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Endometriosis – Pathogenesis, Diagnosis, and Therapeutic Options for Clinical and Ambulatory Care*

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In the last few years, considerable progress has been made understanding endometriosis and developing diagnostic procedures and therapeutic options. Sophisticated endoscopic instruments allow laparoscopic surgery even in progressed stages and deep infiltrating endometriosis of the bowel and bladder. The introduction of GnRH analogues with add-back medication and the development of new progestins have widened the range of options for effective medical therapy. Nevertheless, new prospective studies have demonstrated in the last decade that the success is temporary and the recurrence rates are high even when the surgery was adequate. Often medical treatment is effective during the time of application only. This means that customised long-term therapy concepts based on guidelines developed by medical societies play a central role in the alleviation of pain, the reduction of recurrence rates, the avoidance of repeat operations and the improvement of the patients’ quality of life. J Reproduktionsmed Endokrinol 2013; 10 (Special Issue 1): 102–19.

Key words: endometriosis, pathogenesis, diagnosis, surgical treatment, medical treatment

**Definition**

Endometriosis is the occurrence of endometrial stroma and glands (often also with muscle cells) outside the physiological location, i.e. outside the uterine cavity. Morphologically, the disease can also mimic other differentiations of the Mullerian epithelium, e.g. tuboid (endosalpingiosis), isthmus-like and cervicoid manifestations. The presence of cytogenetic stroma alone is called stromatosis. If the uterine muscles are affected diffusely or focally, this is called adenomyosis and adenomyoma respectively. During the reproductive phase, endometriosis must be considered a chronic disease. All treatment methods currently recommended – surgical removal, medical suppression of ovarian function or a combination of surgical and medical methods – have high recurrence rates ranging between 20 and 80 after 5 years, depending on stage [1].

Depending on the pain symptoms, the patient’s performance at work, her sex life and her quality of life are compromised in various ways. Depending on stage, her fertility is certainly reduced mechanically and perhaps also functionally, although there is a scientific controversy about the causes.

**Epidemiology**

Alongside myomas, endometriosis is one of the most common benign proliferative diseases affecting women in the reproductive years. According to epidemiological data, there are approx. 0.25 new cases per 1000 woman years, corresponding to a frequency of 7.5% among the female population or 1.5 million endometriosis patients in Germany and about 40,000 new cases per year. As there are no exact data about the frequency in the population, our estimate based on prevalence rates is that 10–15% of the women aged between 15 and 50 years are affected by endometriosis. The disease is one of the main causes of abdominal pain and infertility [2].

Among 1st degree relatives, the prevalence is increased 6 to 9-fold [3], suggesting a genetic factor. Scientists recently identified 2 modified regions on chromosomes 7 and 1 as the first reliable evidence for DNA changes leading to the development of this disease affecting an estimated 176 million women worldwide [4]. However, epigenetic factors must also be considered; e.g., DNA methylation and histomodifications can explain the progesterone resistance of the implants and the overexpression of the estrogen receptor beta [5].

Clinical observations showed that extended duration and increased frequency of menstrual bleeding as well as spontaneous and induced abortions especially among young women increase the risk of endometriosis [6].

Endometriosis is a proliferative disease invading the tissue of the affected organ structures, but the risk of malignancy is low. According to literature, it is far below 1% [7]. More than 75% of the carcinomas are located in the ovaries, and histological examination shows that > 90% of them are endometrioid adenocarcinomas, while clear-cell adenocarcinomas are rare (Fig. 1).

Even though women with endometriosis are not generally at a higher cancer risk [8], an association has been described between endometriosis and certain malignomas, e.g. endocrine tumours, ovarian cancer, renal cell carcinoma, brain tumours, malignant melanoma, non-Hodgkin-lymphoma and breast cancer [9, 10]. For example, the standardised incidence ratio (SIR) has been reported as 1.38 for endocrine tumours, 1.37 for ovarian carcinomas and 1.08 for breast cancer. The SIR could be even higher for women with primary infertility, endometriosis and one of the malignomas mentioned [11]. Molecular biology and
Etiology and Pathogenesis

Despite more than 100 years of extensive research, the cause of endometriosis is unknown, and the pathophysiology is understood only partially. It is still unclear why endometriosis may cause symptoms in some women, while others have no complaints although they have been diagnosed with the disease. There are also data suggesting that endometriosis is just an epiphenomenon and that the causes of the abdominal pain are quite different [13].

Transplantation

Particularly in English-speaking countries, a theory proposed by Sampson (1927) [14] has been accepted. He postulated that during menstruation, vital endometrium is transported backwards via the Fallopian tubes into the small pelvis and implants there. This concept has been modified and supplemented by modern studies. Some suggest that the mechanisms of apoptosis are disrupted in the small pelvis, while others refer to indications that the desquamated endometrium has undergone pathological change. The result is in both cases that the endometrial cells survive in the pouch of Douglas with consecutive invasion, angiogenesis and the development of implants which trigger chronic inflammation as a defence reaction (s. Fig. 3a and b).

Metaplasia

The concept of “retrograde menstruation” cannot explain the occurrence of endometrial lesions outside the abdomen whereas the theory of metaplasia can. It postulates that cells can develop and differentiate in situ to become endometrioid tissue structures based on the complex and complete information contained in the genome of each cell [15]. Infectious influences, hormonal imbalances or immunological disorders can induce such metaplastic processes.

Stem cell Concept

By using surface markers, cells have been detected in menstrual blood which are specific for embryonic or adult stem cells. This has led to the modification of the concept of retrograde menstruation to the effect that it is not desquamated differentiated endometrium which reaches the abdominal cavity but endometrial stem cells which implant there and differentiate metaplastically into endometriosis (glands, stroma, muscle cells) [16]. This corresponds to a combination of the transplantation and the metaplasia theories. Antiangiogenesis is being discussed as a new therapy principle since angiogenesis plays a role in the implantation and progression of endometriosis similar to malignant tumours. Substances directed against
Figure 3. Current concept of endometriosis development. (a): Endometriosis results either from retrograde menstruation or the vascular or lymphatic spread of endometrial cells or endometrial stem cells. Under the influence of immune cells, apoptosis occurs in the area of the ectopic colonies e.g. in the peritoneum. (b): If this process is disrupted (e.g. proliferation stimulus or oxidative stress), instead of apoptosis, there is an invasion of the foci with activation of angiogenesis and formation of endometrial implants in the target tissue. From: Petraglia, Pinzauti a. Trosti, 2011, pers. communication, by courtesy of the author.

Figure 4. Cystic ovarian endometriosis with varying activity – ranging from inactive, resting to complex hyperplasia. (a): Cyst wall with clustered, dilated glands (HE, 12,5 ×); (b): Upon larger magnification, the same sample shows the resting epithelium of an endometrioma (HE, 200 ×); (c): Cyst wall with actively proliferating, epithelial lining (HE, 12,5 ×); (d): The same sample in a larger magnification shows the highly prismatic, proliferative epithelium with secretion phenomena (HE, 200 ×); (e): Lining of the cyst wall in ovarian endometriosis with pronounced proliferation (HE, 40 ×); (f): The proliferative activity with areas of simple hyperplasia can also be seen in the cystically dilated glands (HE, 40 ×); (g): Complex hyperplasia of the epithelial lining in cystic ovarian endometriosis (HE, 40 ×); (h): The same sample with CD stain (CD-10, 40 ×).
VGEF (vascular epithelial growth factor) were tested in vitro and in animal experiments [17]. The genesis and development of endometriosis implants was suppressed by these substances.

**Concept of Tissue Trauma**

Years of investigations by Leyendecker’s working group (1998) [18] have suggested that dysrhythmia and disruptions of the basalis and the inner layer of the myometrium may cause tissue defects. This leads to the entrainment of endometrial stem cells from the basalis into the peritoneum, where they differentiate into endometriosis. On one hand, this pathology of the uterine structures explains the reduced fertility in endometriosis caused by disruptions of nidation and sperm transport [19], on the other, dysrhythmic cramps and tissue traumatisation cause pain. Microtraumas (irregular perimenstrual contractions) and macrotraumas (iatrogenic interventions) induce estrogen-dependent, excessive repair processes. The trauma and the repair process lead to pathological changes of the tissue structure and innervation, which is why the theory is called tissue injury and repair (TIAR) [20].

**Organic Manifestations**

Endometriosis is most commonly found in the small pelvis. It mainly affects the peritoneum of the ligaments, the uterus, the pouch of Douglas and the bladder (small nodules) as well as frequently the ovaries (cystic form with morphological variations as shown in Figure 4). While the mesosalpinx and the Fallopian tubes are also frequent locations of endometrial foci, other locations such as the cervix and the vagina are rare. Among the cases of extragenital endometriosis, the most frequent location is the rectum (deep infiltrating form), followed by the sigmoid and the colon. The appendix, the bladder wall and the ureter as well as the small intestine are less frequently affected. Extraabdominal manifestations such as the lung, pleura, CNS, skin or episiotomy scars are rareries with the exception of C-section scars, on which lesions are more common. The frequencies stated in literature for the various organs vary widely depending on whether pain or infertility patients with endometriosis are examined, which specialisation the clinic has or whether material from biopsies is included.

**Classification**

Various classification systems have been suggested for the severity of endometriosis and its impact on fertility. The most common one is the rASRM (revised classification of the American Society of Reproductive Medicine) (Tab. 1), which is based on a score and only includes lesions visible intraoperatively. The ENZIAN stages proposed by the SEF (Society for Research into Endometriosis) in 2005 [22] has added deep infiltrating endometriosis to the rASRM classification [23]. To assess fertility, an Endometriosis Fertility Index (EFI) [24] has also been suggested. Both the AAGL (American Association of Gynecological Laparoscopists) and the European Endometriosis League (EEL) as well as the SEF are currently developing modifications which also account for the clinical situation, the prognosis and, in particular, pain symptoms.

**Diagnosis**

**Diagnostic Problems**

Diagnostic diagnosis is very difficult when a patient presents with pelvic pain, dysmenorrhea, dyspareunia or other non-specific abdominal or back pain. The biggest problem for a woman with these symptoms is to obtain a proper diagnostic work-up and a reliable diagnosis. Since the symptoms can be so varied, the first doctor the women tend to go to is their GP, a gastroenterologist, an internal specialist, a urologist or other specialist, but even gynaecologists often do not immediately think of endometriosis. As a result, there is often a significant delay in making the diagnosis. For example, in Germany, an average of
6 years go by between the first symptoms and the correct diagnosis [25]. Apparently, contraception based on ovulation inhibitors mask endometriosis-related symptoms but do not prevent endometriosis from developing [26].

Early endometriosis has a higher metabolic activity, a higher rate of mitosis, a stronger immunological reaction with prostaglandin and a higher cytokine expression than more advanced stages [27]. Therefore, early endometriosis responds better to hormone withdrawal than more advanced stages. The recurrence rate is lower and the recurrence-free interval is longer. For this reason, early diagnosis is all the more important!

For all these reasons, we call on all colleagues to consider endometriosis as a serious possibility whenever a patient (whatever her age) presents with diffuse pain or therapy-resistant abdominal complaints!

Necessary Diagnostic Steps
A thorough patient history and analysis of the symptoms are mandatory, but this can only raise a suspicion that endometriosis might be present. Evaluating the intensity of pain using the VAS score (visual analogue scale) in a pain diary can be helpful to objectify the complaints and estimate the success of therapy, since long-term, chronic disease can often pose a strain both on patients and doctors. In visible locations (skin scars, vulva, vaginal portion, vaginal fornix), gynaecological inspection can provide certainty, and in nodular forms in the rectovaginal septum and the pouch of Douglas, palpation may give a clear indication. However, only histology can provide absolute evidence. Laboratory parameters are not very helpful. CA 125 is not suitable for diagnosis or follow-up [28].

Imaging techniques only allow for the verification and exact measurement of the disease but cannot be the basis for an exact differential diagnosis. In cases of peritoneal endometriosis, they are useless. For ovarian endometriosis, for example, vaginal sonography has a positive predictive value of no more than 75 [29]. In deep infiltrating endometriosis, MRI is helpful to identify an involvement of the bladder, the rectum, the pelvic wall and a compression of the ureter [30]. Exact information about the extent and infiltration depth of intestinal endometriosis can be obtained from rectal ultrasound up to approx. 15 cm abanally [31]. Experienced gynaecologists can use vaginal ultrasound to examine deep infiltrating endometriosis more sensitively and specifically than radiologists using CT and MRI or gastroenterologists employing colonoscopy and rectal ultrasound [32]. Even today, a laparoscopic biopsy of macroscopically suspicious tissue is still the only reliable diagnostic method and must always be performed as the basis for customised therapy strategies [33].

Here are some arguments in favour of the generous use of laparoscopy and biopsy to work up a suspicion of endometriosis:
- There are no pathognomonic symptoms of endometriosis. The symptoms can be multi-faceted and either cyclical or acyclical!
- The severity of the disease and the severity of the subjective symptoms are not correlated with each other. Instead, the complaints vary with the location of the lesions.
- Although a laparoscopy is invasive, failure to carry it out often leads to the wrong diagnosis and therefore the wrong treatment. Only in 35% of cases is cyclical and/or acyclical pelvic pain caused by endometriosis [34].

All attempts made so far to diagnose endometriosis in a less invasive way using biochemical parameters, tumour markers or auto-antibodies in peripheral plasma are not clinically helpful because they require too much laboratory work [35] and are not sensitive and specific enough.

Practical Recommendation
In order to avoid overdiagnosis and reduce the above-mentioned diagnostic delay, the following practical approach is recommended: In view of the frequency of dysmenorrhea especially among young women, it is not useful to subject every patient with dysmenorrhea and pelvic pain to invasive differential diagnostics. If the gynaecological examination is normal, a combined oral contraceptive should be prescribed for 3–6 months as a symptomatic intervention (so-called COC test). If the symptoms do not improve even after increasing the dosage or changing the progestin, a long-cycle application can be attempted based on the experience of the last few years [36]. If there is still no improvement within 6–9 months, laparoscopy must be performed for further diagnosis (Fig. 5).
In this way, unnecessary laparoscopy can be avoided and the diagnostic delay kept to a maximum of 1–2 years. Therapy-resistant or recurrent “inflammatory adnexal diseases” and chronic pelvic pain must also be worked up laparoscopically since endometriosis is the underlying disease in a third of these cases [34] (Fig. 6). There is a large variety of macroscopic manifestations, ranging from small lesions to cysts or even tumorous nodules (Fig. 7). Figure 7 is a macroscopic and Figure 8 a microscopic illustration of the clinical case of an “appendicitis” with the differential diagnosis “salpingitis” [37].

Adequate diagnostic pelviscopy requires the exact description of the location and severity of endometriosis; there are also calls for an assessment of the growth type and the degree of activity as well as for the histological examination of tissue samples [10]. In a typical case, the histological diagnosis of endometriosis is based on evidence of ectopic endometrial glands and stroma. The glands are mostly inactive or proliferative; in very rare cases, they are secretory transformed or hyperplastic, but the histological pattern does not necessarily correlate with the functional condition of the endometrium [38]. The endometrial stroma is similar to the normal stroma of the inactive or proliferative endometrium; occasionally, a smooth muscle metaplasia of the stroma is found. In many cases, the cytogenic stroma is only very narrow and exclusively found periglandularly. The term “atypical endometriosis” is used for cytologically atypical forms, but also for endometrial hyperplasia (simple or complex) in endometrial lesions [39].

Endometriosis may often be masked by peritoneal changes such as whitish thickening, colourless bubbles, flame-shaped changes, hypervascularisation, defects or fibrosis (Fig. 9a–f). If these atypical cases are not worked up histologically, the patient has been subjected to an invasive but inadequate diagnosis.

Endoscopy is often inadequate in cases of deeply infiltrating, retroperitoneal endometriosis. Vaginal and rectal palpation combined with vaginal sonography are the key examination methods in this case. However, for adequate interdisciplinary surgical planning purposes, it is crucial to know the exact extent of the disease. For this reason, further examinations are helpful when the patient is affected by deeply infiltrating endometriosis (Tab. 2) even in cases where the exact extent of the disease can only be identified intraoperatively.

“Active – Inactive” – A Relevant Criterion?
Electron microscopy of endometrial foci allows an assessment of the degree of proliferation, differentiation and hormonal modulation. Since these sophisticated examination methods are too expensive for clinical routine, simple macroscopic criteria such as growth type and implant colour have been included in the revised classification by the American Society of Reproductive Medicine (1997) [21].

The macroscopic appearance of the disease depends not just on the growth type and the hormone dependency of the implant. Natural ageing and reactive inflammatory processes also influence the progression and regression of these foci. For these reasons, the appearance at the time of the diagnostic pelviscopy is just
Endometriosis

Microscopically, the diversity of the implants is even greater than macroscopically. The important factors are the varying degrees of differentiation, variable hormone dependency (cyclicality, receptor status), variable or absent proliferative activity (mitosis index, proliferation marker), concomitant inflammation and degenerative processes [40]. Studies on steroid hormone receptors and proliferation markers [41] show that medicinal treatment is particularly effective for fresh implants, while older foci must be removed surgically or may possibly not require any therapy at all because they are not actually the cause of the patient’s complaints.

Findings from molecular biology [42] support the view that endometriosis and healthy endometrium are different kinds of tissue. Defective enzyme systems in the ectopic foci, e.g. 17β-steroid dehydrogenase type 2, lead to autonomous estrogen production and acyclical, continuous proliferation. These findings also have practical consequence for medicinal therapy concepts. Low levels or the complete lack of progesterone receptors in implants and disruptions of the intracellular progesterone metabolism (so-called progesterone block) explain the inadequate effect of a progestin therapy against endometriosis (Fig. 10). Activated enzyme systems which are blocked in the eutopic endometrium such as aromatase facilitate local estrogen production, locally amplifying the proliferation of the ectopic focus and also the inflammatory reaction via the effect on the prostaglandin metabolism (Fig. 11). In view of contradictory data, it is not clear whether aromatase is activated in the endometrial lesion itself as first suggested by Noble et al. [43] or whether the endometrial lesions show no aromatase activity themselves but the cells of the affected organs express the enzyme [44].

The answer to this question has no clinical consequences, and the use of aromatase inhibitors is at the experimental stage with some positive case reports but no valid and convincing studies.
Once all the information mentioned above is available, based on the woman’s age, her family planning and her complaints, a symptomatic, a conservative, organ-sparing or an aggressive resective therapy or a combination of these measures can be discussed and agreed upon with the patient.

**Surgical Treatment Strategies**

Differential diagnosis require invasive laparoscopy, if possible with a biopsy. Consequently, surgical measures are at the centre of primary treatment. The obvious choice is that a surgical intervention should directly follow on from the diagnostic laparoscopy under the same anaesthesia (single-stage procedure); if there is a risk of extensive resection, a two-stage procedure can certainly be accepted if it is preferred by the patient because she wants to receive more differentiated advice. The ablative procedures include all surgical techniques removing pathological changes to the organs (endometrial lesion, endometrial cyst [Fig. 12 a–d], scars and adhesions) and preserving healthy organ parts (conservative ablative therapy) or removing the affected organs in toto (radical ablative therapy).

Antiestrogenic or antiinflammatory substances are suitable for a drug-based therapy. The former lead to a suppression of the ovarian estrogen synthesis of varying duration and intensity. This can be achieved temporarily by various drugs (GnRH agonists, GnRH antagonists, antagonodotropins, progestins, combined oral contraceptives) or permanently through surgical ovariectomy. Anti-inflammatory and analgetic prostaglandin synthesis inhibitors have also proven effective. COX-2 inhibitors causally interfere with the metabolism of the areas of endometriosis. Due to cardiac side-effects, these substances have been withdrawn from the market with some exceptions and not been approved for endometriosis therapy.

The third treatment option consists of symptomatic measures which may range from complementary medicine to physical applications and balneotherapeutic measures with a relaxing, cramp-releasing and perfusion-promoting effect. These options also include homeopathy,
TCM and other therapies which can be used successfully especially for chronic pain patients.

**Principles of Surgical Treatment**

Minimally invasive surgical techniques have become standard today. Various endoscopic techniques of destroying or removing endometrial lesions are used. Comparative studies have shown that these different techniques – mono- or bipolar coagulation, heat application, vaporisation or excision – are equivalent as long as the foci are completely removed. However, the cycle phase does have an influence on the relapse rate: When peritoneal endometriosis was endoscopically removed premenstrually, the relapse rate after 2 years was twice as high (15%) than when the intervention had been carried out postmenstrually. It is assumed that this is due to peritoneal defects caused by the operation which had not healed by the time of the subsequent menstruation [45].

**Therapy Goals: Pain Removal and/or Pregnancy**

The hardest facts on the therapeutic value of endoscopic intervention for pain patients – also for low-grade endometriosis – have been produced by the studies of Sutton et al. [46]. In a prospective, double-blind (fake operation!) approach, it was shown that the pain symptoms had improved after 6 months in 63% of the patients in the therapy group while only 23% of the women in the placebo operation group reported pain relief. However, this also means that one third of the women experienced no pain relief as a result of the operation and that adjuvant drug therapies are crucial to improve the results and reduced the relapse rates.

The effectiveness of the surgical therapy for endometriosis can conveniently be compared looking at the subgroup of infertile patients since pregnancy is a more objective treatment goal than pain relief. When used appropriately, the different laparoscopic resection and coagulation techniques lead to results which are comparable or even superior to those of microsurgical laparotomy [47]. However, these older studies are open to criticism for lack of randomisation and retrospective analysis. Only two studies have been carried out in a prospective and randomised way and yielded controversial results. According to a Canadian multicenter study [48], surgery for endometriosis improves the pregnancy rates significantly compared with purely diagnostic laparoscopy (31% vs 18%), but this was not confirmed by an Italian group [49] (20 vs 22%). More recent publications are no better in terms of methodology since it is difficult to establish a control arm with placebo surgery both for infertile and pain patients. Another problem is surgeon quality. It is an open question whether the published data, which originate from centres, can also be achieved in routine care. However, the type of endoscopic removal does not seem to play a role [50]. More recent data suggest that secondary damage such as adhesions are more relevant than the area of endometriosis itself. Maruyama et al. [51] report on 41.8% pregnancies within 18 months of surgical removal for endometriosis without adhesions and only 13.27% for endometriosis with adhesions on both adnexa.

**Customised Surgical Concepts**

Based on the woman’s personal situation and her symptoms, customised treatment strategy must be developed which accounts for not only the acute pathology but also the chronicity of the disease and is specific for the different forms of endometriosis. Peritoneal endometriosis is a particular challenge for the surgeon since its appearance can vary; the surgeon needs to know and recognise even atypical manifestations (see above). Furthermore, the diffuse spread of endometrial lesions and their growth even under adhesions requires a subtle and patient approach. The risk of an incomplete operation is high; many recurrences are probably due to persistent active foci.

In a case of suspected ovarian endometriosis, if there is an indication for surgery due to complaints and in order to investigate an unclear adnexal enlargement, the need for a histological diagnosis is controversial, since old hemorrhagic corpus luteum cysts or follicular cysts have the macroscopic appearance of a typical “chocolat cyst” in a quarter of all cases. However, functional cysts require neither surgical nor drug therapy. The most efficient method is the complete excision of the endometrioma while sparing the healthy residual ovary. Surgical experience is crucial as, by contrast with other benign ovarian cysts, it cannot be avoided that some healthy tissue is also removed and the follicular reserve reduced while resecting endometrial cysts. There have been reports about falling AMH levels, reduced fertility – also in IVF programmes – and, in
Endometriosis often affects the septum rectovaginale, the parametrium, pararectal tissue, the rectum (Fig. 13, 14) and the sigma, but also higher intestinal sections as well as the pelvic wall with consecutive involvement of the ureter. Due to their high proportion of fibrous tissue and muscle cells, these nodular growths show a poor response to drugs. The implants stay vital and start to progress soon after the cessation of the medication. For this reason, surgery is predominant in the treatment of these manifestations; permanent medication is an option only in exceptional cases. If there are no symptoms, intestinal endometriosis which can be easily controlled and does not result in stenosis can be treated observantly; active therapy is only indicated in these cases if there are symptoms or progression.

The goal of therapy is the complete excision of the endometrial foci and their secondary lesions while preserving organ function. In the case of small nodules, the defect on the bladder or the intestine can be closed primarily; in extensive deep infiltrating cases, the affected intestinal segment must be resected and intestinal continuity restored by anastomosis. If the ureter is affected, this often means a psosas hitch reimplantation. Even in cases of advanced intestinal endometriosis, complete removal can be achieved by careful preparation in the muscularis without opening the lumen. A musculo-muscular and sero-muscular two-layer suture is possible so that a resection with anastomosis can often be avoided [53].

These operations are normally carried out by laparotomy; however, there are more and more reports about endoscopic techniques, showing that with adequate training and an interdisciplinary approach, even partial intestinal resections and Stabler-type anastomoses can be performed endoscopically [54]. In terms of therapy success and quality of life, the
route of access is irrelevant as long as the lesion has been removed adequately, as shown by a recent prospective randomised study [55].

If the wall of the uterus is also involved, e.g. in cases of retrocervical endometriosis, or if there is concomitant uterine adenomyosis (Fig. 15), physicians should discuss with the patient whether to perform a hysterectomy as the only way to remove the endometriosis completely so that the risk of recurrence would be greatly reduced.

There is a controversy about whether preoperative drug treatment is useful in cases of intestinal and bladder involvement. The arguments in favour are that the surgical trauma is reduced and that shorter operating times, less blood loss, and pelviscopy rather than laparotomy are possible; the arguments against are that the preparation of the more fibrosed tissue is more difficult and there is a risk of missing small, regressive, non-palpable implants and of reduced circulation in the operating area, possibly leading to healing disorders and insufficient anastomosis. Whether the success rates and relapse rates are improved by the preoperative use of e.g. GnRH agonists as a depot is unknown because of a lack of follow-up data.

These carefully chosen customised treatment options avoid surgical overtherapy and are tuned to the type of endometriosis and progression risk. On the other hand, the surgeon is required to make a substantial diagnostic effort and be very knowledgeable about the different therapeutic options: surgery, drugs and a combination of both. Based on current knowledge, this is the only way to remove or alleviate the symptoms and sequelae of this disease, which has a tendency to recur (Fig. 16). It should be noted that there is still a lack of comprehensive controlled studies, and the long-term value of the exclusively surgical treatment of a pain patient is just as overrated [56] as the improvement of fertility in a fertility patient [57].

**Drug Therapy**

Basic research has shown in vitro and in vivo that various immunological, inflammatory, paracrine and endocrine factors are relevant for the progression of endometriosis. Although some interesting therapeutic concepts can be derived from them (Fig. 17), they have so far only been tested experimentally in vitro or in animal studies. The existing drug treatments which are still used in practice rest on two pillars: (1.) Suppression of ovarian function and (2.) reduction of the reactive concomitant infection. The clinically tested substances are, on one hand, steroid hormones interfering with the negative feedback of the hypothalamic-pituitary-ovarian axis but where these hormones or their metabolites do not develop any estrogenic properties (progestins, selective progesterone receptor modulators) and, on the other, substances such as GnRH analogues (agonists and antagonists) which directly block the release of gonadotropin at the pituitary level. Pain through endometriosis can be influenced by PG synthesis.
inhibitors. Whether these merely suppress the inflammatory reaction in the involved tissue or directly influence the endometrial lesions themselves is the subject of current research, since COX-2 expression was found in all three forms of endometriosis [58].

As endometriosis is a chronically recurring and systemic disease, neither a temporary drug-based nor a surgical therapy can protect the patient from recurrence unless castration or chronic medication lead to permanent estrogen withdrawal. This is a crucial fact when it comes to advising the patient and setting up a therapy plan. As a result, repeated intermittent or long-lasting continuous drug therapies are often required: The question is not just whether a substance is effective in terms of leading to endometriosis regression and pain relief but also how it is tolerated and whether the individual side-effects are acceptable.

**Progestin Treatment**

For decades, low-dosed progestins have been used successfully in clinically routine – alone or in combination with low-dosed estrogens, even though the scientific data about specific mechanisms of action of progestins for endometriosis are still patchy. In contrast with their status in uterine endometrium, specific enzyme systems are blocked (e.g. 17β-HSD Type 2) or activated (e.g. aromatase) in endometrial lesions, the progestin receptor concentrations are low and progestins reduce the synthesis of progestin receptors so that long-term therapy further reduces the sensitivity of the implants to the therapeutic substance. This is described as a so-called progesterone block in ectopic foci (Fig. 10). Earlier animal experiments also suggest that there is no direct effect of progestins on the implant. In castrated animals with endometriosis, progestin alone did not lead to disease regression; there was a persistence of vital implants [59].

The choice of substance depends on subjective tolerance, while dosage is based on the biological effect on the endometrium (transformation dose). However, since the continuous administration of progestins leads to low estrogen levels, this frequently results in spotting or breakthrough bleeding, whereupon the dosage is often increased or estrogen is added. What is clear is that the endometriosis-related symptoms can be suppressed in up to 80% of the cases, but the recurrence rate after discontinuing the medication is high.

**Mechanism of Action of Progestins**

Physiologically, progestins oppose estrogens. There is a large number of substances which are either derivatives of progesterone (medroxyprogesterone acetate, dydrogesterone etc.) or or C-19-nortestosterone (norethisterone, lynestrenol, desogestrel etc.). They differ by their active profile and intensity of action on the metabolism of various organ systems. They all cause the secretory transformation of the estrogen-pretreated endometrium, but their biological activity varies so that adequate transformation requires different amounts of active substance (Fig. 18).

In addition to the progestinic effects, all synthetic progestins also have other effects which can be explained by their structural similarity with other steroids; for example, progesterone derivatives have estrogenic effects and nortestoster-
one derivatives have androgenic effects. Progestins reduce the frequency and increase the amplitude of the GnRH pulse, thereby suppressing the release of gonadotropin, which leads to an anovulatory situation with low peripheral estrogen and progestin levels. Their mechanism of action for endometriosis is complex. Apart from the negative feedback effect on the centrally controlled estrogen production of the ovaries, progestins are also assumed to lead to the suppression of the concomitant local intraperitoneal inflammation (Fig. 19) and of the resulting pain. They reduce the increased number and activity of macrophages in the pouch of Douglas fluid [60].

Under the influence of estrogen, the increase of TNF-alpha in the pouch of Douglas fluid stimulates the nuclear factor Kappa-β and increases various interleukins as inflammation mediators [61]. Progestins also interfere suppressively with this metabolic pathway. In addition, direct changes are assumed to occur in the endometrial implant similar to those leading to the secretory transformation and decidualisation of the endometrium. Morphological [37] and in-vitro studies [42] suggest that this assumption is incorrect. This would explain clinical findings showing that there was still microscopic evidence of vital endometrial lesions after 6 months of treatment with 5 mg/day of lynestrenol in all cases at the time of surgical removal [62]. The histological changes under progestin therapy and the precise mechanism of action is still not clear after years of experience with this therapy.

Results of Treatment for Endometriosis

Low-dose oral progestins (5–20 mg/day) have been described as effective for symptoms of endometriosis. The reported subjective success rates vary between 60 and 94%. Due to short follow-up periods, there are not many meaningful data about the rate of recurrence; however, in the long term, they are above 50% [63].

As nearly all progestins used for endometriosis treatment have been withdrawn from the market in Germany (e.g. lynestrenol, medrogestone, norethisterone acetate) and the use of estrogen-progestin combinations (oral contraceptives) is in line with the guidelines but off-label, the newly approved dienogest in a dosage of 2 mg/d has become particularly important. Under this treatment, the subjective symptoms of endometriosis improve significantly even though breakthrough bleeding is frequent [64].

The estrogen receptor concentrations in the uterine endometrium only return to the level of the normal secretion phase after three months of dienogest treatment, and delayed maturation as well as the appearance of a late proliferation phase were seen histologically. Examinations of endometrial lesions showed a very disparate rate of regression under progestin therapy, confirming that the reaction may vary greatly, apparently depending on the varying receptor expression in ectopic foci. Prospective randomised studies with dienogest 2 mg/d compared with leuprorelin [65] showed the same effectiveness in treating the symptoms and a clear superiority compared to placebo (Fig. 20) [66]. Pregnancy rates after treatment with medroxyprogesterone acetate, lynestrenol, norethisterone acetate or dienogest vary between 5 and 90% on account of different selection criteria in the study groups and therefore do not allow a scientifically proven statement.

Other routes of application have also been tested successfully. Depot medroxyprogesterone acetate (100–200 mg) effectively suppresses subjective endometriosis symptoms, but the suppressive effect may last for months or even years, so it is only recommended for older patients who do not wish to have children [67].

The intravaginal continuous progestin-estrogen application in a three-weekly rhythm or the continuous application of the progestin over two years as a subcutaneous implant are also theoretically suitable for symptomatic therapy and have been used successfully in some cases [68]. However, there is a lack of systematic prospective studies, and the direct effect on the endometrial lesions is unknown. Furthermore, progestins can be locally applied by an intrauterine system releasing 20 µg levonorgestrel daily. The suppression of the endometrium, the reduction of apoptotic processes as well as antiinflammatory effects have been shown [69].

Endometriosis-related complaints in cases of adenomyosis or rectovaginal endometriosis such as dysmenorrhea or dyspareunia are reduced. Apart from high local progestin concentrations in the utero, the low systemic concentrations of levonorgestrel also seem to play a role. This is the explanation given for the positive effects on peritoneal forms of endometriosis [70], and the ovulation inhibition in 85% of the users – at least in the first few months after the introduction of the system – is also evidence of systemic effects. An advantage is that the system remains in place for 5 years, although the effect on endometriotic complaints seems to subside after 12–18
months. The disadvantage is that spotting and breakthrough bleeding still occurs in the first 6 months before the system reaches its full effects. In terms of clinical practice, it should be noted that all these useful applications are off-label applications in Germany.

**GnRH Analogue Treatment**

GnRH analogues are agonists and antagonists of the natural LH-RH. They act directly on the pituitary-hypothalamic system. While the antagonists are used in oncology and reproductive medicine, GnRH agonists have become widespread in endometriosis treatment despite their initial stimulation effect. Regression and atrophy of the endometrial lesions without relevant metabolic side-effects is achieved by reversible medicinal ovarian suppression caused by desensitising the pituitary (Fig. 21). There is no difference between the substances used in terms of the subjective and objective success rates [71]. Because of improved compliance and reliable suppression, depot preparations are preferred in practice. The side-effects are mainly hypoestrogenic and comparable with menopausal complaints. The treatment period is limited to 6 months despite good tolerability because the hypoestrogenic situation causes a reversible bone demineralisation by 4–6% on average with big variations, similar to the lactation period. In order to reduce demineralisation without minimising the therapeutic effect, a so-called “add back” therapy [72] with low-dosed estrogens or progestins has been introduced. If the add-back dosage is too high or in the case of cyclical application, the therapeutic effect of the GnRH agonists is obviously reduced or suspended.

Compared with progestins, GnRH analogues are more effective in achieving a regression of the endometrial implants as confirmed by prospective randomised studies [73]. They are at least as effective in reducing the symptoms, as corroborated by a comprehensive Cochrane analysis [74]. It is important to note that the much-used inexpensive combined oral contraceptives are inferior to GnRH agonists in terms of their effectiveness [75]. The different commercially available GnRH agonists are similarly effective in terms of pain reduction and endometriosis regression, as confirmed by a review by Shaw et al. [76]. However, after 6 months of therapy, 50% of the patients still have residual scarby lesions containing vital endometrial glands and stroma [37, 77]. This explains why endometriosis which persists after this potent treatment can become symptomatic again, and a recurrence is merely a question of time.

**Antiinflammatory Treatment**

In order to prevent the development of a chronic pain syndrome, pain therapy concepts should be integrated directly into the treatment plan. The synthesis of COX-2 in normal endometrium, endometriosis and adenomyosis has been described [78], and women with endometriosis overexpress this enzyme. This explains its high concentrations in endometrial lesions and pouch of Douglas fluid [79]. Apart from proliferative and inflammatory effects, specific prostaglandins cause vasoconstriction, ischemia, cell necrosis, spasms and tissue pain. Non-steroidal antiinflammatory drugs (Aspirin®, Ibuprofen®, Voltaren®) inhibit the activity of cyclooxygenase non-specifically, thus reducing the synthesis of prostaglandin. This explains their varying clinical success in cases of endometriosis-related abdominal pain [80]. The specific COX-2 inhibitors developed some years ago block the intracellular COX-2 activity and have fewer gastrointestinal side-effects. So far, they have not been approved for endometriosis, and their use should first be investigated in studies as no data are available about possible teratogenic effects [81]. Since all drugs except Etoricoxib (Arcoxia®) have been taken from the market due to cardiac side-effects, practitioners will have to make do with non-selective preparations for the time being.

If no adequate pain relief can be achieved by these substances in combination with combined oral contraceptives or progestins, additional retarded opioids of WHO stages I and II must be used. The drug-based pain therapy should be accompanied by pain coping seminars. Physical therapy like baths, local thermal treatment and relaxation exercises are useful complements. These methods should aim to prevent pain from becoming the focal point in the patient’s life.

**Practical Recommendations**

**Pain Patients**

Although the surgical removal of endometriosis is the primary treatment, depending on stage, location and type of the disease, the rate of recurrence within 5 years after endoscopic surgery ranges between 25 and 70%. Surgeon quality and the timing of the intervention within the menstrual cycle contribute to this problem [45]. The adjuvant use of GnRH agonists reduces the rate of recurrence and prolongs the recurrence-free interval significantly [82].

A treatment period of only 3 months can be equally effective in terms of pain re-
duction, but the recurrence-free interval is significantly longer if the suppression phase lasts 6 months.

The clinical benefit of an additional drug therapy can be significant especially in patients with pain due to active peritoneal endometriosis. Although the use of oral contraceptives in the treatment of endometriotic complaints is widespread, a prospective randomised study [83] has shown that their postoperative use is not as effective as the administration of GnRH agonists. On the other hand, oral contraceptives are less expensive and have a different side-effect spectrum. The additive use of these drugs should be considered after adjuvant treatment in order to further prolong the recurrence-free interval.

Possibilities of Long-Term Treatment
Extensive and/or progressive cases as well as deeply infiltrating forms of endometriosis are often problematic. In these cases, even primary intervention is often technically difficult and confronts the surgeon with many problems. This is all the more true in cases of recurrence. Since substantial fibrosis and myohyperplasia lead to tumorous changes, extensive resection is necessary but fraught with the problem of incomplete removal and the risk of intra- and postoperative complications. In order to achieve an improvement of the symptoms of this type of endometriosis, various forms of treatment such as oral contraceptives, progestins, GnRH analogues as depot drugs, physical therapy or homeopathy as well as the intrauterine release of progestins can be attempted permanently or intermittently alongside surgical removal while taking the chronicity of the disease into account (Fig. 22). A particular advantage of GnRH analogues is the possibility to reduce side-effects through add-back medication, which explains their increasing importance as a very effective long-term treatment [85]. A progressive reduction of the pain symptoms has been achieved by the long-term administration of dienogest over a period of 15 months [86].

Recurrence
If the patient has recurrent complaints and/or a recurrence is diagnosed, she can be offered another surgical intervention or another course of drug treatment or a combination of both (Fig. 23). Since endometriosis is a chronic disease, a therapeutic approach must be discussed with the patient which is acceptable for her, has the least possible side-effects, is cost-efficient and, in particular, is what the patient herself asks for after having been appropriately informed. Although repeat operations cannot always be avoided, it is absolutely paramount to choose a medicinal treatment concept after such an operation. The spectrum of possible drug therapies has been listed above. Progestins as permanent medication or continuous oral contraceptives are often used primarily as a symptomatic treatment in view of the costs. If this is not sufficient, GnRH agonists are effective even when used repeatedly in cases of recurrence. Combined with add-back medication, they also have few side-effects.

Another option is the titration of the “therapeutic estrogen window” in which low-dosed GnRH analogues are used [87]. A still further possibility is to carry out intermittent 3-monthly treatment episodes with a GnRH agonist and a low-dose continuous combined estrogen/progestin add-back medication. This is an inexpensive and well-tolerated treat-
Recommendations for Cases of Infertility Caused by Endometriosis

The management of infertile patients suffering from chronic recurrent endometriosis is discussed controversially. In severe cases with excessive endometriosis, organic damage and adhesions lead to mechanical infertility; in mild or moderate endometriosis, however, the disease can be associated with functional infertility or it can be an irrelevant additional finding. Drug-based therapies alone will not improve fertility. A few years ago, a Chochrane analysis clearly showed that the suppression of the ovarian function by minimal or mild endometriosis does not influence the infertility [88]. It should be borne in mind that this statement is based on studies with low case numbers. There is a lack of international multicenter studies which would produce sufficient case numbers and result in scientifically robust findings.

Down-regulation with GnRH agonists prior to the stimulation phase in IVF protocols prevents the premature LH peak, leads to more oocytes and improves pregnancy rates compared with therapy protocols in which no GnRH agonist was used [89]. The positive effect of GnRH agonists used up to 6 months before an IVF cycle irrespective of the stage of endometriosis (ultra-long protocol) needs to be discussed carefully on a case by case basis. Especially in older patients, prolonged suppression cannot be a useful therapy option since the subsequent stimulation can be compromised in view of the age-related low ovarian reserve [90]. The same is true for women who have been operated for ovarian endometriomas repeatedly or bilaterally. So far, there is no consensus in the literature about how long the GnRH medication should be carried out in the ultra-long protocol.

In the case of low-grade peritoneal endometriosis – especially if macroscopic and microscopic aspects suggest that the implants are inactive – the endometriosis should not be a factor determining the infertility treatment. Once other infertility factors have been excluded or treated successfully and the stimulation of the ovaries does not lead to pregnancy after 6–12 cycles, the endometriosis can be accepted as the cause of infertility and should be treated as such. In this situation, the endoscopic excision or vaporisation of all lesions is recommended since this has resulted in improved pregnancy rates in at least one prospective randomised study [48].

In advanced stages, endoscopic surgery must be performed to resect the implants and cysts, and the reproductive organs must be repaired microsurgically as far as possible. If extensive adhesiolysis is necessary, if the surgical intervention is incomplete and insufficient or if a repeat operation is required, assisted reproduction offers the best chance of achieving pregnancy if GnRH agonists are used in the ultra-long protocol. Treatment with GnRH analogues alone after surgical intervention for endometriosis does not improve the chances of achieving pregnancy.

Conclusion/Relevancy to Practice

This review of the surgical and medical therapies suggests recommendations based on scientific literature and German as well as European (ESHRE) guidelines. On the one hand, surgical excellence is required in order to adequately perform the often difficult interventions for endometriosis endoscopically but also to recognise the limits of surgery. Even well-trained and experienced surgeons are sometimes only partially successful, and recurrence may require adequate medication, possibly over prolonged periods. For this reason, precise knowledge of the different mechanisms of action and side-effects of the available drugs is required in order to use them in a targeted way, sometimes in combination. While non-steroidal anti-inflammatory drugs, oral contraceptives and many progestins have proven worth-while empirically in the treatment of pain, GnRH agonists with add-back medication are currently the standard treatment to effect regression of active endometriosis. New progestins in an appropriate dosage are an equivalent, inexpensive option with a different side-effect spectrum.

The patient must always be comprehensively informed and involved in the decision-making process about the most suitable therapy. Merely applying the guidelines in a standardised way would not be a responsible medical approach. As the network of certified endometriosis centres is growing in Germany, Austria and Switzerland [91], doctors should not be afraid to consult their experienced colleagues in particularly difficult cases or refer patients to specialised centres in order to develop a customised and effective treatment strategy.

Conflicts of Interest

In the last three years, the corresponding author has worked as a speaker for the companies BayerHealthCare, Solvay and Takeda.

Thomas Rabe: has held talks for Jenapharm receiving payment and travel expenses.

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