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Adenomyosis: diagnostics and treatment

Adenomyosis can cause dysmenorrhea, dyspareunia, bleeding disorders and pelvic pain and has a negative impact on fertility. The benign uterine disease can be found in almost 50% of patients with deep endometriosis, but also can appear without additional endometriosis. Adenomyosis is still underestimated and underdiagnosed and an exact incidence, especially related to patient age, is still not known. This might be related to the difficulties in diagnosing adenomyosis, although the diagnostic tools have a high accuracy in the hands of the skilled examiner. Considering adenomyosis allows the individualization of medicinal and surgical treatment in symptomatic and/or infertile patients.

The uterus is the central organ of the female pelvis and plays an indispensable role in reproduction. Adenomyosis is a benign disease of this important organ and knowledge about the impact of adenomyosis on symptomatology and fertility and its relation to additional peritoneal or deep endometriosis has been increasing over the years. Although the exact incidence of adenomyosis remains unclear, the disease seems to affect women from adolescence to menopause. Many patients with adenomyosis are symptomatic and report dysmenorrhea, dyspareunia, central pelvic pain and bleeding disorders. The negative impact of adenomyosis on fertility is still under discussion but several publications have shown reduced pregnancy and birth rates and higher abortion rates in

patients with adenomyosis undergoing reproductive treatment [1]. A risk for obstetric complications in patients with adenomyosis has recently been reported regarding premature birth, premature rupture of membranes, uterine rupture, postpartum hemorrhage, placentation failure and intrauterine fetal growth reduction [2]. It has been reported in various publications that medicinal and surgical treatment of adenomyosis may improve fertility [3] and reduces symptoms, although a standard for the treatment of infertile women with adenomyosis has not yet been established [4]. Hence it is of importance to consider adenomyosis as a possible factor in the diagnosis and treatment of all patients with endometriosis, corresponding symptoms or infertility. The identification of patients with adenomyosis allows individualized treatment approaches in relation to family planning status.

From anamnesis to transvaginal ultrasound—The diagnosis

As always, the clinical diagnosis starts with a detailed anamnesis. The clinical symptoms can lead to the suspicion of adenomyosis as most of the patients have typical symptoms, such as dysmenorrhea, bleeding disorders, chronic pelvic pain and dyspareunia. Adenomyosis might also be the reason for persistent symptoms after surgical interventions for peritoneal and deep endometriosis [5]. The gynecological examination may reveal a dolorous enlarged uterus and an additional palpable deep endometriosis of the retrocervical area

[6]. Almost 50% of patients with deep endometriosis also have an involvement of the uterus. The most important diagnostic tool in the daily gynecological practice is the transvaginal ultrasound [7]. Several typical ultrasound signs have been described in the literature: myometrial cysts, subendometrial microcysts, question mark sign, heterogeneous myometrium, uterine asymmetry, hyperechoic myometrial lesions, subendometrial thickening, disruption of the junctional zone, subendometrial linear striae and uterine enlargement (■ Fig. 1).

» The most important diagnostic tool in daily gynecological practice is transvaginal ultrasound

Although the meaning of the particular signs is not yet clear and a score system does not yet exist, the overall accuracy of 2D transvaginal ultrasound in the diagnosis of adenomyosis is high with a pooled sensitivity of 83.8% and a pooled specificity of 63.9% [8]. The 10-year meta-analysis [8] described the feature heterogeneous myometrium as the sign with the highest pooled sensitivity, while globular uterine enlargement was the most specific sign. The combination with the feature question mark sign increased the accuracy. A similar review showed comparable results pointing out the high heterogeneity between the included studies and the missing consensus in adenomyosis classification [9]. Different publications showed a high variation

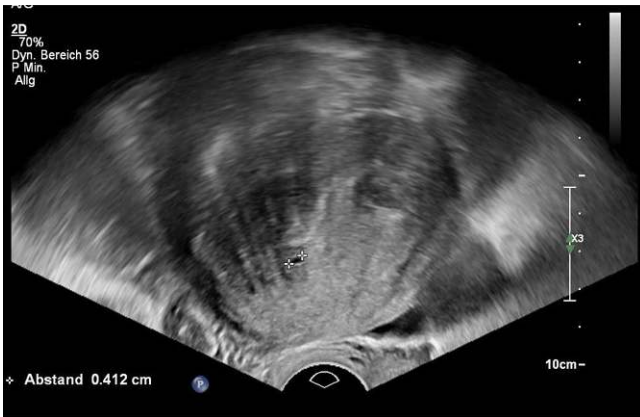


Fig. 1 ▲ Transvaginal ultrasound image of the uterus showing a subendometrial microcyst in adenomyosis (size 4 mm) with associated linear striae. (With permission © H. Krentel, all rights reserved)

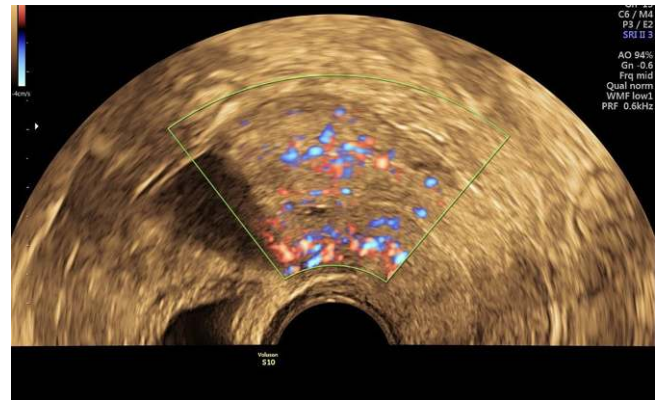


Fig. 2 ▲ Transvaginal ultrasound image of the uterus showing a subendometrial microcyst in adenomyosis. The additional colored doppler sonography helps to distinguish blood vessels (blue and red color) from microcysts with no color signal. (With permission © H. Krentel, all rights reserved)



Fig. 3 ▲ Native tissue sample after hysterectomy showing myometrial tissue with subendometrial layer including microcysts in adenomyosis (3 mm). (With permission © H. Krentel, all rights reserved)

in the most useful ultrasound features, varying between linear striation, myometrial cysts, question mark sign, heterogeneous myometrium and asymmetrical myometrial thickening. Additional sonographic techniques can help to confirm the diagnosis of adenomyosis. In the examination of the junctional zone and its typical irregularities in adenomyosis, the 3D transvaginal ultrasound seems to be superior to 2D sonography. Doppler sonography can be used to distinguish adenomyosis (central flow) from fibroids (circular flow) by its typical flow characteristics and to differentiate small myometrial blood vessels from microcysts ([10]; ■ Fig. 2 and 3).

In combination with the clinical history and gynecological examination, transvaginal ultrasound is a potent diagnostic tool in the hands of the experienced examiner. The consensus statement of

the morphological uterus sonographic assessment (MUSA) group on sonographic uterine features and the use of terminology summarized the actual status quo [11]. Specialized training and a standard ultrasound examination in all patients with typical symptoms may help to detect adenomyosis.

» Magnetic resonance imaging is a potential diagnostic tool with high accuracy

In order to detect focal and diffuse adenomyosis and to presurgically localize and measure the affected uterine tissue, magnetic resonance (MR) imaging is a potential diagnostic tool with high accuracy. The most important diagnostic sign in MR imaging seems to be the irregularity of the junctional zone (JZ), followed by focal or diffuse thickening of the JZ, a JZ(max) to myometrial thickness ratio >40%, areas of myometrial low signal intensity and high signal intensity spots in the T2-weighted technique are the typical findings [12, 13]. Bazot et al. compared transvaginal ultrasound with MR imaging and reported no difference in accuracy. In patients with additional uterine myomas the sensitivity was higher in MR imaging [12].

Surgical diagnosis and histological proof

The non-invasive diagnostic steps can be combined with operative diagnostic procedures, such as diagnostic hysteroscopy and bipolar mini-resectoscopy. These techniques allow the retrieval of biopsy samples and thus the histological proof of the presence of adenomyosis and can be easily performed during surgery for endometriosis and infertility (■ Fig. 4). In diagnostic hysteroscopy the uterine cavity and the endometrial layer can be inspected. Typical signs in adenomyosis are tiny openings in the endometrial surface, irregular endometrium, hypervascularization, strawberry pattern, fibrous cystic appearance of intrauterine lesions and cystic hemorrhagic lesions [14]. Simultaneously subendometrial adenomyotic tissue resection and histopathologic examination can be performed. The diagnostic specificity can be increased by the combination of transvaginal ultrasound and endomyometrial biopsy [15].

» Diagnostic findings can change in relation to patient age, hormonal treatment and menstrual cycle

Laparoscopic signs of adenomyosis can be uterine enlargement, a pillowy resistance of the uterine wall, the blue sign and cystic subserous hemorrhagic lesions

(**Fig. 5**). Laparoscopy-guided myometrial biopsy techniques have been described as an accurate tool for obtaining a definitive diagnosis in patients with a clinical suspicion of adenomyosis [16].

The histologic proof can be helpful in therapeutic decisions, especially in cases of adenomyosis-related infertility. The accuracy of percutaneous, transvaginal, hysteroscopic and laparoscopic sampling techniques varies in relation to examiner experience and quality of ultrasound detection [17]. All diagnostic findings in adenomyosis can change in relation to patient age, hormonal treatment and menstrual cycle. In conclusion the diagnosis or exclusion of adenomyosis by the experienced gynecologist is possible. The individual combination of different diagnostic tools including imaging techniques and minimally invasive surgical approaches provide a high accuracy in the diagnosis of adenomyosis and in some cases even histological certainty.

Surgical treatment when family planning is completed

Adenomyosis can be treated by medicinal and/or surgical approaches including reproductive techniques. The decision on how to treat adenomyosis individually depends on the following factors: type of symptoms, family planning status, additional peritoneal and/or deep endometriosis and age. In patients with completed family planning adenomyosis can be definitively treated by laparoscopic total hysterectomy or laparoscopic subtotal hysterectomy when the uterine cervix is free of adenomyosis or retrocervical deep endometriosis. The laparoscopic approach allows the inspection of the complete pelvis and thus the simultaneous resection of additional endometriosis. In cases of subtotal hysterectomy, laparoscopic in bag morcellation of the uterine corpus should be performed in order to avoid iatrogenic new onset intraperitoneal or retroperitoneal adenomyosis, endometriosis, metastatic myomatosis, sarcoma or late onset malignant transformation of uterine tissue. Abdominal, laparoscopic or hysteroscopic adenomyectomy in focal or cystic adenomyosis

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Adenomyosis: diagnostics and treatment

Abstract

Background. Adenomyosis is a frequent additional condition in patients with endometriosis and should be included in diagnostic and treatment concepts.

Objective. Description of diagnostic and therapeutic approaches in patients with adenomyosis in relation to patient age, family planning status, peritoneal and/or deep endometriosis and symptoms.

Methods. The current literature on adenomyosis including case reports was analyzed. Due to the lack of evidenced-based approaches the most probable trends in diagnostics and treatment are discussed.

Results. Adenomyosis plays an important role in fertile patients with dysmenorrhea, dyspareunia and pelvic pain, with or without additional peritoneal or deep endometriosis.

It has a negative impact on fertility and can cause a variety of symptoms. The disease can be diagnosed by a skilled examiner and treatment concepts exist.

Conclusion. Adenomyosis can be diagnosed by a combination of clinical history, gynecological examination, transvaginal ultrasound and magnetic resonance imaging. Various medical and surgical treatment approaches are available to reduce symptoms and to increase fertility. The course of action depends on the family planning status of the patient.

Keywords

Endometriosis · Infertility · Dyspareunia · Dysmenorrhea · Transvaginal ultrasound

Adenomyose: Diagnostik und Therapie

Zusammenfassung

Hintergrund. Die Adenomyose ist eine häufig auftretende Begleiterkrankung bei Patientinnen mit Endometriose und sollte in Diagnostik und therapeutischen Behandlungskonzepten mit einbezogen werden.

Ziel. Beschreibung der diagnostischen und therapeutischen Ansätze bei Patienten mit Adenomyose in Bezug auf Alter, Familienplanungstatus, Peritoneal- und/oder tiefe Endometriose und Symptome.

Methoden. Die aktuelle Literatur zur Adenomyose einschließlich der Fallberichte wurde analysiert. Aufgrund mangelnder evidenzbasierter Ansätze werden die wichtigsten Entwicklungen in Diagnostik und Therapie diskutiert.

Ergebnisse. Die Adenomyose spielt eine bedeutende Rolle bei fruchtbaren Patientinnen mit Dysmenorrhö, Dyspareunie und Beckenschmerzen, mit oder ohne zusätzliche Peritoneal- oder tiefe Endometriose. Sie

wirkt sich negativ auf die Fruchtbarkeit aus und kann eine Vielzahl von Symptomen verursachen. Die Erkrankung kann von einem qualifizierten Untersucher diagnostiziert werden. Für die Therapie stehen diverse Behandlungskonzepte zur Verfügung.

Schlussfolgerung. Die Adenomyose kann durch eine Kombination aus klinischer Anamnese, gynäkologischer Untersuchung, transvaginalen Ultraschall und Magnetresonanztomographie (MRT) diagnostiziert werden. Zur Linderung der Symptome und zur Erhöhung der Fruchtbarkeit stehen verschiedene medizinische und chirurgische Behandlungsansätze zur Verfügung. Das weitere Vorgehen richtet sich nach dem Familienplanungstatus der Patientin.

Schlüsselwörter

Endometriose · Infertilität · Dyspareunie · Dysmenorrhö · Transvaginaler Ultraschall

and cytoreductive surgical procedures in diffuse adenomyosis can reduce symptoms in patients who wish to preserve the uterus. Focal subendometrial or intramural cystic adenomyotic lesions and intracavitary polypoid adenomyoma can be treated by hysteroresectoscopy. New instruments with a smaller diameter also provide a minimally invasive approach

in very young nulliparous women. The hysteroscopic resection of adenomyotic lesions improves symptoms. Larger intramural cystic lesions should be treated by laparoscopic resection and uterine suturing (**Fig. 6**; [18]). The influence of these procedures on patient fertility should be further investigated.



Fig. 4 ▲ Bipolar mini-hysteroscopic biopsy technique. (With permission © H. Krentel, all rights reserved)

Endometrial ablation offers a less invasive treatment option in patients who want to preserve the uterus; however, the efficacy in controlling bleeding decreases over time [19].

Medical treatment options

Another treatment option is the use of a levonorgestrel intrauterine device (LNG-IUD), gestagens or combined oral contraceptives. In the subgroup of patients with ongoing family planning the medical treatment can only be an option as a pretreatment before reproductive procedures or as a prophylactic treatment in very young women with adenomyosis and a pregnancy wish in the future. In these cases a long-term treatment with low complication rates and the aim to prevent a worsening of the uterine situation is required. All medical therapeutic possibilities in patients with adenomyosis have been recently reviewed by various authors [20, 21]. The suppressive hormonal treatments with high dose progestins, oral contraceptives, LNG-IUDs, gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors, selective estrogen receptor modulator (SERM) and selective progesterone receptor modulator (SPRM) are able to reduce symptoms by reduction of adenomyosis; however, each of these treatments is related to specific side effects. Currently, all medical approaches represent an off-label use as no medical solution is licensed in the specific treatment of adenomyosis.

Dienogest is able to reduce adenomyosis-related pelvic pain and dysmenorrhea but is combined with a high risk of irregular uterine bleeding as the most common adverse reaction. Therefore, patients treated with dienogest have a certain risk of treatment discontinuation especially when they are of young age, have anemia before treatment and/or have mildly suppressed or unsuppressed estradiol after starting dienogest treatment [22]. Also, progestins such as norethisterone acetate or medroxyprogesterone acetate can reduce pain in patients with adenomyosis but are related to side effects, such as acne, edema and reduction of libido causing high discontinuation rates. Combined oral contraceptives represent another evidence-based therapeutic option. The data show a pain reduction but also bleeding disorders as the main adverse effect. The LNG-IUD seems to be the most effective option in reducing pain and menstrual blood loss [23]. The LNG-IUDs can be used in women with completed family planning instead of hysterectomy, and as a maintenance therapy after adenomyosis surgery. In a retrospective analysis of treatment with LNG-IUD in patients with a large uterine adenomyosis and heavy menstrual bleeding, 10% underwent premature LNG-IUD removal and 16.7% underwent subsequent hysterectomy [24]. The incidence of spontaneous expulsion of the IUD is higher in patients with adenomyosis and/or uterine fibroids than in women with a normal uterus and seems to depend on the insertion technique and the placement timing. The role of LNG-releasing intrauterine systems in the treatment of adolescent or very young women with adenomyosis, especially the use of low-dose IUDs should be investigated. The use of LNG-IUDs prior to assisted reproduction also has been described but has not yet been scientifically evaluated. Another medical treatment option is the use of GnRH agonists or antagonists. The application can be presurgical, postsurgical, prior to assisted reproductive techniques or as an individual approach instead of other medical treatments. The presurgical treatment can reduce complications and bleeding in

adenomyosis surgery. The combination of GnRH agonist application with conservative surgery seems to result in longer symptom control and better reproductive outcomes in symptomatic and subfertile patients with adenomyosis compared with GnRH treatment alone. In infertile women with adenomyosis the treatment with GnRH agonists is indicated before fertility treatment in order to increase pregnancy and birth rates and decrease abortion rates [25]. The efficacy of GnRH agonists in adolescents with refractory chronic pelvic pain, failed therapy with combined oral contraceptives and positive MR imaging for adenomyosis has been reported. The treatment improved symptoms and repeated MR imaging showed regression of the lesions [26]. As estrogen, estrogen receptors and aromatase play a role in the pathogenesis of adenomyosis, the therapeutic use of aromatase inhibitors is an additional option. The reduction of adenomyosis volume and symptoms has been shown; however only a few publications exist and further investigations are needed. Selective progesterone receptor modulators, selective estrogen receptor modulators, valproic acid and antiplatelet treatment represent another group of treatment options, which needs to be investigated before used in the daily routine. So far, the medical treatment of adenomyosis especially in patients with ongoing family planning is an individual recommendation, while the situation in patients with completed family planning is based on a large number of publications, especially regarding the use of LNG-IUDs.

Surgical or combined treatment options in patients with ongoing family planning

Patients with adenomyosis and infertility have various treatment options; however none of these options is evidence based. One way could be the direct reproductive approach with or without medical pretreatment. Another way could be the combination with uterus-sparing surgery, such as adenomyectomy or cytotoreduction. The questions are if surgery has an additional benefit for infertile pa-

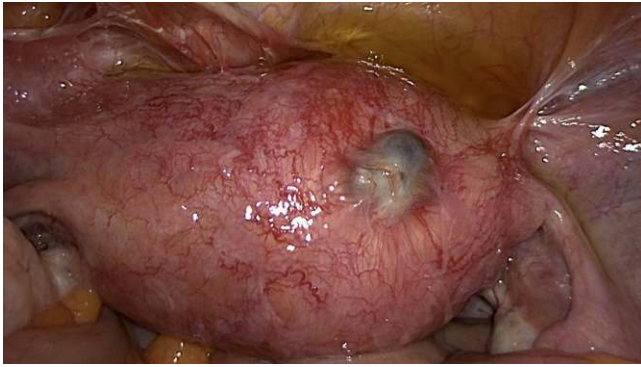


Fig. 5 ▲ Laparoscopic view of subserous cystic adenomyosis. (With permission, © H. Krentel, all rights reserved)



Fig. 6 ▲ Transvaginal ultrasound image of an intramural cystic adenomyosis in patient with ongoing family planning. (With permission © H. Krentel, all rights reserved)

tients with adenomyosis and what would be the right moment for surgery? In a recent literature review these options including medical and surgical methods, highlighting treatment strategies, but also the lack of knowledge and the difficulties in suggesting evidence-based treatments, has been discussed [27]. An important factor in the patient selection for surgery is the patients age, which should be less than 39 years [28]. Additional surgery might be an option in symptomatic patients, who are not able to undergo reproductive procedures, patients with infertility despite in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) and as a last resort in extreme cases of diffuse adenomyosis. Surgery might be helpful in matters of fertility but the effect of surgery needs to be proven in the future [3].

» **Important in patient selection for surgery is that patients should be less than 39 years old**

In a recent review an overall clinical pregnancy rate of 18.2% after surgical treatment of adenomyosis was described. The additional postoperative treatment with GnRH agonists increased the rate up to 40% [29]. The risks of surgical procedures in adenomyosis should not be underestimated. The surgery can be difficult and the loss of organs due to severe intraoperative bleeding has been described. Adenomyosis surgery can cause uterine

rupture, postsurgical intrauterine and intra-abdominal adhesions and irregular placentation. In order to minimize complications adenomyosis surgery should be carried out in specialized centers with experienced gynecological surgeons.

New minimally invasive treatment options

High-intensity focused ultrasound (HIFU) and radiofrequency ablation are alternative treatment methods for focal and diffuse adenomyosis. Both techniques provide symptom relief and a low rate of major and minor complications in patients who wish to preserve the uterus or to conceive in the future. In recent publications patients undergoing HIFU for adenomyosis showed high conception and live birth rates after treatment [30]; however, the role of HIFU in patients who wish to conceive should be further investigated. The transcervical radiofrequency ablation for symptomatic adenomyosis has also been reported to be a safe and effective method. Also, uterine artery embolization can reduce symptoms and improve the quality of life in patients with symptomatic adenomyosis. The impact of uterine artery embolization on fertility and pregnancy requires further evaluation. The literature describes a wide range of therapeutic options, but none of them are evidence based and in relation to effectiveness, fertility outcome, reliability and side effects many questions still remain unanswered.

Prospective randomized trials are needed in order to show if medicinal, surgical or reproductive treatment alone or a combination is the best way to improve fertility in patients with adenomyosis. Patients with adenomyosis need an individual approach with detailed diagnosis of the extent of the disease and an accurate planning of the medicinal and/or surgical treatment.

Recommendations for daily practice

- Adenomyosis is a frequent benign uterine disease,
- Dysmenorrhea, dyspareunia, pelvic pain and bleeding disorders are typical symptoms,
- Adenomyosis has a negative impact on fertility,
- Adenomyosis can be diagnosed by a combination of clinical history, gynecological examination and transvaginal 2D ultrasound,
- MR imaging can be useful as an additional diagnostic tool,
- The treatment approach depends on the patient's family planning and the type and localization of the disease,
- Medicinal treatment and surgical resection of adenomyosis can reduce symptoms,
- Adenomyosis surgery should only be performed in specialized centers.

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Compliance with ethical guidelines

Conflict of interest. H. Krentel and R.L. De Wilde declare that they have no competing interests.

Ethical standards. For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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