hormonal therapy in our proposed scheme: gonadotropin-releasing hormone agonist for 4–6 months – Dienogest for 6–12 months – combined hormonal contraceptives (COCs) in continuous mode for 6 months or more. Simultaneously with hormonal treatment from the first days of the postoperative period, all the patients were administered to epigenetic therapy for 12–18 months.

Normally, we administered Triptorelin acetate in the dose of 3.75 mg monthly by 3 or 4 injections or in a dose of 11.25 mg once in 3 months by two injections, which ensured the active effect of the drug for 4–6 months. Immediately after the end of GnRH agonists therapy, the patients were prescribed to Dienogest (Visanne) in a dose of 2 mg per day for the period from 6 up to 12 months.

Epigenetic processes play a key role in the pathogenesis of malignant and benign proliferative processes, in particular – of endometriosis, endometrial hyperplasia and uterine fibroids [31–34]. From 12 to 18 months postoperatively, the patients were assigned to the drug Promisan (one capsule contains 90 mg indole-3-carbinol and 45 mg epigallocatechin-3-gallate) as this drug normalizes the balance of estrogen in the body and inhibits their negative effect, and also blocks other (hormone-independent) mechanisms that trigger pathological cell growth, and has the ability to cause selective death of transformed cells with abnormally high proliferative activity (Figure 2).

Discussion

The assignment of GnRH analogs was justified by their action aimed at blocking the allocation by the anterior pituitary gonadotropins FSH and LH and their direct impact on the key mechanisms that play an important role in the development of endometriosis (pro apoptotic action, anti-proliferative, anti-inflammatory).

Inclusion of Dienogest in the treatment program may be explained by the inability of prolonged use of GnRH (for more than 6 months) due to their side effects; as well as there is an obvious advantage of Dienogest in the treatment of endometriosis. It is proved that the efficiency of Dienogest (2 mg) equals current standard of therapy with GnRH agonists, while Dienogest does not cause clinically significant hypoestrogenic side effects arising from the application of GnRH agonists. Dienogest affects endometriosis by reducing the endogenous production of estradiol and thereby suppressing its atrophic effects. In continuous use, Dienogest creates a hypoestrogenic, endocrine environment, which ultimately contributes to atrophy of

endometriosis lesions. Additional properties of Dienogest such as immunologic and antiangiogenic effects obviously contribute to its suppressing effect on cell proliferation.

The period of active hormonal therapy in patients operated on adenomyosis of the 3rd, 4th stages, ranged from 12 to 18 months (they have had medical treatment with GnRH agonist and Dienogest). In case, the patients were not planning pregnancy, then they were not prescribed to post-operative hormonal therapy but were administered to combined hormonal contraceptives continuously to prevent recurrence of adenomyosis.

Period of observation of the operated patients currently ranges from 4 to 45 months. It should be noted that normalization of menstrual function was observed in all patients (100%), complaints of pain (100%) disappeared and sexual function normalized (100%). The recurrence of the pathological symptoms of the disease was not registered in any patient. Two patients became pregnant; in both cases, the pregnancy was spontaneous. Both patients were delivered by cesarean section at 38–39 weeks and gave birth to healthy and full-term infants. Currently, 11 patients are on postoperative hormone medication, six patients are included into the program of extracorporeal fertilization.

Conclusions

Thus, our experience of intraoperative radical resection by the method of Osada suggests that this technique may be a surgery of the patient's choice, especially for women of reproductive age with common diffuse and diffuse-nodular adenomyosis, for those who have not realized their fertility as yet. Also, this type of surgery may be recommended for patients of late reproductive age, who have no future reproductive plans, but hysterectomy is not their preference. For the successful treatment of these patients, in addition to high quality surgical equipment and high quality surgical technique, it is necessary to conduct adequate pathogenetic and hormone therapy right after the surgery with the inclusion of epigenetic therapy (as an impact on a key chain of pathological processes), and a continuous and careful follow up.

Disclosure statement

There is no conflict of interest.

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