Endometriosis: contemporary concept of treatment

Endometriosis - Update of Therapeutic Management

Orthodontic splint therapy of patients with limited bone supply

Orthodontic Splint Treatment of Patients with Limited Bone Supply

Giant thoracic osteochondroma case report - Diagnosis and therapy

Monstrous Thoracic Osteochondroma Case Report - Diagnosis and Therapy

Cystic tumors of the pancreas

Cystic Tumors of the Pancreas

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Introduction

Endometriosis is one of the most common gynecological benign diseases in premenopausal women. It is diagnosed in approximately 6-10% of all women and in 35-50% in women with abdominal and pelvic pain or infertility. In Germany, about 40,000 cases of endometriosis are diagnosed per year, with almost 20,000 patients being evaluated in hospitals for further management [1]. Health care expenses for endometriosis are estimated to amount up to 22 billion USD.

Endometriosis is an estrogen-dependent disorder exhibiting endometrial glands and stroma outside the uterine cavity. Main symptoms are abdominal or pelvic pain and infertility. Due to still unknown etiology and pathogenesis of endometriosis, therapy focuses on symptom relief. Current standard therapy for endometriosis concentrates on surgery with complete resection of all endometriosis lesions, if possible, by laparoscopy. Following surgical treatment, further options include hormonal substitution and analgesia. Primary aim of hormonal therapy is to suppress and antagonize the estrogen production. Complementary Medicine and Alternative Therapies can be considered to improve symptoms, however randomized studies are lacking [2]. In this manuscript, current aspects for surgical and medical treatment of endometriosis are summarized.

General Considerations

Indications for laparoscopic evaluation in case of suspected endometriosis include pain, destruction of organs and/or fertility [3]. If a patient with endometriosis is asymptomatic and has no desire to have children, treatment is not necessary. As an exception to this rule, patients with impaired organ function (e.g. ureterstenosis with consecutive hydronephrosis) due to endometriosis lesions may still require therapeutic interventions despite lack of clinical symptoms.

In the present manuscript, possible clinical presentations of endometriosis with their
related treatment options are discussed. Hormonal treatment options are described more detailed at the end of the manuscript.

**Peritoneal Endometriosis**

**Medical Treatment**

The primary aim of the hormonal treatment is to obtain a hypoestrogenic state by suppressing the ovarian function and achieving the regression of endometriosis implants. Treatment options including progestagens, continuous use of combined oral contraceptives and Gonadotropin-releasing hormone (GnRH) agonists effect the reduction of endometriosis-associated symptoms. In terms of dysmenorhoea and dyspareunia GnRH agonists were most effective in some studies [4]. Two current, prospective randomized trials regarding endometriosis-associated pain demonstrated a comparable outcome between GnRH agonists and oral progestagen (Dienogest).

In the current article, possible clinical manifestations of endometriosis with corresponding treatment methods are described, including hormonal therapy. In the conclusion, the authors present varied treatment options for endometriosis. The treatment options include progestagens, continuous use of combined oral contraceptives and GnRH agonists, which effectively reduce endometriosis-associated symptoms. In some studies [4], two current, prospective randomized trials regarding endometriosis-associated pain demonstrated comparable outcomes between GnRH agonists and oral progestagens (Dienogest).
Dienogest was better tolerated than GnRH agonists [5, 6]. Despite the frequent use in daily practice, a definitive proof for positive effect of antirheumatic and antiphlogistic drugs on endometriosis-associated pain is missing [7].

**Surgical Treatment**

Primary aim is the completely removal of all endometriosis lesions by laparoscopy. This procedure may result in significant pain reduction [8]. In contrast, an equal effectivity of other different procedures like coagulation, vaporization or excision has not been proven so far [9, 10]. To further reduce pain following surgery, application of a levonorgestrel-releasing IUD can be considered [11].

**Ovarian Endometrioma**

**Medical Treatment**

Hormonal treatment alone can neither eliminate nor compensate an incomplete removal of ovarian endometrioma, so that hormonal treatment in ovarian endometrioma is not recommended [3].

**Surgical Treatment**

Most effective treatment of ovarian endometriomas is the surgical removal. In this context, complete resection of the cystic wall is warranted. In a meta-analysis, ovary-preserving cystectomy in comparison to thermic destruction of the cyst wall is more effective regarding pain relief, relapse and pregnancy rates [12]. Due high risk for relapse, only opening and flushing the ovarian endometrioma as a solely surgical procedure is not sufficient. In addition, postoperative treatment with GnRH agonists could not postoperatively balance the incomplete surgical resection [13].

**Deep Infiltrating Endometriosis (DIE)**

**Medical Treatment**

Benefits for pre- or postoperative GnRH agonists application in DIE is not proven and is therefore not generally recommended [13]. If patients refuse surgery or still suffer from pain following surgery, hormonal treatment is one option. As the effect of hormonal therapy is usually expected only during the treatment period, continuous application of this treatment is recommended. Therapeutic options include continuous use of oral contraceptives, progestagen monotherapy and GnRH agonists (in continuous application with “add back” estrogen therapy for bone protection) leading to therapeutic amenorrhoea. As an alternative treatment, positive effects of a levonorgestrel-releasing IUD can be considered [11].

**Gynecology**

**Therapeutic options include**

- Continuous use of oral contraceptives
- Progestagen monotherapy
- GnRH agonists (in continuous application with “add back” estrogen therapy for bone protection)

Leading to therapeutic amenorrhoea.

**Endometrioma яичников**

**Консервативное лечение**

Одна лишь гормональная терапия не может ни элиминировать, ни компенсировать неполное хирургическое удаление эндометриоза яичников, поэтому такое лечение при поражении яичников не рекомендуется (3).

**Хирургическое лечение**

Наиболее эффективным методом лечения овариального эндометриоза является хирургия, поскольку только такое радикальное вмешательство гарантирует полную резекцию стенки кисты. Мета-анализ показал, что цистэктомия с сохранением яичника, по сравнению с терапевтической деструкцией стенки кисты, является более эффективным методом относительно облегчения боли, рецидивов и показателя наступления беременности (12). Из-за высокого риска рецидива, только хирургическое открытие и промывания эндометриомы яичника недостаточно. Кроме того, послеоперационное лечение гонадотропинами ГнРГ не может компенсировать неполную хирургическую резекцию (13).

**Глубокий инфилтративный эндометриоз (ГИЭ)**

**Консервативное лечение**

Преимущества применения агонистов ГнРГ до и после операции при ГИЭ не доказаны исследованиями, поэтому такая терапия не рекомендуется (13). Если пациентки отказались от операции или продолжают страдать от боли после хирургического вмешательства, показана гормональная терапия. Поскольку эффект от лечения гормонами обычно ожидается только во время проведения терапии, рекомендуется постоянное применение гормо-
estrel-releasing IUD regarding pain and lesion size in deep infiltrating endometriosis have been described [14].

Surgical Treatment
If possible, complete resection of endometriosis lesions should be achieved [3]. In this context, surgeries may include rectum resection (mostly en-bloc with the rectovaginal septum and the vagina), and partial resection of the sacrouterine ligament and/or parametria as well as partial bladder resection. Ureter resections with re-anastomosis (e.g. Psoas-hitch ureteroneocystostomy) are only indicated in rare cases. Therefore, the extent of resection, including possible perioperative complications, should be carefully discussed with the patient preoperatively. In some cases, endometriosis can only incompletely removed in order to preserve fertility. In several cases, endometriosis can only incompletely removed in order to preserve fertility.

Fig. 2: Intraoperative image of peritoneal endometriosis

Рис. 2: Интраоперационный вид перitoneального эндометриоза

nov. Терапевтические варианты включают непрерывное применение оральных контрацептивов, монотерапию прогестинами и лечение агонистами ГнРГ (при постоянной возвратной терапии эстрогенами для защиты костной ткани), что приводит к терапевтической аменорее. В качестве альтернативного лечения может быть использована внутриматочная левоноргестрел - рилизинг система, положительные эффекты от которой относительно боли и уменьшения размеров эндометриоидных очагов при инфильтративном эндометриозе описаны в литературе (14).

Хирургическое лечение
По возможности должна быть достигнута полная резекция всех очагов эндометриоза (3). В этом контексте хирургическое вмешательство может включать резекцию прямой кишки (в основном, единным блоком с ректовагинальной перегородкой и влагалищем)
studies abdominal pain, quality of life and fertility is positively affected by surgical treatment in DIE [15].

Treatment of patients with DIE should only be performed in specialized centers with an active interdisciplinary cooperation (at least gynecology, surgery, urology). Urinary retention – due to extrinsic or intrinsic DIE of the ureter – requires immediate surgical intervention to prevent persisting damage to the kidneys [3]. Therefore, regular kidney sonography is indispensable in gynecologic evaluation of DIE patients.

Adenomyosis Uteri

Medical Treatment

Progestagens, combined contraceptives in longterm use and levonorgestrel-releasing IUDs are effective alternatives to hysterectomy [16]. The therapeutic value is based on the induction of amenorrhoea. Interventional-radiologic procedures such as embolization [17] and MRI-guided focussed ultrasound surgery are still experimental [18] and should currently be offered only to patients as part of clinical trials.

Surgical Treatment

After finishing family planning, the most helpful treatment of symptomatic patients is hysterectomy [3]. Patients, who wish to maintain the uterus, probably benefit from uteruspreserving surgical treatment with removal of focal adenomyosis. However, and partial resection of the fascia and / or the parietes, as well as partial resection of the bladder. Resections of the ureters with re-anastomosis (e.g. Psoas-hitch method) are only indicated in rare cases.

The volume of resection including perioperative complications should be carefully discussed with the patient before the operation.

In some cases, foci of endometriosis may be removed not completely in order to preserve fertility. Several studies have shown that surgical treatment of DIE reduces pain, improves quality of life and fertility (15).

Fig. 3: Ultrasound of ovarian endometrioma in vaginal examination

Fig. 3: Ультразвуковое вагинальное исследование при эндометриоиде яичников
this method has not yet been proven in clinical trials.

Medical Treatment

**GnRH Agonists / GnRH Antagonists**

GnRH agonists suppress the pulsatile activity of the hypothalamus. After an initial gonadotropin “flare” up, LH (luteinizing hormone) and FSH (follicle stimulating hormone) are decreasing. Consecutively, estradiol levels drop down, the endometriosis lesions are diminished and amenorrhea with secondary insufficiency of the ovaries results [19]. Usually, GnRH agonists are used as a depot e.g. Goserelin and Leuprolerin. However, patients often suffer from typically postmenopausal symptoms such as hot flushes and sleep disorders. In addition, a reduction of bone density (Osteoporosis) can be observed.

Because of these side effects, the use of GnRH agonists is only recommended for 6 months. An additional add-back therapy with a combination of estrogen/gestagen or only estrogen should be initiated to reduce symptoms and to protect the bone density without influencing the effectivity in endometriosis treatment.

A novel treatment option is an orally bioavailable GnRH antagonist (Elagolix) [20]. The

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**Conservative treatment**

**GnRH agonists / GnRH antagonists**

GnRH agonists and antagonists are effective in the treatment of endometriosis. After initial gonadotropin “flare” up, LH and FSH decrease. Consequently, estradiol levels also decrease, and the endometriosis lesions are diminished and amenorrhea with secondary insufficiency of the ovaries results [19]. GnRH agonists are usually used as a depot e.g. Goserelin and Leuprolerin. However, patients often suffer from postmenopausal symptoms such as hot flushes and sleep disorders. Additionally, a reduction in bone density (Osteoporosis) can be observed. Because of these side effects, the use of GnRH agonists is only recommended for 6 months. An additional add-back therapy with a combination of estrogen/gestagen or only estrogen should be initiated to reduce symptoms and protect the bone density without affecting the effectivity in endometriosis treatment.

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**Surgical treatment**

After the completion of the planning of the family, the most effective treatment for symptomatic patients is hysterectomy (3). Patients, who wish to keep the uterus, may be treated with organ-preserving surgery with removal of adenomyosis. However, the advantages of this method are not yet proven in clinical studies.
advantage is the oral application with fewer side effects, especially with respect to bone density.

**Progestagens**
Progestagens suppress the hypothalamus-pituitary-gonadal axis and reduce the estrogen level consecutively. Furthermore, progestagens directly affect the endometrium by decidualization and atrophy of eutrop endometrium and endometriosis lesions. Additionally, progestagens suppress the matrix metalloproteinases, playing an important role in the growth of ectopic endometrium [21].

Progestagens also have an anti-inflammatory effect by inhibition of prostaglandin expression. As a result, menstrual bleeding and other respective complaints are reduced. Negative side effects are vaginal spotting, edemas, impure skin or psychological changes. Progestagens are commercially available as so called minipill (Desogestrel 0,075 mg) or 3-month-injection. Since 2010, special progestagens are used predominantly for endometriosis treatment. Because of the significant effect of Dienogest on the endometrium, a combination should contain Dienogest as progestagen component e.g. Valette® (0.03mg Ethinylestradiol, 2mg Dienogest). In order to treat endometriosis-associated pain two ways of application are possible: cyclic or continuous use, respectively. Two systematic reviews postulate a superiorly effective of continuous application regarding the improvement of endometriosis-associated pain [22, 23].

**Aromatase Inhibitors**
The use of aromatase inhibitors is currently an off-label use and is only indicated for patients with refractory endometriosis-associated pain. Aromatase inhibitors are regulating the estrogen production in endometriosis lesions additionally to the inhibition of the estrogen production in the ovaries, the muscle and fatty tissue [24]. A systematic review could demonstrate that aromatase inhibitors in combination with progestagens, continuous oral contraceptives or GnRH agonists are associated with significantly greater pain reduction compared to GnRH agonists with fewer side effects, especially with respect to bone density.

**Combined Oral Contraceptives**
The effect of estrogen-progestagen combination is comparable with progestagen only. Because of the significant effect of Dienogest on the endometrium, a combination should contain Dienogest as progestagen component e.g. Valette® (0.03mg Ethinylestradiol, 2mg Dienogest). In order to treat endometriosis-associated pain two ways of application are possible: cyclic or continuous use, respectively. Two systematic reviews postulate a superiorly effective of continuous application regarding the improvement of endometriosis-associated pain [22, 23].

**Progestines**
Progestines are available as so called minipill (Desogestrel 0,075 mg) or 3-month-injection. Since 2010, special progestagens are used predominantly for endometriosis treatment. Because of their local effect, Levonorgestrel-releasing IUDs are used particularly in patients with adenomyosis or deep infiltrating endometriosis.

**Aromatase Inhibitors**
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nists alone [25]. Disadvantages in treatment with aromatase inhibitors are a loss of bone density and risk of developing ovarian cysts. The used substances are Anastrozol 1mg or Letrozol 2,5mg.

Selective Progesterone Receptor Modulator (SPRM)
SPRM treatment leads to anovulation, amenorrhoea and low levels of progesterone. These effects result in pain reduction along with a regression of endometriosis lesions [26]. Since 2012, Esmya® (5mg Ulipristalacetat) is used for preoperative treatment of patients with symptomatic uterus myomatosus. Currently, the treatment of endometriosis patients with SPRMs is an off-label use.

Pain Management
Analgesics used to treat endometriosis patients are Acetylsalicylic Acid, Ibuprofen, Diclofenac, Naproxen or Indometacine. So far, evidence for positive effects of treatment with antirheumatica and antiphlogistica [7] in endometriosis patients are missing. In addition to the pharmacological approach, therapeutic exercise, massage, yoga and mud baths are useful for treatment of dysmenorrhoea. Another therapeutic option is

Ингибиторы ароматазы
Ингибиторы ароматазы в настоящее время не используются, однако показаны пациентам с рефрактерной болью при эндометриозе. Ингибиторы ароматазы регулируют продукцию эстрогенов в очагах эндометриоза дополнительно к такому ингибированию в яичниках, мышцах и жировой ткани (24).

Систематический обзор продемонстрировал, что ингибиторы ароматазы в сочетании с прогестинами, непрерывным приемом оральных контрацептивов или агонистов ГнРГ обеспечивают более значительное уменьшение болей, по сравнению с одними агонистами ГнРГ (25). Недостатками при лечении ингибиторами ароматазы являются уменьшение плотности костной ткани и риск развития кисты яичников. Используются препараты Анастрозол 1 мг или Летрозол 2,5 мг.

Селективный модулятор рецепторов прогестерона (СМПР)
Лечение СМПР приводит к ановуляции, аменорее и низкому уровню прогестерона. Эти эффекты обеспечивают уменьшение боли наряду с регрессией эндометриоидных очагов (26).

С 2012 года препарат Эсмия (Улипристала ацетат 5 мг) используется только для предоперационного лечения пациентов с симптоматическим миоматозом матки. В настоящее время лече-
the Complementary Medicine such as Acupuncture, Traditional Chinese Medicine (TCM), Homeopathy, Phytotherapy and Physiotherapy. For most of these treatments randomized studies are missing. Further on, additional positive effects can be obtained by the integration of Psychosomatic Therapy [3].

Summary

So far, causal therapies for endometriosis do not exist. In symptomatic patients, primary aim is the complete removal of all endometriosis lesions, mostly by laparoscopy. If a patient with endometriosis is asymptomatic and has no desire to have children, treatment is not necessary.

Exceptions represent organ destruction e.g. ureterstenosis with consecutive hydronephrosis due to endometriosis lesions. An individualized therapy with good interdisciplinary team work is necessary for surgical treatment of deep infiltrating endometriosis (e.g. bowel, bladder and/or ureter). The extent of surgery has to be evaluated regarding morbidity and relapse risk. As alternative to surgical treatment, different medical treatment options are useful. Progestagens, combined oral contraceptives and

Лечение болевого синдрома

Анальгетиками, используемыми для лечения пациентов с эндометриозом, являются ацетилсалициловая кислота, ибупрофен, диклофенак, напроксен или индометацин. До настоящего времени отсутствуют данные о положительном эффекте терапии антиревматическими и противовоспалительными препаратами (7). В дополнение к фармакологическому подходу для лечения дисменореи полезны лечебная гимнастика, массаж, йога и грязевые ванны. Другим терапевтическим вариантом является методы комплементарной медицины, такие как акупунктура, традиционная китайская медицина, гомеопатия, фитотерапия и физиотерапия. Для большинства из этих видов лечения рандомизированные исследования отсутствуют. Кроме того, дополнительные положительные эффекты могут быть получены с помощью психосоматической терапии (3).

Заключение

До настоящего времени этиотропной терапии эндометриоза не существует. Основная цель лечения пациенток с симптомами – полное удаление всех очагов эндометриоза, в основном, лапароскопиче-
GnRH agonists are comparable in their efficacy.

Levonorgestrel-releasing IUD is a effective option especially in adenomyosis uteri and deep infiltrating endometriosis.

Therapy with aromatase inhibitors and SPRMs are currently an off-label use.
Literature


