Results of implication of aromatase inhibitors in therapy of genital endometriosis

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• Endometriosis is certainly the disease itself, while endometriotic heterotopies is a symptom of the disease.

• Disease can not be cured only by surgical removement of endometriotic lesions. We need to impact etiopathogenesis of this condition.
• Till nowadays, there have not been any regimen or scheme of treatment of genital endometriosis that can guarantee absence of recurrence of the disease.

• This shows the necessity of search for new groups of drugs for treatment of endometriosis. One of the priority directions is the study of aromatase activity, which is the enzyme, responsible for estrogen synthesis.
The role of aromatase in conversion of androgens to estrogens

Aromatase is the key enzyme of estrogen synthesis which converses androstendion and testosterone into estron and estradiol.
Immunohistochemical analysis

- Immunohistochemical study of 49 patients with endometriosis and 18 healthy women of comparison group was performed. The diagnosis of endometriosis was stated by laparoscopy with histological verification.
- Determination of aromatase expression was conducted in endometrioid heterotopies excised from peritoneum of women with endometriosis.
- As a control group we studied fragments of endometrium of healthy women.
- **Results:** Endometriotic heterotopies are characterized by increased expression of aromatase: value of its expression in foci of endometriosis is 34 times higher than in eutopic endometrium of healthy women (11.94% and 0.35%, respectively).
Determination of aromatase expression

Aromatase expression in endometrium of control group (×400)

Expression of aromatase in endometriotic heterotopies (×400)
• After surgery, 127 patients of reproductive age with genital endometriosis were prescribed aromatase inhibitors (letrozole 2.5 mg, 1 tablet per day) in combination with progestagens from the group of 19-nortestosterone derivates (lynestrenol 5 mg, 1 tablet 2 times a day) continuously for 6 months.

• This scheme of treatment was approved by Local Ethic Committee of Ott’s Research Institute of Obstetrics, Gynecology and Reproductology and all the patients signed informed consent forms.
Mechanism of action

Hypoestrogenaemia leads to increased FSH levels, followed by ovarian stimulation and can stimulate formation of functional cysts.
• It is known that aromatase inhibitors cannot be prescribed as monotherapy, due to stimulating effect on ovaries.

• This explains the importance of adding of progesterogenic component with antigonadotropin action into the treatment scheme.
Patients & methods:

- Diagnosis for all the patients was stated during laparoscopy and confirmed by histological examination.
- In 73.3% of patients it was a recurrence of the disease.
• First stage of endometriosis according to R-AFS classification was revealed in 1.6% of patients, II stage - in 6.3%, III stage - in 26.0% and IV stage - in 66.1% of women.
• 86.7% of patients had severe endometriosis.
• Infiltrative endometriosis was diagnosed in 51.6% of women.
• Pelvic adhesive disease was found in 81.3% of cases.
• In 53% of patients cystectomy was performed, in 46.8% - excision of endometriotic lesions on peritoneum of pelvis minor was done.
• In 51.6% - we performed removal of endometrioid infiltrate, 4.2% underwent resection of recto-sigmoid part of colon.
Indications for treatment with aromatase inhibitors were formulated as follows:

- Endometriosis confirmed during surgery in combination with history of ineffective treatment with aGnRH and/or reduced ovarian reserve.
• It is noted that 53.7% of patients with endometriosis who received therapy with aromatase inhibitors, previously received aGnRH,
• 38.1% of women more than once (from 2 to 4 courses).
• Total duration of treatment with aGnRH varied from 3 to 18 months.
For assessment of ovarian reserve before prescription of therapy, we determined levels of follicle stimulating hormone (FSH) and antimullerian hormone (AMH) in blood on the 2d-3d day of menstrual cycle.

On the basis of serum levels of FSH and AMH, 12.2% of patients had preserved ovarian reserve, in 87.8% of patients ovarian reserve was significantly reduced.
Prior to therapy

- chronic pelvic pain was observed in 67.7% of patients,
- dyspareunia in 30.7%,
- infertility in 55.9% of women, its duration varied from 1 to 18 years (average duration was 5.33 ± 0.78 years)
• The results of treatment were estimated by the duration of recurrence-free period, disappearance/decrease of pain, overcoming of infertility.

• During the course of treatment, pelvic pain disappeared in 97.6% of patients. It should be noted that in these patients during previous therapy with aGnRH, pain was observed in 18% of cases.
Side-effects

Among side-effects we frequently observed:

➢ spotting  (in 32.3% of patients)
➢ acne  (in 14.6% of women), mainly localized on face and back.
➢ During treatment, hot flashes were reported in 8% of women (not more than 5 times a day).
➢ 22.1% of patients had a slight weight gain during treatment (2,46 ± 0,56 kg on average).

None of these side effects were the reason for early termination of treatment.
• On the basis of physical and laboratory examination, we didn’t find any symptoms, showing recurrence of endometriosis.

• In 9 patients we performed control laparoscopy and confirmed regression of endometriotic lesions.
Before treatment with inhibitors of aromatase

After treatment with aromatase inhibitors
Before treatment with inhibitors of aromatase

After 6 months of treatment with aromatase inhibitors
After the end of treatment with aromatase inhibitors, 31% of patients with infertility, genital endometriosis and repeated courses of ineffective hormone therapy became pregnant (among them in 18.2% of women pregnancy occurred spontaneously, in 31.8% - after ovulation induction with gonadotropins, in 50% - in IVF protocol with the use of own (16.7%) or donor (33.3%) oocytes).
Conclusion:

- The study shows that aromatase inhibitors can be used for treatment of patients of reproductive age with endometriosis. Application of aromatase inhibitors is an effective, safe and well tolerated method of endometriosis treatment, especially for patients with recurrence of endometriosis after GnRH agonist treatment and/or with reduced ovarian reserve.

- But introduction of this drug in routine practice requires further in-depth study.
Thank you for your attention