National German Guideline (S2k): Guideline for the Diagnosis and Treatment of Endometriosis

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Leitlinie für die Diagnostik und Therapie der Endometriose

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Authors

U. Ulrich¹, O. Buchweitz², R. Greb³, J. Keckstein⁴, I. von Leffern⁵, P. Oppelt⁶, S. P. Renner⁷, M. Sillem⁸, W. Stummvoll⁹, R.-L. De Wilde¹⁰, K.-W. Schweppe¹¹, for the German and Austrian Societies for Obstetrics and Gynecology

Affiliations

The affiliations are listed at the end of the article.

Key words

- endometriosis
- laparoscopy
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Schlüsselwörter

- Endometriose
- Laparoskopie
- Reproduktionsmedizin
- Gesundheitswesen

Abstract

In this guideline, recommendations and standards for optimum diagnosis and treatment of endometriosis are presented. They are based on the analysis of the available scientific evidence as published in prospective randomized and retrospective studies as well as in systematic reviews. The guideline working group consisted of experts from Austria, Germany, Switzerland, and the Czech Republic.

Zusammenfassung

Mit dieser Leitlinie werden Empfehlungen und Standards für eine optimale Diagnostik und Therapie der Endometriose vorgestellt. Sie basieren auf einer Analyse prospektiv-randomisierter und retrospektiver Studien sowie systematischer Übersichten. Die Arbeitsgruppe bestand aus Experten aus Deutschland, Österreich, der Schweiz und Tschechien.

The Guideline is Supported by the Following Professional Associations and Organizations:

- ▶ German Society for Obstetrics and Gynecology (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V., DGGG)
 - ▶ Gynecological Endoscopy Study Group (Arbeitsgemeinschaft für Gynäkologische Endoskopie, AGE)
 - ▶ Gynecological Oncology Study Group (Arbeitsgemeinschaft für Gynäkologische Onkologie e.V., AGO)
- ▶ German Society for Gynecological Endocrinology and Reproductive Medicine (Deutsche Gesellschaft für Gynäkologische Endokrinologie und Fortpflanzungsmedizin e.V.)
- ▶ German Society for Psychosomatic Obstetrics and Gynecology (Deutsche Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe, DGPF)
- ▶ German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e.V., DGAV)
- ▶ German Society for Urology (Deutsche Gesellschaft für Urologie e.V.)
- ▶ Austrian Society for Obstetrics and Gynecology (Österreichische Gesellschaft für Gynäkologie und Geburtshilfe e.V., ÖGGG)

- ▶ Swiss Society for Obstetrics and Gynecology (Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe, SGGG)
- ▶ Czech Society for Obstetrics and Gynecology
- ▶ Endometriosis Research Foundation (Stiftung Endometriose-Forschung, SEF)
- ▶ European Endometriosis League (EEL)
- ▶ Endometriosis Association of Germany (Endometriose-Vereinigung Deutschland e.V.)
- ▶ Endometriosis Association of Austria (Endometriose-Vereinigung Austria)

Project Management and Lead Author:

Prof. Dr. U. Ulrich, Berlin

Task Force Members:

Dr. O. Buchweitz, Hamburg (Germany)
 Dr. R. Chvatal, Znamim (Czech Republic)
 Prof. Dr. R.-L. De Wilde, Oldenburg (Germany)
 Prof. Dr. Dr. Dr. A. D. Ebert, Berlin (Germany)
 Dr. B. Engl, Bruneck (South Tyrol)
 Dr. I. von Leffern, Hamburg (Germany)
 Prof. Dr. R. Greb, Dortmund (Germany)
 Dr. D. Haas, Linz (Austria)
 Dr. G. Halis, Berlin (Germany)

Bibliography

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Correspondence

Prof. Dr. U. Ulrich
 Department of Obstetrics and Gynecology
 Martin Luther Hospital
 Caspar-Theyß-Straße 27–31
 14193 Berlin
 u.ulrich@mlk-berlin.de

DGGG-Leitliniensekretariat

Prof. Dr. med. Matthias W. Beckmann, DGGG-Leitlinienbeauftragter
 Frauenklinik
 Universitätsklinikum Erlangen
 Universitätsstraße 21–23
 91054 Erlangen
 Tel.: 091 31-85-3 35 07/44063
 Fax: 091 31-85-3 39 51

Prof. Dr. J. Hücke, Wuppertal (Germany)
 Prof. Dr. J. Keckstein, Villach (Austria)
 Prof. Dr. M. Müller, Bern (Switzerland)
 Prof. Dr. P. Oppelt, Linz (Austria)
 Dr. S.P. Renner, Erlangen (Germany)
 Dr. M. Sillem, Mannheim (Germany)
 Prof. Dr. K.-W. Schweppe, Westerstede (Germany)
 Dr. W. Stummvoll †, Linz (Austria)
 Prof. Dr. H.-R. Tinneberg, Gießen (Germany)
 Dr. F. Tuttlies, Villach (Austria)
 Prof. Dr. U. Ulrich, Berlin (Germany)
 Prof. Dr. L. Wildt, Innsbruck (Austria)

1 Background

In this guideline, a standard is recommended for the diagnosis and treatment of endometriosis on the basis of the previously published scientific knowledge and of the experience of the authors. Doctors providing care for patients with endometriosis represent the target group for this guideline.

The recommendations are based on an analysis of the scientific literature (PubMed, MEDLINE search, Cochrane Library), although only a limited number of prospective, randomized studies are available on the diagnosis and treatment of endometriosis. The recommendations and publications of the following professional associations were also taken into consideration:

- ▶ Endometriosis Research Foundation (<http://www.endometriose-sef.de>)
- ▶ The Royal College of Obstetricians and Gynaecologists Clinical Green-Top Guidelines for the Investigation and Management of Endometriosis (<http://www.rcog.org.uk/>)
- ▶ ESHRE Guideline for the Diagnosis and Treatment of Endometriosis (<http://www.eshre.eu>)
- ▶ The American College of Obstetrics and Gynecology Committee on Practice Bulletins (<http://www.acog.org/>)
- ▶ awmf.de [86]

2 Introduction

2.1 Definition and epidemiology

Core statements:

- a. Endometriosis is defined as the presence of endometrium-like groups of cells outside the uterine cavity.
- b. The cardinal symptom is pelvic pain, and infertility is common.

Endometriosis is one of the most common gynecological diseases. It occurs predominantly after sexual maturity has been reached and is considered to be estrogen-dependent. In one study, adolescents in the 10- to 15-year-old age group represented 0.05% and in the 15- to 20-year-old age group 1.93% of all women with endometriosis. Postmenopausal women accounted for 2.55% of the cases [78]. Endometriosis is a cause of significant morbidity [5, 68, 172].

Reliable information on frequency is lacking, and there are significant fluctuations in the prevalence rates quoted in the literature. It is estimated that approx. 40 000 new cases occur in Germany each year. Around 20 000 women are admitted for hospital treatment for endometriosis each year in Germany [78]. The economic impact is considerable in terms of medical cost and reduced work

productivity. Despite this, the disease is under-represented in clinical and basic scientific research [168].

The dilemma of endometriosis is caused partly by the long interval between the appearance of the first symptoms and the correct diagnosis – 10 years on average in Austria and Germany [91] – and partly by the repeated operations in chronic forms of the disease.

Although endometriosis is a histopathologically benign disease, it can spread to other organs as a result of infiltrative growth and require extensive surgery [189].

2.2 Etiology, pathology and staging

Core statement:

The etiology and pathogenesis of endometriosis are still not fully understood. There is, therefore, no known causal treatment at present.

Recommendation:

All known staging systems have their limitations. For the purpose of international comparability, the rASRM staging system should be used, with the addition of the ENZIAN classification in deep infiltrating endometriosis.

Various theories on the etiology and pathology of endometriosis have been presented in the literature: implantation theory [164, 165], celomic metaplasia theory [126], archimetra or “tissue injury and repair” concept [113, 114].

The most widely used classification is that of the American Society for Reproductive Medicine (the “rASRM score”, [11]). This rASRM score shows only a weak correlation with the cardinal symptoms of pain and infertility [72, 194]. The description of retroperitoneal and deep infiltrating growth forms is also inadequate with this system. The Endometriosis Research Foundation has attempted to overcome this shortcoming by creating an appropriate classification – the ENZIAN classification [77, 79, 80, 157, 186]. Like the rASRM score, the ENZIAN classification is also morphologically descriptive. At present, no data exist showing whether the ENZIAN classification correlates with symptoms such as pain and infertility. The traditional division into external and internal genital endometriosis and extragenital endometriosis [9] has proven useful in routine clinical practice; it takes into account the concept of a single disease entity.

In decreasing order of frequency, the following are involved: pelvic peritoneum, ovaries, uterosacral ligaments, rectovaginal septum/vaginal fornix, and extragenital sites (e.g., rectosigmoid colon and urinary bladder).

The incidence of involvement of the uterus (adenomyosis) and tubes is not entirely clear. The diaphragmatic peritoneum [137, 155], the vermiform appendix [71] and the umbilicus [197] are rare but typical extragenital sites. Endometriosis also occurs in surgical scars following hysterectomy, cesarean section, episiotomy, and perineal lacerations [19, 62, 144, 167]. It is debated that this may be caused by the mechanical transfer of endometrial particles. Manifestations in the spleen, lungs, kidneys, brain or skeleton are rare.

Patient information – Causes of endometriosis

The causes of the development of endometriosis have not yet been scientifically proven. No causal treatment options are, therefore, available at present which might enable endometriosis to be eliminated completely or cured.

There is also no treatment available that prevents endometriosis from developing in the first place.

Endometriosis and malignancy

Core statements:

- In very rare cases, malignancy may arise from endometriosis – usually ovarian cancer.
- An association with the occurrence of other, non-gynecological malignancies can also be found in the literature. The clinical significance of this observation is unclear.

Risk of malignant diseases in women with endometriosis

Even though there is no statistically detectable increase in the risk of cancer for women with endometriosis in general [122, 181], an association has been described between the existence of endometriosis and certain malignancies such as endocrine tumors, ovarian cancer, renal cell carcinoma, brain tumors, malignant melanoma, non-Hodgkin lymphomas and breast cancer [28, 82, 122, 136, 139, 148, 198]. The standardized incidence ratio (SIR) is stated as, for example, 1.38 for endocrine tumors, 1.37 for ovarian cancer and 1.08 for breast cancer [122]. The SIR might be even higher in women with primary infertility, endometriosis and one of the aforementioned malignancies [27]. The validity of these data and their clinical significance are unclear.

Endometriosis-associated malignancies Malignant tumors may arise from endometriosis. Ovarian cancer accounts for around 80% and extragonadal tumors for 20% of these cases [187, 199], with the positive correlation persisting even if it was many years previously that the woman had the endometriosis [148]. Endometriosis is considered to be a risk factor that can accelerate the development of ovarian cancer by 5 years [12]. According to one study, the overall risk is approx. 2.5% [190]. Histologically, the tumors are mainly of the endometrioid (OR 3.05) or clear cell (OR 2.04) type, although a correlation has been found recently between endometriosis and well differentiated (G1) serous carcinomas (OR 2.11) [148]. The association between poorly differentiated (high-grade) serous and mucinous ovarian carcinomas or borderline ovarian tumors is not statistically significant [148]. Other histologic entities occur (endometrial stromal sarcoma, mixed tumors, etc.) [200]. Furthermore, an ovarian endometrioma diameter of ≥ 9 cm, a postmenopausal situation [106] and a hyperestrogenic state [206] are reported to be independent risk factors (single center data). In the Swedish Hospital Discharge Registry of 2004, the presence of endometrial cysts in women between 10 and 29 years of age was defined as an additional risk factor for the subsequent development of ovarian cancer [25]. Ovulation inhibitors, births, tubal sterilization or hysterectomy might reduce the risk, on the other hand [128]. Extragonadal endometriosis-associated carcinomas have virtually been described in almost all tissues in which endometriosis occurs [121].

Summary On the basis of the described incidence rates and risk factors, the possibility of endometriosis-associated malignant disease should be included in considerations relating to differential diagnosis, and patients should be informed about this accordingly. At the same time, it is important to exercise prudence and to keep a sense of proportion when confronting endometriosis patients with these statements.

Patient information – Endometriosis and malignancy

Even if women with endometriosis are not generally at increased risk of malignant disease, some malignant diseases may occur more frequently than in women who do not have endometriosis.

The work-up for and treatment of endometriosis should, therefore, take this fact and the individual situation of the woman concerned into account. Specific additional investigations may thus be required in individual cases.

3 Diagnosis and Treatment of Endometriosis

Core statements:

- Indications for endoscopic diagnosis and treatment in endometriosis are as follows:
 - Pain
 - Organ destruction, and/or
 - Infertility
- Surgical removal of the lesions is considered the “gold standard” for symptom control [1, 50, 67].

Recommendation:

In general, the diagnosis of endometriosis is to be established histologically. Hence, laparoscopy is essential for the diagnostic work-up [202].

3.1 General remarks

Some of the women affected are asymptomatic. Furthermore, the disease stage does not correlate with the severity of the symptoms [70, 161]. The determination of CA-125 levels is not helpful either for diagnosis or follow-up and is not recommended (see section 3.3.1, [131]). In some cases, it is difficult to prove whether a causal relationship actually exists between endometriosis and certain symptoms. Asymptomatic endometriosis in a patient who does not wish to become pregnant is not generally an indication for surgical or medical intervention. There are exceptions to this, e.g., endometriosis-induced ureteral stenosis with hydronephrosis (absolute indication). Almost all women with *symptomatic* endometriosis suffer from dysmenorrhea. If this cardinal symptom is absent, other causes of pelvic pain must be considered in the differential diagnosis [173, 174].

For the sake of clarity, the different forms of endometriosis are discussed separately. Nevertheless, they are often combined [188].

Patient information – General notes on diagnosis and treatment

In the presence of suspected endometriosis, a histologic assessment should be performed. As a general rule, laparoscopy is necessary for this. Persistent pain, desire to conceive and/or functional impairment of an affected organ (e.g. ovaries, bowel or ureter) are reasons for the surgical and/or pharmacological treatment of endometriosis. Conversely, it follows that a woman who has endometriosis but does not have any symptoms, does not wish to conceive and does not exhibit any organ damage, does not need to be treated, although it is always important to consider the patient's individual situation.

3.2 Peritoneal endometriosis

Core statements:

- Peritoneal endometriosis is diagnosed laparoscopically.
- The treatment of choice is laparoscopic removal of the implants.

Recommendation:

Following medical suppression of the ovarian function, endometriotic implants may undergo regression. To reduce endometriosis-associated symptoms, progestins, oral contraceptives or GnRH analogs can be used in order to induce therapeutic amenorrhea.

3.2.1 Morphology and symptoms

In peritoneal endometriosis, a distinction is made between red, white and black lesions [11] and/or between pigmented and non-pigmented (atypical) lesions [95, 138]. The red and non-pigmented lesions are seen as early manifestations of endometriosis. They are considered to be particularly active. In terms of response to hormone therapy, peritoneal endometriosis appears to differ from ovarian and deep infiltrating endometriosis [138]. It is not known, however, whether the different forms of peritoneal endometriosis behave differently in relation to pain, fertility and course of the disease [75]. Patients with pronounced symptoms prior to surgery are at higher risk of recurrence than patients who do not feel much pain [156]. The lifetime risk of endometriosis recurrence depends on the age at initial diagnosis and is 1.75-fold higher for 20- to 29-year-old than for 30- to 39-year-old patients [171]. Early diagnosis of endometriosis, including in adolescent girls, might be of significance in terms of the subsequent course of the disease and the maintenance of fertility [4, 204].

3.2.2 Diagnosis

Following a detailed past medical history-taking and vaginal/rectal examination, the key measure for diagnosing peritoneal endometriosis is laparoscopy with histologic confirmation [67]. Transvaginal ultrasonography or MRI are equally irrelevant to the detection of peritoneal implants, although the former serves to rule out ovarian endometriosis [132], and the latter may provide additional information where deep infiltrating endometriosis is present at the same time [105].

3.2.3 Treatment

Surgical treatment Laparoscopic removal of the lesions is the primary therapeutic objective. This has been shown to reduce the pain [93]. Whether the methods available (coagulation, vaporization, excision) are equivalent is unclear [81]. Additional LUNA (laparoscopic uterine nerve ablation) does not lead to any improvement in outcome in patients with minimal to moderate endometriosis who have pain [196]. It has not been proven whether postoperative pharmacological suppression of ovarian function is successful in improving the effect of surgery or maintaining it for longer [64].

One option for reducing persistent pain after surgery is the insertion of a levonorgestrel-releasing IUD [2].

Primary medical treatment Suppression of ovarian function produces regressive changes in endometriotic implants. A reduction in endometriosis-associated symptoms can be achieved equally with progestins, oral contraceptives (continuous) or GnRH analogs [29, 73, 211], while GnRH analogs were more effective for dysmenorrhea and dyspareunia in some studies. Differences exist in terms of the adverse effect profiles and costs, however [30, 47, 84, 193]. In two current, prospective and randomized studies, continuous oral administration of a progestin (dienogest) has been shown to have the same efficacy as a GnRH analog in endometriosis-associated pain, while dienogest offered advantages for the patient in terms of clinical tolerability [74, 180]. Long-term data show a sustained clinical effect continuing beyond the period of administration [151].

When administered over a more prolonged period of time, GnRH analogs should be administered concomitantly with appropriate protective add-back medication because of the potential effects of estrogen deficiency. The duration of treatment with GnRH analogs is 6 months in patients with pain. Although a 3-month treatment period is just as effective, it is associated with a shorter

recurrence-free interval [83]. No data are available on the benefit of extended GnRH-a therapy. According to the findings of one prospective study, treatment with dienogest as maintenance therapy after GnRH-a was effective in maintaining the GnRH-a-induced effect for at least 12 months [103]. Although non-steroidal and other anti-inflammatory drugs are used frequently in routine clinical practice, there is no evidence at present that they have a positive influence on the specific symptoms associated with endometriosis [10].

3.3 Ovarian endometriomas

Core statement:

The diagnosis of ovarian endometriomas is primarily made by transvaginal ultrasound.

Recommendations:

- For primary treatment of ovarian endometriomas, the cyst wall should be removed surgically. Fenestration alone is insufficient.
- Hormonal drug treatment alone is neither effective in eliminating an ovarian endometrioma and thus to replace its surgical removal, nor in compensating for incomplete surgical removal. Therefore, it is not recommended.

3.3.1 Diagnosis

In 20–50% of all women with endometriosis, the ovaries are affected [89]. The preoperative work-up is based on the clinical examination and transvaginal ultrasound, with ovarian endometrioma often exhibiting a typical echo texture [88]. However, sonographically complex ovarian masses with a heterogeneous appearance are also found, which makes it difficult to distinguish between functional cysts on the one hand and dermoid cysts, cystomas or ovarian cancer on the other in individual cases [109] (Table 1). In the case of planned laparoscopic procedures in the presence of unclear ovarian findings, reference is made to the relevant S1 Guideline of the German Society for Obstetrics and Gynecology (Guideline: laparoscopic surgery for ovarian tumors, AWMF no. 015-003). Any unclear ovarian mass should be evaluated histologically.

If there is pain, additional deep infiltrating endometriosis is probably present [40] which must be taken into consideration during the clinical examination.

Table 1 Ultrasound appearance of ovarian endometrioma in premenopausal women (modified according to [88, 191]).

Appearance:	heterogeneous
Size:	up to 15 cm
Borders:	smooth
Wall thickness:	increased
Echogenicity:	not anechogenic (hypo- to hyperechogenic)
Internal echoes:	fine, uniformly distributed
Further features:	one or more compartments
	uni- or bilateral
	The same characteristics are associated with a higher risk of malignancy in postmenopausal women.

Determination of tumor markers The CA-125 value is often assessed in the differential diagnostic work-up of complex ovarian masses. As the CA-125 value is commonly elevated in endometriosis patients, however, it is of no relevance in terms of the differential diagnosis (Guideline: laparoscopic surgery for ovarian tumors, AWMF no. 015-003). It is not sufficiently specific. Therefore, its determination for the evaluation of suspected endometriosis is not recommended in the clinical routine. In the course of the disease (e.g., in a suspected recurrence), the clinical situation is the decisive factor rather than the CA-125 level. The same applies at present to serum levels of human epididymis secretory protein 4 (HE4) [112,207].

3.3.2 Treatment

The most effective treatment for ovarian endometriomas is their surgical removal. The method of choice for this is surgical laparoscopy [32]. According to a meta-analysis, ovary-sparing removal (extraction) of the cyst wall is superior overall to thermal destruction using a high-frequency current, laser vaporization or argon plasma coagulation in terms of pain symptoms and recurrence and pregnancy rates [76]. Whether this recommendation should apply only to endometriomas with a diameter of >4 cm is a moot point [85,100]. The problem of the potential loss of oocytes following the excision of recurrent endometriomas in infertility patients resulting in the procedure not being performed prior to assisted reproduction (but therefore also in no histologic confirmation being obtained) in the case of smaller endometriomas, will be examined later in detail in section 4.3. The experience of the surgeon may have an influence on this oocyte loss [205].

The opening and drainage of the cyst capsule of the endometrioma cannot be recommended as a surgical procedure alone because 80% of patients receiving this treatment suffer a recurrence within six months [7,162]. This high recurrence rate cannot be reduced by subsequent treatment with GnRH analogs [192].

Medical (hormonal) treatment for ovarian endometriomas alone is not sufficient and is not recommended. Pre-operative administration of GnRH analogs may lead to a decrease in the size of the endometrioma. Whether this results in surgical benefits or a reduction in recurrence rates is the subject of controversy in the literature [53,134]. Postoperative GnRH analogs do not compensate for incomplete surgery [33]. While some working groups have been able to show that postoperative administration of a hormonal contraceptive resulted in a reduction in the recurrence rate [135,169,182], two other prospective, randomized, placebo-controlled trials showed low recurrence rates irrespective of the treatment arm [8,170].

Patient information – Ovarian endometriosis

An endometriotic ovarian cyst should be removed completely by means of laparoscopy.

Hormonal treatment alone is not sufficient.

3.4 Deep infiltrating endometriosis

Core statements:

- Deep infiltrating endometriosis (DIE) is defined as the involvement of the rectovaginal septum, the vaginal fornix, the retroperitoneum (pelvic side wall, parametrium), the bowel, ureter, and urinary bladder.
- The primary diagnosis is made clinically with rectovaginal palpation, inspection with divided specula, transvaginal ultrasound and transabdominal ultrasound of the kidneys being mandatory.

Recommendations:

- For treatment, complete resection should be performed. Nonetheless, compromises must be made as preservation of fertility often is imperative.
The extent of the resection should be decided in close agreement with the patient against the background of benign disease and possible relevant complications.
- The treatment of DIE should take place in dedicated specialist centers on the basis of an interdisciplinary approach.
- In the case of conservatively managed patients and before and after surgery, kidney ultrasound is mandatory in order to avoid overlooking clinically silent hydronephrosis. Hydronephrosis associated with DIE is an absolute indication of appropriate diagnosis and treatment.

3.4.1 Symptoms

DIE refers to the forms which manifest in the rectovaginal septum, in the vaginal fornix, in the retroperitoneum (pelvic side walls, parametrium) and in the bowel, ureter and urinary bladder. In the case of ureteral endometriosis, a distinction is made between the intrinsic (infiltration of the ureter itself; rare) and extrinsic (external compression) subtypes. The way in which the aforementioned structures are involved may be very complex [189].

The symptoms depend on the site. In the case of bowel involvement, various intestinal symptoms occur, including dyschezia, feeling of pressure, flatulence, tenesmus, blood and mucus in the stool, diarrhea and constipation, and altered bowel habits. The absence of symptoms does not rule out bowel involvement. Endometriosis of the bladder can cause voiding difficulties and hematuria. Ureteral endometriosis can lead to hydronephrosis. Endometriosis-induced back-up of urine develops slowly and is, therefore, usually clinically silent [177]. Dyspareunia is typically caused by alteration of the pelvic plexus [154]. Although most patients with DIE complain of a variety of bowel symptoms, it has not been possible so far to reproduce any sensitive anorectal dysfunction by means of manometry in studies on this subject [118].

Rectovaginal septum involvement is most common, followed by involvement of the rectum, the sigmoid colon, the cecum and the vermiform appendix, the bladder and ureters and, much more rarely, the ileum while multiple sites involvement is possible.

3.4.2 Diagnosis

A clinical diagnosis of suspected disease is made initially on the basis of the patient's history, which is often indicative, and on vaginal and rectal palpation, followed by an investigation-based diagnosis by means of transvaginal ultrasound. Various investigations have been found to be useful in connection with the subsequent work-up (• Tables 2 and 3):

Table 2 Clinical investigations for the work-up of deep infiltrating endometriosis.

Investigation	Evidence provided
Inspection (double-bladed speculum)	Visible endometriosis in the posterior fornix
Palpation (always including rectal)	Uterus often retroverted; dense, nodular, tender infiltration of the rectovaginal septum (retrocervical)
Transvaginal ultrasound	Changes in the uterus in the presence of concurrent adenomyosis and information about possible ovarian endometriomas, good visualization of deep rectal involvement
Renal ultrasound	Be alert to back-up of urine (parametrial, pelvic wall and ureteral endometriosis)

Table 3 Optional investigations for the evaluation of deep infiltrating endometriosis.

Investigation	Evidence provided
Proctosigmoidoscopy	External impression, mucosal involvement (rare), differential diagnosis of primary bowel disease
Magnetic resonance imaging	Involvement of the bowel wall, the bladder; adenomyosis?
Transrectal endoscopic ultrasound	Involvement of the bowel wall?
Contrast enema	Bowel involvement in higher sections
Intravenous pyelogram or computed tomography	Ureteral stenosis, hydronephrosis
Cystoscopy	Bladder involvement

Proctosigmoidoscopy is used very frequently in the presence of suspected rectosigmoid involvement. However, infiltration of the mucosa is extremely rare. In the presence of extensive disease, an external impression is rather to be expected – around 26% of patients with rectal endometriosis exhibit stenosis [161], so a negative proctoscopic mucosal finding is the rule, and by no means excludes involvement of the muscularis. The importance of proctoscopy thus lies in the evaluation of other causes of rectal bleeding as part of the differential diagnosis. MRI exhibits a high sensitivity for the diagnosis of DIE and provides useful information [18]. Transrectal endoscopic ultrasound provides a reliable and simple means of predicting the presence of deep rectal infiltration [18]. Transvaginal ultrasound also provides a straightforward means of DIE visualization, including the diagnosis of deep rectal involvement with a high level of sensitivity and specificity combined with minimal patient discomfort [87,90]. In a comparative study, the aforementioned methods were found to be equivalent overall in terms of diagnostic effectiveness, although MRI had the highest sensitivity in some cases [18]; in another study, transvaginal ultrasonography was favored [3]. Regardless of the pre-operative diagnosis, the extent of the resection is often not decided until during the operation (e.g. multiple intestinal foci: rectum, sigmoid colon, cecum).

3.4.3 Treatment

The treatment of choice for symptomatic deep infiltrating endometriosis is resection, leaving a free margin on all sides [42,61,98,125,127,153]. In many studies, a positive effect on pain, overall quality of life and fertility has been demonstrated [17]. Vari-

ous methods are available for this: vaginal resection, laparoscopy, laparoscopically assisted vaginal surgery, laparotomy. In the presence of infiltration-related manifestations of endometriosis (rectosigmoid colon, bladder, ureter), the pre-operative counseling for and planning and performance of the intervention should be carried out on the basis of interdisciplinary consensus (including Visceral Surgery and/or Urology, depending on the situation). If hydronephrosis is present (i.e., an absolute indication of treatment), it is vital to refer the patient to a urologist who will carry out an assessment of renal function and decide whether, how, and to what extent treatment should be carried out [117]. If there is a desire to conceive, the need to preserve the uterus and ovaries often results in incomplete resection of the endometriosis.

The benefits of the resection are to be confronted with the morbidity associated with surgery [31,36,45,154] as well as the recurrence rate of endometriosis. Recurrences after bowel resection for DIE occur in about 14% of cases (5–25%, see [49,124]). Complications, some of which can be severe (anastomotic leaks), must be anticipated during surgery and in the immediate post-operative period in approx. 5–14% of cases. This applies especially to segmental rectal resection (associated with an incidence of up to 24%, see [108,127,147,150,160]), which is why some research teams warn against segmental rectal resection for benign endometriotic disease and recommend the mucosa-sparing “shaving” technique or full-thickness resection of the wall without incontinuity resection [54,69]. The long-term consequences – some of which being irreversible – must always be weighed against the desired positive effect of the operation. Besides fistula and rectal dysfunction [13], bladder atony – sometimes associated with the need for permanent self-catheterization by the patient – is of particular clinical relevance [15,160]. This is caused by surgical alteration of the hypogastric plexus (splanchnic nerves) which is unavoidable in some cases. The risk of postoperative bladder atony with self-catheterization was stated as 29% in one study; the risk was associated with simultaneous partial colectomy [210]. Whether nerve-sparing surgical techniques can prevent such urological complications is under investigation [37,97]. A particular situation also arises when complex colorectal and urological procedures are performed in one session – in these cases, it is important to consider whether it would not be better to adopt a two-step approach [159].

Owing to the complexity of the procedures, surgical treatment of DIE should be carried out in centers with relevant experience [56]. Asymptomatic findings should always be monitored with the inclusion of renal ultrasound, and do not necessarily require surgery in the absence of progression. Spontaneous bowel perforation and ileus are extremely rare [51]. Because of the risk of these occurring, however (e.g., including during pregnancy with considerable maternal and fetal consequences in some cases), the pros and cons of a deliberate decision not to operate should also be discussed in detail. This gives rise to the dilemma that both surgery for deep rectovaginal endometriosis and leaving it in situ may possibly result in a higher risk of spontaneous perforation/vulnerability during pregnancy and delivery (posterior vaginal fornix rupture), which is attributed to decidualization during pregnancy [24,41,152]. Against this background, the primary method of delivery (spontaneous delivery versus cesarean section) is a subject which should definitely be broached with the patient and considered carefully (expert opinion, Weissensee meeting of the Endometriosis Research Foundation, 2013). Conclusion: Possible surgical and non-surgical alternatives for DIE must always be explained in both directions (documentation).

The benefit of pre- or postoperative GnRH analog therapy for deep infiltrating endometriosis is not proven [33,64], and, therefore, cannot generally be recommended. Medical hormonal therapy will be given, however, if the patient wishes to avoid surgery or if there are postoperative symptoms. An effect can only be expected during therapy, and long-term treatment is therefore necessary. Progestin monotherapy, a monophasic continuous oral contraceptive or GnRH analogs (with add-back therapy) for the induction of therapeutic amenorrhea are options. Another possible alternative to surgery is the insertion of a levonorgestrel-releasing IUD under which pain relief and a reduction in rectovaginal endometriosis size have been observed [59].

Estrogen and progestogen replacement therapy in endometriosis Premenopausal patients following hysterectomy for endometriosis receive combined estrogen and progestin replacement therapy if indicated. In postmenopausal women, estrogen and progestogen combinations or tibolone are also recommended following hysterectomy in view of the fact that there is a risk of recurrence and malignancy (see section entitled “Endometriosis-associated malignancies”) [129,175]. The problem of the risk of breast cancer must nevertheless be weighed against this and discussed with the patient so that an individual decision can be made (AWMF-S3 Guideline: Hormone replacement therapy in peri- and postmenopausal women, AWMF Registry no. 015-062, 2009).

Patient information – Deep infiltrating endometriosis

Where endometriosis involves the vagina, bowel, bladder and ureters, complete surgical removal of the lesions is the best treatment at present. Extensive surgery is often needed for this, which requires good cooperation between gynecologists, surgeons and urologists and should be performed in a dedicated specialist unit.

Before surgery for deep infiltrating endometriosis, the risks and benefits must always be weighed up carefully, because even extensive surgery with complete removal of the endometriosis cannot guarantee the desired pain relief which is the aim of surgery.

3.5 Uterine adenomyosis

Core statement:

The diagnosis of adenomyosis is primarily established clinically, by vaginal ultrasound and/or MRI; confirmation is usually provided only by the histological findings based on the hysterectomy specimen.

Recommendations:

- a. Given completion of family planning and presence of respective symptoms, hysterectomy can be recommended.
- b. If the patients opts for preservation of the uterus, therapeutic amenorrhea may be induced or a progestin-releasing IUD inserted.

3.5.1 Symptoms

Adenomyosis is defined as the infiltration of the myometrium by endometriosis. The main symptoms are painful, heavy and acyclic bleeding together with infertility [65].

3.5.2 Diagnosis

In clinically suspected cases, the following investigations have proved effective (Table 4):

Table 4 Work-up for adenomyosis.	
Measure/ investigation	Finding
Past medical history	Dysmenorrhea (including with neurodystonia), hypermenorrhea
Clinical examination	Occasionally tender, enlarged uterus (bimanual, rectovaginal palpation)
Transvaginal ultrasound	Poorly demarcated heterogeneous areas, cystic intramural changes in some cases, areas of variable echogenicity, irregular halo effect, discrepancy between anterior and posterior wall
MRI	Changes in the zonal anatomy of the uterus, Irregular junctional zones on T1- and T2-weighted images, areas of low signal intensity and subendometrial foci of high signal intensity, anterior-posterior wall asymmetry as a sign of muscle hyperplasia

Transvaginal ultrasound is of greatest significance in day-to-day practice with approx. 65–70% sensitivity and 95–98% specificity [89,123]. MRI, with high sensitivity and specificity for the diagnosis of adenomyosis, is also suitable and useful in individual cases [38,101,104,149]. Although desirable, there is no suitable routine method for the histologic confirmation of adenomyosis. Various groups have worked on biopsy methods, while only positive results are exploitable. It cannot be used to rule out the disease (e.g. [99]). The definitive diagnosis, therefore, is ultimately based on the hysterectomy specimen in most cases. Adenomyosis can occur in isolation or together with various forms of endometriosis. DIE is often associated with adenomyosis [110].

3.5.3 Treatment

If the patient’s family planning is complete, hysterectomy represents the most effective treatment [65]. The decision regarding which method to be used for this (vaginal, abdominal, laparoscopically assisted vaginal, total laparoscopic, laparoscopic supracervical) is left to the discretion of patient and surgeon. Vaginal hysterectomy on its own without simultaneous laparoscopy rules out the possibility of peritoneal implant removal, however, and should therefore be the exception. Laparoscopic supracervical hysterectomy (LASH) appears to be suitable for this indication with careful reference to the S1 Guideline of the German Society for Obstetrics and Gynecology (AWMF no. 015-064) as the cervix is involved only in extremely rare cases [14,166]. Irrespective of this general recommendation of hysterectomy, consideration must still be given to the potentially negative consequences of hysterectomy in women with chronic pelvic pain (AWMF Guideline of the German Society for Psychosomatic Obstetrics and Gynecology, AWMF no. 016-001). The benefit of uterus-preserving surgical treatment for patients wishing to conceive or desiring organ preservation in focal forms of adenomyosis is not demonstrated by studies. If this is attempted in individual cases (e.g. encouraging results by [142]), an MRI scan or preoperative administration of a GnRH analog may be useful for planning the operation [133,143,149]. The risk of uterine rupture during pregnancy or childbirth, especially if

larger myometrial defects arise, should be taken into account in the subsequent management of the patient [149,201].

The use of interventional radiology procedures for the treatment of adenomyosis, such as embolization [26] and MRI-guided focused ultrasound ablation [63], hitherto, should be limited to studies.

Progestins, oral contraceptives and progestin-releasing intra-uterine systems are used as an alternative to hysterectomy [58]. The therapeutic effect is based on the induction of amenorrhea. Contraceptives (monophasic products) and progestins should be taken continuously [44,195].

4 Endometriosis and Infertility

Core statements:

- While a causal relationship has not been resolved yet, endometriosis and infertility are frequently associated.
- For the treatment of women with both endometriosis and infertility, appropriate skills and experience in infertility surgery as well as cooperation with centers for reproductive medicine are required.

Recommendations:

- In women with endometriosis who wish to conceive, implants should be removed surgically to improve fertility.
- In cases of recurrence, assisted reproductive technologies are superior to repeat surgical interventions in terms of the pregnancy rate. In repeat operations for ovarian endometriosis, the surgery-related potential reduction in ovarian reserve is to be considered.
- Postoperative treatment with GnRH analogs has not been effective in improving the spontaneous pregnancy rate in infertility patients and is, therefore, not recommended.
- Any drug treatment of endometriosis alone does not improve fertility and should not be applied from a reproductive medicine perspective.

4.1 Pathophysiology of infertility associated with endometriosis

Infertility and endometriosis are often associated, although it is not clear whether there is a causal relationship. Mechanical alteration of the adnexa is unequivocally accepted as the cause of infertility. However, whether the endometriosis creates an immunologically "hostile" environment for implantation or whether it leads to impairment of sperm transport, Fallopian tube mobility and oocyte maturation is unclear [102]. Nevertheless, results from egg donation programs indicate that oocyte and early embryonic development may be impaired in women with endometriosis [66].

4.2 Medical and surgical treatment

Medical treatment alone

In the presence of rASRM stage I and II endometriosis, no improvement in fertility was shown in a meta-analysis of 16 randomized and controlled studies following medical treatment (GnRH analogs, progestins) compared with placebo or a wait-and-see approach [92].

Surgical treatment

a) Minimal and mild endometriosis (in accordance with rASRM)

Two randomized, controlled studies on the effect of surgical removal (coagulation/excision) of endometriotic lesions in patients with infertility and AFS stage I and II endometriosis have been identified: Marcoux et al. [119] and Parazzini et al. [146]. Marcoux et al. randomized a total of 341 patients (average age: 30.5 years, average duration of infertility: 31 months) intra-operatively. Over a follow-up period of 36 weeks, 30.7% of the patients in the group who underwent excision of the endometriosis (50 out of 179) became pregnant compared with 17.7% (29 out of 169; cumulative incidence ratio 1.7; 95% CI 1.2–2.6) in the group who underwent diagnostic laparoscopy alone. The birth rate was not given. Parazzini et al. [146] intraoperatively randomized 101 patients with ASF stage I and II endometriosis who had experienced infertility for 38 months on average. During the follow-up period of at least one year, 12 patients in the excision group (12 out of 54 = 22.2%) and 13 in the diagnostic laparoscopy group (13 out of 47 = 27.6%) became pregnant. No statistically significant difference was found between the results, including in terms of birth rate of $n = 10$ in each group. In a meta-analysis based on these two studies, Jacobson et al. [94] came up with a positive overall result with respect to a benefit of excision in terms of an improved pregnancy rate, although the magnitude of the effect was uncertain (odds ratio 1.66; 95% CI 1.09–2.51). The confidence interval shows the possible variability in the actual effect in the presence of non-parallel results for the two studies.

In a retrospective cohort study ($n = 661$) of patients with AFS stage I and II endometriosis undergoing IVF, a 10.7% increase in the first IVF cycle pregnancy rate (29.4% compared with 40.1%, $p = 0.004$) and a 6.9% increase in the birth rate ($p = 0.04$; [140]) was found in those patients ($n = 399$) whose endometriotic lesions were excised before IVF.

b) Deep infiltrating endometriosis No controlled, randomized studies are available for deep infiltrating endometriosis including bowel involvement in which the primary objective was to compare surgical against non-surgical treatment in terms of the pregnancy and birth rates. Some non-randomized studies show that excision of DIE may improve the spontaneous and IVF-induced pregnancy rate [23,39,46,69,98,115,179].

In deep infiltrating endometriosis with bowel involvement, a prospective cohort study showed a significantly higher IVF-induced pregnancy rate when complete surgical removal was performed before [23]. Another prospective cohort study showed a higher pregnancy rate in patients with bowel endometriosis who underwent segmental rectosigmoid resection compared to leaving the bowel endometriosis in place (28.3% compared with 20% p -value not specified; [179]). In another study in pregnant women with DIE who wished to conceive, spontaneous pregnancies were observed only after laparoscopy compared with open surgery [46]. The outcome of a case-control study, on the other hand, indicated that radical, retroperitoneal excision of DIE did not confer any additional benefit in terms of reproductive function (and was associated with a significantly higher complication rate) compared with removal of intraperitoneal lesions alone [55].

In patients with endometriotic cysts, endometrioma excision is superior to fenestration and coagulation in terms of the spontaneous pregnancy rate [7,76]. Preoperative medical treatment does not improve the outcome [53,76].

Postsurgical medical treatment

Postsurgical treatment with GnRH analogs did not produce an improvement in the spontaneous pregnancy rate in infertility patients and is, therefore, not recommended [33,92].

4.3 Assisted reproduction Intrauterine insemination (IUI)

In the presence of minimal and mild endometriosis, IUI leads to an improvement in the pregnancy rate, while some studies have shown a benefit of ovulation induction compared with spontaneous cycles prior to IUI in terms of the pregnancy [48] and live-birth rate [185]. In one study, in contrast to the initial hypothesis, the cumulative endometriosis recurrence rate after 21 months was significantly higher following stimulation for IUI cycles than following controlled ovarian hyperstimulation for IVF [52].

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI)

Data from national treatment registries and current retrospective analyses show similar pregnancy rates following IVF in endometriosis patients compared with patients with tubal factor infertility [141]. Thus, conflicting results in a previous review could not be confirmed [16].

The effect of ovarian endometriomas on the outcome of IVF is unclear. Systematic reviews have shown that surgical treatment for endometriomas is not a prerequisite for success of IVF (i.e. with regard to pregnancy rates) [22,184]. On the other hand, it makes needle insertion easier and reduces the risk of infection. Consideration must also be given to the (very rare) possibility of ovarian cancer arising from endometriosis [120,130]. The question of whether doing without surgery in patients who are desperate to conceive in view of the ovarian reserve potentially being compromised by the ablation [43] arises in the presence of bilateral and recurrent endometriomas in particular [34,176]. The individual decision, based on these considerations, not to operate or re-operate (and thus to do without a histologic analysis or complete excision of the endometriosis as is desirable) but with the risk of relevant ovarian disease being overlooked, is a difficult one and should be made only in consultation with the patient, taking into account existing symptoms, safety concerns and differential diagnostic considerations [34]. If loss of ovarian function is imminent, some authors have considered cryopreservation of oocytes following ovarian stimulation or of ovarian tissue as an option for very young women not wishing to conceive at the present time [57].

In cases of recurrence of extensive endometriosis, assisted reproduction is superior to repeat surgical treatment in terms of the pregnancy rate [145]. Considerations regarding whether to operate yet again or to attempt assisted reproductive techniques without intervention should take into account the tubal status, duration of infertility, the patient's age, the extent of the endometriosis and the endometriosis-induced symptoms not associated with infertility, along with the patient's wishes [6]. Although the possibility of endometriosis exacerbation during stimulation for IVF should be considered this has not been demonstrated in controlled studies [20,21]; nevertheless, the cumulative rate of endometriosis recurrence was 7% for IVF cycles after 21 months in one study [52]. As a general rule, the more extensive the endometriosis and the older the patient, the earlier assisted reproduction should be recommended [107]. Nevertheless, younger patients with endometriosis who wish to conceive should also definitely be made aware of this option. According to a systematic

Cochrane review, ultra-long GnRH analog therapy after surgical treatment and (3–6 months) prior to IVF/ICSI leads to significantly higher pregnancy rates in rASRM stage III and IV endometriosis [158,163].

Patient information – Infertility and endometriosis

The surgical removal of endometriotic lesions is generally recommended in women who wish to conceive. It has been shown that an improvement in fertility can be achieved with surgery alone if the Fallopian tubes were intact and the sperm analysis normal. The treatment of these patients should be left in expert hands.

If endometriosis recurs (particularly after several operations), in vitro fertilization is a better way to achieve pregnancy than undergoing surgery again.

5 Psychosomatic Aspects

Recommendation:

Psychosomatic aspects in the treatment of patients with endometriosis should be considered and integrated early on.

Even if the evidence suggests that the pain a woman is suffering is caused by the presence of endometriosis, this does not rule out emotional conflict or psychosocial stress as co-factors. Generally speaking, chronic pelvic pain is accompanied by a considerable loss of quality of life and is frequently associated with a somatoform pain disorder (Guideline: Chronic pelvic pain in women, AWMF Registry no. 016-001). A desire to conceive and dysfunctional sick-role behavior (e.g. avoidance of physical activity), which can have an exacerbating effect on pain, leading to a vicious circle, may be additional psychological stress factors in endometriosis.

The integration of psychosomatic approaches to treatment for patients with chronic pelvic pain against a background of endometriosis (as an adjunct to surgical and medical measures) may, on the other hand, improve the patients' quality of life and their handling of the chronic pelvic pain and thus have a positive influence on treatment outcomes [50,173]. The integration of sex counseling into psychological support is also important.

Many authors are now calling for multidisciplinary approaches to treatment when it comes to dealing with chronic pelvic pain [35,116,178,203]. Causes other than endometriosis should also always be considered in the differential diagnosis of chronic pelvic pain [173,174].

In addition, there are some epidemiological studies that suggest an association between endometriosis and other chronic pain conditions such as migraine and chronic irritable bowel syndrome [111,183].

6 Complementary and Integrative Approaches to Treatment

Core statement:

Owing to the lack of controlled, randomized studies to date on complementary and integrative approaches to the treatment of endometriosis, no recommendations can be made.

Women with chronic recurrent endometriosis and corresponding symptoms may obtain relief of symptoms and an improve-

ment in quality of life from the use of complementary therapies [208]. In particular, these include the methods of acupuncture and Chinese medicine, classical homeopathy, herbal medicine, physiotherapy, etc. This should always be preceded by appropriate clinical screening for potential organ changes (endometriomas, hydronephrosis).

Although results from larger scale, randomized and controlled studies are not yet available, initial investigations clearly point to acupuncture [209] and Chinese herbal medicine having an effect on endometriosis-induced pain [60].

7 Rehabilitation, Follow-up and Self-help

Core statement:

After extensive surgical interventions (particularly for deep infiltrating endometriosis), repeat surgery for endometriosis, or in patients with chronic pain, there is often a need for rehabilitation.

Recommendation:

This need should be assessed and rehabilitation measures or follow-up treatment initiated.

All efforts in the area of rehabilitation are focused on the restoration of physical, mental and social well-being. Coping with a disease that frequently follows a chronic course and is sometimes associated with unavoidable limitations and pain is also an important aspect, however. In Germany, specialist centers exist that have considerable experience in the rehabilitation of endometriosis patients.

Follow-up should be based on symptoms, with the focus being on the patient's quality of life. All doctors should be aware of the limitations of the treatment options – particularly in cases where the endometriosis keeps recurring.

Self-help options exist to assist women with endometriosis in coping with the physical and mental problems they face. The independent endometriosis associations in Germany and Austria, the members of which are sufferers themselves, represent the interests of women with endometriosis. Besides free advice, they can provide addresses of self-help groups, rehabilitation centers and specialist doctors.

Patient information – Rehabilitation and aftercare

Following extensive surgery for endometriosis, additional follow-on treatment is also helpful.

The medical treatment of endometriosis has its limitations. Even after careful surgery in the hands of an expert, many patients continue to suffer from chronic pain – even if all the endometriosis was removed successfully. And not all women wishing to conceive will manage to become pregnant. In order to cope with the physical and mental problems that women with endometriosis can face, patients should be informed about the opportunities for self-help. The independent endometriosis associations in Germany and Austria, the members of which are sufferers themselves, represent the interests of women with endometriosis. Besides free advice, they can provide addresses of self-help groups, rehabilitation centers and specialist doctors in the different regions.

8 Summary

Endometriosis is one of the most common gynecological diseases. Women affected may suffer a considerable loss of quality of life [96]. Besides the individual health problem, the economic impact caused by the high level of morbidity, reduced work productivity and repeated therapeutic interventions should also be considered.

The etiology and pathogenesis are unclear. There is no known causal therapy. Laparoscopic removal is considered to be the surgical “gold standard”. Because the patients affected often wish to conceive and organ preservation is a top priority, radical surgery must often be limited. A patient with asymptomatic endometriosis who does not wish to conceive does not generally need to be treated (exception: hydronephrosis).

Careful patient selection and good interdisciplinary cooperation are prerequisites for surgical therapy in cases of endometriotic infiltration of the bowel, urinary bladder and/or ureter. The extent of surgery must always be weighed up against the morbidity associated with surgery and the unavoidable tendency to recur. Counseling regarding alternatives to surgery (medical treatment) must be documented as carefully as any decision by the patient not to undergo surgery (despite a clear indication).

While pre-operative medical treatment is not recommended with the products available at present, postoperative administration may prolong the recurrence-free interval in cases of peritoneal endometriosis. Various medical options for the treatment of pain symptoms can be considered as an alternative to the surgical approach or in the event of problems with recurrence, with progestins, monophasic oral contraceptives and GnRH analogs (with concomitant add-back medication to eliminate hypo-estrogenic side effects) having similar efficacy with different adverse effect profiles. Progestin-releasing intrauterine systems are another option.

Hormone therapy alone does not result in an improvement in fertility in endometriosis. Surgical removal of the endometriosis and the associated sequelae increased the spontaneous pregnancy rate in some studies. In the presence of severe endometriosis with destruction of organs (i.e. tubes and ovaries), assisted reproduction may be a better option, although surgery beforehand may increase the associated pregnancy rate. There are other reasons (pain, disease unrelated to pregnancy) for which such surgical correction should be considered in individual cases before planned assisted reproduction.

Almost all patients with endometriosis require medication for pain relief in the course of their disease. Depending on the circumstances, professional pain therapy should be provided, with psychosomatic support where necessary.

9 Important Internet Addresses

<http://www.dggg.de>
<http://www.oeggg.at>
<http://www.sggg.ch>
<http://leitlinien.net> (<http://www.awmf.de>)
<http://www.AGEndoskopie.de>
<http://www.endometriose-sef.de>
<http://www.endometriose-liga.eu>
<http://www.endometriose-vereinigung.de>
<http://www.eva-info.at>

The validity of the guideline has been approved by the Board of the DGGG [German Society for Gynecology and Obstetrics] and the DGGG Guidelines Commission in August 2013. The guideline will remain valid until September, 2016.

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Affiliations

¹ Department of Obstetrics and Gynecology, Martin Luther Hospital, Berlin

² Gynecological Outpatient Surgery Altonaer Straße, Hamburg

³ Center for Reproductive Medicine, Dortmund

⁴ Department of Obstetrics and Gynecology, Provincial Hospital, Villach

⁵ Department of Obstetrics and Gynecology, Albertinen Hospital, Hamburg

⁶ Department of Obstetrics and Gynecology, Provincial Women's and Children's Hospital, Linz

⁷ Department of Obstetrics and Gynecology, University of Erlangen School of Medicine

⁸ Gynecological Practice and Clinic Rosengarten, Mannheim

⁹ Department of Gynecology, Hospital of the Sisters of Mercy, Linz

¹⁰ Department of Obstetrics, Gynecology, and Gynecologic Oncology, Pius Hospital Oldenburg, University of Oldenburg School of Medicine

¹¹ Endometriosis Center Ammerland, Ammerland Clinic, Westerstede

10 References

- Abbott J, Hawe J, Hunter D et al. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004; 82: 878–884
- Abou-Setta AM, Houston B, Al-Inany HG et al. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. *Cochrane Database Syst Rev* 2013; 1: CD005072
- Abrao MS, Goncalves MO, Dias JA jr. et al. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. *Hum Reprod* 2007; 22: 3092–3097
- ACOG Committee Opinion. Endometriosis in adolescents. *Obstet Gynecol* 2005; 105: 921–927
- ACOG Committee on Practice Bulletins–Gynecology. ACOG practice bulletin. Medical management of endometriosis. No. 11, December 1999. Clinical management guidelines for obstetrician-gynecologists. *Int J Gynecol Obstet* 2000; 71: 183–196
- Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. *Fertil Steril* 2010; 94: 1609–1615
- Alborzi S, Momtahan M, Parsanezhad ME et al. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril* 2004; 82: 1633–1637
- Alborzi S, Hamed B, Omidvar A et al. A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. *Arch Gynecol Obstet* 2011; 284: 105–110
- Albrecht H. Die Endometriose. In: Seitz L, Amreich AI, Hrsg. *Biologie und Pathologie des Weibes*. Bd. IV. Berlin, Innsbruck, München, Wien: Urban & Schwarzenberg; 1955: 190–288
- Allen C, Hopewell S, Prentice A et al. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev* 2009; 2: CD004753
- American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis. *Fertil Steril* 1997; 67: 817–822
- Aris A. Endometriosis-associated ovarian cancer: a ten-year cohort study of women living in the Estrie Region of Quebec, Canada. *J Ovarian Res* 2010; 3: 2
- Armengol-Debeir L, Savoye G, Leroi AM et al. Pathophysiological approach to bowel dysfunction after segmental colorectal resection for deep endometriosis infiltrating the rectum: a preliminary study. *Hum Reprod* 2011; 26: 2330–2335
- Asher-Walsh CJ, Tu JL, Du Y et al. Location of adenomyosis in total hysterectomy specimens. *J Am Assoc Gynecol Laparosc* 2003; 10: 360–362
- Ballester M, Chereau E, Dubernard G et al. Urinary dysfunction after colorectal resection for endometriosis: results of a prospective randomized trial comparing laparoscopy to open surgery. *Am J Obstet Gynecol* 2011; 204: 303.e1–303.e6
- Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002; 77: 1148–1155
- Bassi MA, Podgaec S, Dias JA jr. et al. Quality of life after segmental resection of the rectosigmoid by laparoscopy in patients with deep infiltrating endometriosis with bowel involvement. *J Minim Invasive Gynecol* 2011; 18: 730–733
- Bazot M, Lafont C, Rouzier R et al. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. *Fertil Steril* 2009; 92: 1825–1833
- Bektaş H, Bilsel Y, Sari YS et al. Abdominal wall endometrioma; a 10-year experience and brief review of the literature. *J Surg Res* 2010; 164: e77–e81
- Benaglia L, Somigliana E, Vercellini P et al. The impact of IVF procedures on endometriosis recurrence. *Eur J Obstet Gynecol* 2010; 148: 49–52
- Benaglia L, Somigliana E, Santi G et al. IVF and endometriosis-related symptom progression: insights from a prospective study. *Hum Reprod* 2011; 26: 2368–2372
- Benschop L, Farquhar C, van der Poel N et al. Interventions for women with endometrioma prior to assisted reproductive technology. *Cochrane Database Syst Rev* 2010; 11: CD008571
- Bianchi PH, Pereira RM, Zanatta A et al. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009; 16: 174–180
- Boileau L, Borie F, Laporte S et al. Pelvipерitonitis by colorectal perforation in the third trimester of pregnancy after surgery for deep pelvic endometriosis. *Fertil Steril* 2011; 96: e42–e44
- Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cyst and endometriosis. *Acta Obstet Gynecol Scand* 2004; 83: 395–400
- Bratby MJ, Walker WJ. Uterine artery embolisation for symptomatic adenomyosis: mid-term results. *Eur J Radiol* 2009; 70: 128–132
- Brinton LA, Gridley G, Persson I et al. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997; 176: 572–579
- Brooks JJ, Wheeler JE. Malignancy arising in extragonadal endometriosis. *Cancer* 1977; 40: 3065–3073
- Brown J, Pan A, Hart RJ. Gonadotropin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev* 2010; 2: CD008475
- Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. *Cochrane Database Syst Rev* 2012; 3: CD002122
- Bryant CL, Lunniss PJ, Knowles CH et al. Anterior resection syndrome. *Lancet Oncol* 2012; 13: e403–e408
- Busacca M, Fedele L, Bianchi S et al. Surgical treatment of recurrent endometriosis: laparotomy versus laparoscopy. *Hum Reprod* 1998; 13: 2271–2274
- Busacca M, Somigliana E, Bianchi S et al. Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III–IV: a randomized controlled trial. *Hum Reprod* 2001; 16: 2399–2402
- Busacca M, Vignali M. Endometrium excision and ovarian reserve: a dangerous relation. *J Minim Invasive Gynecol* 2009; 16: 142–148
- Butrick CW. Chronic pelvic pain: how many surgeries are enough? *Clin Obstet Gynecol* 2007; 50: 412–414
- Camagna O, Dhainaut C, Dupuis O et al. [Surgical management of rectovaginal septum endometriosis from a continuous series of 50 cases]. *Gynecol Obstet Fertil* 2004; 32: 199–209
- Cecaroni M, Clarizia R, Bruni F et al. Nerve-sparing laparoscopic eradication of deep endometriosis with segmental rectal and parametrial resection: the Negrar method. A single-center, prospective, clinical trial. *Surg Endosc* 2012; 26: 2029–2045
- Champaneria R, Abedin P, Daniels J et al. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy. *Acta Obstet Gynecol Scand* 2010; 89: 1374–1384
- Chapron C, Fritel X, Dubuisson JB. Fertility after laparoscopic management of deep endometriosis infiltrating the uterosacral ligaments. *Hum Reprod* 1999; 14: 329–332

- 40 Chapron C, Santulli P, de Ziegler D et al. Ovarian endometrioma: severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod* 2012; 27: 702–711
- 41 Chen ZH, Chen M, Tsai HD et al. Intrapartum uterine rupture associated with a scarred cervix because of a previous rupture of cystic cervical endometriosis. *Taiwan J Obstet Gynecol* 2011; 50: 95–97
- 42 Chopin N, Vieira M, Borghese B et al. Operative management of deeply infiltrating endometriosis: results on pelvic pain symptoms according to a surgical classification. *J Min Invas Gynecol* 2005; 12: 106–112
- 43 Coccia ME, Rizzello F, Mariani G et al. Ovarian surgery for bilateral endometriomas influences age at menopause. *Hum Reprod* 2011; 26: 3000–3007
- 44 Cosson M, Querleu D, Donnez J. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. *Fertil Steril* 2002; 77: 684–692
- 45 Daraï E, Thomassin I, Barranger E et al. Feasibility and clinical outcome of laparoscopic colorectal resection for endometriosis. *Am J Obstet Gynecol* 2005; 192: 394–400
- 46 Daraï E, Lesieur B, Dubernard G et al. Fertility after colorectal resection for endometriosis: results of a prospective study comparing laparoscopy with open surgery. *Fertil Steril* 2011; 95: 1903–1908
- 47 Davis L, Kennedy SS, Moore J et al. Modern combined oral contraceptives for pain associated with endometriosis. *Cochrane Database Syst Rev* 2007; 3: CD001019
- 48 Deaton JL, Gibson M, Blackmer KM et al. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. *Fertil Steril* 1990; 54: 1083–1088
- 49 De Cicco C, Corona R, Schonman R et al. Bowel resection for deep endometriosis: a systematic review. *Br J Obstet Gynaecol* 2011; 118: 285–291
- 50 Deguara CS, Pepas L, Davis C. Does minimally invasive surgery for endometriosis improve pelvic symptoms and quality of life? *Curr Opin Obstet Gynecol* 2012; 24: 241–244
- 51 Decker D, König J, Wardelmann E et al. Terminal ileitis with sealed perforation – a rare complication of intestinal endometriosis: case report and short review of the literature. *Arch Gynecol Obstet* 2004; 269: 294–298
- 52 D'Hooghe TM, Denys B, Spiessens C et al. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? *Fertil Steril* 2006; 86: 283–290
- 53 Donnez J, Nisolle M, Gillet N et al. Large ovarian endometriomas. *Hum Reprod* 1996; 11: 641–646
- 54 Donnez J, Jadoul P, Colette S et al. Deep rectovaginal endometriotic nodules: perioperative complications from a series of 3,298 patients operated on by the shaving technique. *Gynecol Surg* 2013; 10: 31–40
- 55 Douay-Hauser N, Yazbeck C, Walker F et al. Infertile women with deep and intraperitoneal endometriosis: comparison of fertility outcome according to the extent of surgery. *J Minim Invasive Gynecol* 2011; 18: 622–628
- 56 Ebert AD, Ulrich U, Keckstein J et al. Implementation of certified endometriosis centers: 5-year experience in German-speaking Europe. *Gynecol Obstet Invest* 2013; 76: 4–9
- 57 Elizur SE, Chian RC, Holzer HE et al. Cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis: a new indication for fertility preservation. *Fertil Steril* 2009; 91: 293.e1–293.e3
- 58 Fedele L, Bianchi S, Raffaelli R et al. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. *Fertil Steril* 1997; 68: 426–429
- 59 Fedele L, Bianchi S, Zanonato G et al. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. *Fertil Steril* 2001; 75: 485–488
- 60 Flower A, Liu JP, Lewith G et al. Chinese herbal medicine for endometriosis. *Cochrane Database Syst Rev* 2012; 5: CD006568
- 61 Ford J, English J, Miles WA et al. Pain, quality of life and complications following the radical resection of rectovaginal endometriosis. *Br J Obstet Gynaecol* 2004; 111: 353–356
- 62 Francica G. Reliable clinical and sonographic findings in the diagnosis of abdominal wall endometriosis near cesarean section scar. *World J Radiol* 2012; 4: 135–140
- 63 Fukunishi H, Funaki K, Yamaguchi K et al. Early results of magnetic resonance-guided focused ultrasound surgery of adenomyosis: analysis of 20 cases. *J Minim Invasive Gynecol* 2008; 15: 571–579
- 64 Furness S, Yap C, Farquhar C et al. Pre and post-operative medical therapy for endometriosis surgery. *Cochrane* 2010; DOI: 10.1002/14651858.CD003678.pub2
- 65 Garcia L, Isaacson K. Adenomyosis: review of the literature. *J Min Invas Gynecol* 2011; 18: 428–437
- 66 Garrido N, Navarro J, Garcia Velasco J. The endometrium versus embryonic quality in endometriosis-related infertility. *Hum Reprod Update* 2002; 8: 95–103
- 67 Garry R. The effectiveness of laparoscopic excision of endometriosis. *Curr Opin Obstet Gynecol* 2004; 16: 299–303
- 68 Giudice LC, Kao LC. Endometriosis. *Lancet* 2004; 364: 1789–1799
- 69 Gordts S, Puttemans P, Campo R et al. Outcome of conservative surgical treatment of deep infiltrating endometriosis. *Gynecol Surg* 2013; 10: 137–141
- 70 Gruppo Italiano per lo Studio dell' Endometriosi. Relationship between stage, site and morphological characteristics of pelvic endometriosis and pain. *Hum Reprod* 2001; 16: 2668–2671
- 71 Gustofson RL, Kim N, Liu S et al. Endometriosis and the appendix: a case series and comprehensive review of the literature. *Fertil Steril* 2006; 86: 298–303
- 72 Guzik DS, Silliman NP, Adamson GD et al. Prediction of pregnancy in infertile women based on the American Society for Reproductive Medicine's revised classification of endometriosis. *Fertil Steril* 1997; 67: 822–829
- 73 Guzik DS, Huang LS, Broadman BA et al. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. *Fertil Steril* 2011; 95: 1568–1573
- 74 Harada T, Momoeda M, Taketani Y et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis—a randomized, double-blind, multicenter, controlled trial. *Fertil Steril* 2009; 91: 675–681
- 75 Harrison RF, Barry-Kinsella C. Efficacy of medroxyprogesterone treatment in infertile women with endometriosis: a prospective, randomised, placebo-controlled study. *Fertil Steril* 2000; 74: 24–30
- 76 Hart RJ, Hickey M, Maouris P et al. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008; 2: CD004992
- 77 Haas D, Chvatal R, Habelsberger A et al. Comparison of revised American Fertility Society and ENZIAN staging: a critical evaluation of classifications of endometriosis on the basis of our patient population. *Fertil Steril* 2011; 95: 1574–1578
- 78 Haas D, Chvatal R, Reichert B et al. Endometriosis – a premenopausal disease? Age pattern in 42,079 patients with endometriosis. *Arch Gynecol Obstet* 2012; 286: 667–670
- 79 Haas D, Chvatal R, Habelsberger A et al. Preoperative planning of surgery for deeply infiltrating endometriosis using the ENZIAN classification. *Eur J Obstet Gynecol Reprod Biol* 2013; 166: 99–103
- 80 Haas D, Shebl O, Shamiyeh A et al. The rASRM score and the Enzian classification for endometriosis: their strengths and weaknesses. *Acta Obstet Gynecol Scan* 2013; 92: 3–7
- 81 Healey M, Ang WC, Cheng C. Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. *Fertil Steril* 2010; 94: 2536–2540
- 82 Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms arising in endometriosis. *Obstet Gynecol* 1990; 75: 1023–1028
- 83 Hornstein MD, Yuzpe AA, Burry KA et al. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis-associated pelvic pain. *Fertil Steril* 1995; 63: 955–962
- 84 Howard FM. An evidence-based medicine approach to the treatment of endometriosis-associated chronic pelvic pain: placebo-controlled studies. *J Am Assoc Gynecol Laparosc* 2000; 7: 477–488
- 85 Online: <http://www.eshre.eu/ESHRE/English/Specialty-Groups/SIG/Endometriosis-Endometrium/Guidelines/page.aspx/244>
- 86 Online: <http://www.awmf.de>
- 87 Hudelist G, Tuttles F, Rauter G et al. Can transvaginal sonography predict infiltration depth in patients with deep infiltrating endometriosis of the rectum? *Hum Reprod* 2009; 24: 1012–1017
- 88 Hudelist G, Oberwinkler KH, Singer CF et al. Combination of transvaginal sonography and clinical examination for preoperative diagnosis of pelvic endometriosis. *Hum Reprod* 2009; 24: 1018–1024
- 89 Hudelist G, Keckstein J. Die Wertigkeit der Vaginalsonographie in der präoperativen Diagnostik der Adenomyose und tief infiltrierenden Endometriose. *praxis* 2009; 98: 603–607

- 90 Hudelist G, English J, Thomas AE *et al.* Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2011; 37: 257–263
- 91 Hudelist G, Fritzer N, Thomas A *et al.* Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod* 2012; 27: 3412–3416
- 92 Hughes E, Fedorkow D, Collins J *et al.* Ovulation suppression for endometriosis. *Cochrane Syst Rev* Cochrane Library, Issue 1. Chichester, UK: John Wiley & Sons, Ltd.; 2005
- 93 Jacobson TZ, Duffy JM, Barlow D *et al.* Laparoscopic surgery for pelvic pain associated with endometriosis. *Cochrane Database Syst Rev* 2009; 4: CD001300
- 94 Jacobson TZ, Duffy JM, Barlow D *et al.* Laparoscopic surgery for subfertility associated with endometriosis. *Cochrane Database Syst Rev* 2010; 1: CD001398
- 95 Jansen RP, Russel P. Nonpigmented endometriosis: clinical, laparoscopic, and pathological definition. *Am J Obstet Gynecol* 1986; 155: 1154–1159
- 96 Jia SZ, Leng JH, Shi JH *et al.* Health-related quality of life in women with endometriosis: a systematic review. *J Ovarian Res* 2012; 5: 29
- 97 Kavallaris A, Mebes I, Evagelinos D *et al.* Follow-up of dysfunctional bladder and rectum after surgery of a deep infiltrating rectovaginal endometriosis. *Arch Gynecol Obstet* 2011; 283: 1021–1026
- 98 Keckstein J, Ulrich U, Kandolf O *et al.* Die laparoskopische Therapie der Darmendometriose und der Stellenwert der medikamentösen Therapie. *Zentralbl Gynäkol* 2003; 125: 259–266
- 99 Keckstein J, Ulrich U. Endokrine und operative Therapie der Adenomyose. *Gynäkol Endokrinol* 2004; 2: 11–18
- 100 Kennedy S, Bergqvist A, Chapron C *et al.*; on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005; 20: 2698–2704
- 101 Kishi Y, Suginami H, Kuramori R *et al.* Four subtypes of adenomyosis assessed by magnetic resonance imaging and their specification. *Am J Obstet Gynecol* 2012; 207: 114.e1–114.e7
- 102 Kissler S, Hamscho N, Zangos S *et al.* Uterotubal transport disorder in adenomyosis and endometriosis—a cause for infertility. *Brit J Obstet Gynaecol* 2006; 113: 902–908
- 103 Kitawaki J, Kusuki I, Yamanaka K *et al.* Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pain. *Eur J Obstet Gynecol Reprod Biol* 2011; 157: 212–216
- 104 Krüger K, Behrendt K, Niedobitek-Kreuter G *et al.* Location-dependent value of pelvic MRI in the preoperative diagnosis of endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2013; 169: 93–98
- 105 Krüger K, Behrendt K, Balzer M *et al.* Relevance of MRI for endometriosis diagnosis. *Röfo* 2011; 183: 423–431
- 106 Kobayashi H, Sumimoto K, Kitanaka T *et al.* Ovarian endometrioma—risks factors of ovarian cancer development. *Eur J Obstet Gynecol Reprod Biol* 2008; 138: 187–203
- 107 Kodama H, Fukuda J, Karube H *et al.* Benefit of in vitro fertilization treatment for endometriosis-associated infertility. *Fertil Steril* 1996; 66: 974–979
- 108 Kondo W, Bourdel N, Tamburro S *et al.* Complications after surgery for deeply infiltrating pelvic endometriosis. *Br J Obstet Gynaecol* 2011; 118: 292–298
- 109 Kupfer M, Schwimmer S, Lebonic J. Transvaginal sonographic appearance of endometrioma: Spectrum of findings. *J Ultrasound Med* 1992; 11: 129–133
- 110 Lazzeri L, Di Giovanni A, Exacoustos C *et al.* Preoperative and postoperative clinical and transvaginal ultrasound findings of adenomyosis in patients with deep infiltrating endometriosis. *Reprod Sci* 2014; 21: 1027–1033
- 111 Lea R, Bancroft K, Whorwell PJ. Irritable bowel syndrome, chronic pelvic inflammatory disease and endometriosis: a comparison of symptomatology. *Eur J Gastroenterol Hepatol* 2004; 16: 1269–1272
- 112 Lenhard M, Stieber P, Hertlein L *et al.* The diagnostic accuracy of two human epididymis protein 4 (HE4) testing systems in combination with CA125 in the differential diagnosis of ovarian masses. *Clin Chem Lab Med* 2011; 49: 2081–2088
- 113 Leyendecker G, Kunz G, Noe M *et al.* Endometriosis: a dysfunction and disease of the archimetra. *Hum Reprod Update* 1998; 4: 752–762
- 114 Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet* 2009; 280: 529–538
- 115 Littman E, Giudice L, Lathi R *et al.* Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. *Fertil Steril* 2005; 84: 1574–1578
- 116 Lovrinčević M. Chronic pelvic pain in women of childbearing age. *Curr Opin Anaesthesiol* 2003; 16: 275–280
- 117 Lusuardi L, Hager M, Sieberer M *et al.* Laparoscopic treatment of intrinsic endometriosis of the urinary tract and proposal of a treatment scheme for ureteral endometriosis. *Urology* 2012; 80: 1033–1038
- 118 Mabrouk M, Ferrini G, Montanari G *et al.* Does colorectal endometriosis alter intestinal functions? A prospective manometric and questionnaire-based study. *Fertil Steril* 2012; 97: 652–656
- 119 Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. *Canadian Collaborative Group on Endometriosis*. *N Engl J Med* 1997; 337: 217–222
- 120 Matalliotakis I, Mahutte NG, Koukoura O *et al.* Endometriosis-associated stage IA clear cell ovarian carcinoma in a woman with IVF-ET treatments in the Yale series. *Arch Gynecol Obstet* 2006; 274: 184–186
- 121 McDermott S, Oei TN, Iyer VR *et al.* MR imaging of malignancies arising in endometriomas and extraovarian endometriosis. *Radiographics* 2012; 32: 845–863
- 122 Melin A, Sparen P, Bergqvist A. The risk of cancer and the role of parity among women with endometriosis. *Hum Reprod* 2007; 22: 3021–3026
- 123 Meredith SM, Sanchez-Ramos L, Kaunitz AM. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis. *Am J Obstet Gynecol* 2009; 201: 107.e1–107.e6
- 124 Meuleman C, Tomassetti C, D'Hoore A *et al.* Surgical treatment of deeply infiltrating endometriosis with colorectal involvement. *Hum Reprod Update* 2011; 17: 311–326
- 125 Meuleman C, Tomassetti C, D'Hooghe TM. Clinical outcome after laparoscopic radical excision of endometriosis and laparoscopic segmental bowel resection. *Curr Opin Obstet Gynecol* 2012; 24: 245–252
- 126 Meyer R. Über den Stand der Frage der Adenomyositis, Adenomyome im Allgemeinen und insbesondere über Adenomyositis seroepithelialis und Adenomyometritis sarcomatosa. *Zentralbl Gynäkol* 1919; 36: 745–750
- 127 Minelli L, Fanfani F, Fagotti A *et al.* Laparoscopic colorectal resection for bowel endometriosis: feasibility, complications, and clinical outcome. *Arch Surg* 2009; 144: 234–239
- 128 Modugno F, Ness RB, Allen GO *et al.* Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004; 191: 733–740
- 129 Moen MH, Rees M, Brincat M *et al.*; European Menopause and Andropause Society. EMAS position statement: managing the menopause in women with a past history of endometriosis. *Maturitas* 2010; 67: 94–97
- 130 Moini A, Riaz K, Amid V *et al.* Endometriosis may contribute to oocyte retrieval-induced pelvic inflammatory disease: report of eight cases. *J Assist Reprod Genet* 2005; 22: 307–309
- 131 Mol BW, Bayram N, Lijmer JG *et al.* The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998; 70: 1101–1108
- 132 Moore J, Copley S, Morris J *et al.* A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. *Ultrasound Obstet Gynecol* 2002; 20: 630–634
- 133 Morita M, Asakawa Y, Nakakuma M *et al.* Laparoscopic excision of myometrial adenomyomas in patients with adenomyosis uteri and main symptoms of severe dysmenorrhea and hypermenorrhea. *J Am Assoc Gynecol Laparosc* 2004; 11: 86–89
- 134 Muzii L, Marana R, Caruana P *et al.* The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. *Fertil Steril* 1996; 65: 1235–1237
- 135 Muzii L, Maneschi F, Marana R *et al.* Oral estrogestins after laparoscopic surgery to excise endometriomas: continuous or cyclic administration? Results of a multicenter randomized study. *J Minim Invasive Gynecol* 2011; 18: 173–178
- 136 Nagle CM, Olsen CM, Webb PM *et al.*; Australian Cancer Study Group; Australian Ovarian Cancer Study Group. Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors. *Eur J Cancer* 2008; 44: 2477–2484

- 137 Nezhat C, Seidman DS, Nezhat F et al. Laparoscopic surgical management of diaphragmatic endometriosis. *Fertil Steril* 1998; 69: 1048–1055
- 138 Nisolle M, Casanas-Roux BS, Anaf V et al. Morphometric study of the stromal vascularization in peritoneal endometriosis. *Fertil Steril* 1993; 59: 681–684
- 139 Olson JE, Cerhan JR, Janney CA et al. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. *Cancer* 2002; 94: 1612–1618
- 140 Opoien HK, Fedorcsak P, Byholm T et al. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. *Reprod Biomed Online* 2011; 23: 389–395
- 141 Opoien HK, Fedorcsak P, Omland AK et al. In vitro fertilization is a successful treatment in endometriosis-associated infertility. *Fertil Steril* 2012; 97: 912–918
- 142 Osada H, Silber S, Kakinuma T et al. Surgical procedure to conserve the uterus for future pregnancy in patients suffering from massive adenomyosis. *Reprod Biomed Online* 2011; 22: 94–99
- 143 Ozaki T, Takahashi K, Okada M. Live birth after conservative surgery for severe adenomyosis following magnetic resonance imaging and gonadotropin-releasing hormone agonist therapy. *Int J Fertil Womens Med* 1999; 44: 260–264
- 144 Ozel I, Sagioglu J, Unal A et al. Abdominal wall endometriosis in the cesarean section surgical scar: a potential diagnostic pitfall. *J Obstet Gynaecol Res* 2012; 38: 526–530
- 145 Pagidas K, Falcone T, Hemmings R et al. Comparison of reoperation for moderate (stage III) and severe (stage IV) endometriosis-related infertility with in vitro fertilization-embryo transfer. *Fertil Steril* 1996; 65: 791–795
- 146 Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. *Hum Reprod* 1999; 14: 1332–1334
- 147 Payá V, Hidalgo-Mora JJ, Diaz-Garcia C et al. Surgical treatment of rectovaginal endometriosis with rectal involvement. *Gynecol Surg* 2011; 8: 269–277
- 148 Pearce CL, Templeman C, Rossing MA et al.; on behalf of the Ovarian Cancer Association Consortium. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet* 2012; 13: 385–394
- 149 Pepas L, Deguara C, Davis C. Update on the surgical management of adenomyosis. *Curr Opin Obstet Gynecol* 2012; 24: 259–264
- 150 Pereira RM, Zanatta A, Preti CD et al. Should the gynecologist perform laparoscopic bowel resection to treat endometriosis? Results over 7 years in 168 patients. *J Minim Invasive Gynecol* 2009; 16: 472–479
- 151 Petraglia F, Hornung D, Seitz C et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. *Arch Gynecol Obstet* 2012; 285: 167–173
- 152 Pisanu A, Deplano D, Angioni S et al. Rectal perforation from endometriosis in pregnancy: case report and literature review. *World J Gastroenterol* 2010; 16: 648–651
- 153 Possover M, Diebolder H, Plaul K et al. Laparoscopically-assisted vaginal resection of rectovaginal endometriosis. *Obstet Gynecol* 2000; 96: 304–307
- 154 Possover M. Laparoscopic management of neural pelvic pain in women secondary to pelvic surgery. *Fertil Steril* 2009; 91: 2720–2725
- 155 Redwine DB. Diaphragmatic endometriosis: diagnosis, surgical management, and long-term results of treatment. *Fertil Steril* 2002; 77: 288–296
- 156 Renner SP, Rix S, Boosz A et al. Preoperative pain and recurrence risk in patients with peritoneal endometriosis. *Gynecol Endocrinol* 2009; 28: 1–6
- 157 Revidierte ENZIAN Klassifikation. 10. Weissenseetreffen der Stiftung Endometriose Forschung. Weissensee, Kärnten, 25.–27. Februar 2011
- 158 Rickes D, Nickel I, Kropf S et al. Increased pregnancy rates after ultralong postoperative therapy with gonadotropin-releasing hormone analogs in patients with endometriosis. *Fertil Steril* 2002; 78: 757–762
- 159 Rozsnyai F, Roman H, Resch B et al.; CIRENDO Study Group. Outcomes of surgical management of deep infiltrating endometriosis of the ureter and urinary bladder. *JSLs* 2011; 15: 439–447
- 160 Roman H, Rozsnyai F, Puscasiou L et al. Complications associated with two laparoscopic procedures used in the management of rectal endometriosis. *J Soc Laparoendosc Surg* 2010; 14: 169–177
- 161 Roman H, Ness J, Suciu N et al. Are digestive symptoms in women presenting with pelvic endometriosis specific to lesion localizations? A preliminary prospective study. *Hum Reprod* 2012; 27: 3440–3449
- 162 Saleh A, Tulandi T. Reoperation after laparoscopic treatment of endometriomas by excision and fenestration. *Fertil Steril* 1999; 72: 322–324
- 163 Sallam H, Garcia-Velasco J, Dias S et al. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006; 2: CD004635
- 164 Sampson JA. Peritoneal endometriosis due to menstrual dissemination of the endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927; 14: 422
- 165 Sampson JA. Metastatic or embolic endometriosis due to the menstrual dissemination of endometrial tissue into the venous circulation. *Am J Pathol* 1927; 3: 93–109
- 166 Sarmini R, Lefholz K, Froeschke H. A comparison of laparoscopic supracervical hysterectomy and total abdominal hysterectomy outcomes. *J Min Invas Gynecol* 2005; 12: 121–124
- 167 Schuster MW, Wheeler TL 2nd, Richter HE. Endometriosis after laparoscopic supracervical hysterectomy with uterine morcellation: a case control study. *J Minim Invasive Gynecol* 2012; 19: 183–187
- 168 Schweppe KW. Endometriose – Eine Erkrankung ohne Lobby. *Zentralbl Gynäkol* 2003; 125: 233
- 169 Seracchioli R, Mabrouk M, Frascà C et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. *Fertil Steril* 2010; 93: 52–56
- 170 Sesti F, Capozzolo T, Pietropolli A et al. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. *Eur J Obstet Gynecol Reprod Biol* 2009; 147: 72–77
- 171 Shakiba K, Bena JF, McGill KM et al. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstet Gynecol* 2008; 111: 1285–1292
- 172 Shaw RW. *An Atlas of Endometriosis*. Carnforth-Pearl River: Parthenon Publishing Group; 1993
- 173 Siedentopf F, Hrsg. Chronischer Unterbauchschmerz der Frau. Leitlinie der Deutschen Gesellschaft für Psychosomatische Frauenheilkunde und Geburtshilfe. Berlin: Verlag S. Kramarz; 2009
- 174 Sillem M, Teichmann AT. Patientinnenzentrierte Aspekte der Endometriose. *Gynäkologe* 2003; 36: 41–52
- 175 Soliman NF, Hillard TC. Hormone replacement therapy in women with past history of endometriosis. *Climacteric* 2006; 9: 325–335
- 176 Somigliana E, Arnoldi M, Benaglia L et al. IVF-ICSI outcome in women operated on for bilateral endometriomas. *Hum Reprod* 2008; 23: 1526–1530
- 177 Soriano D, Schonman R, Nadu A et al. Multidisciplinary team approach to management of severe endometriosis affecting the ureter: long-term outcome data and treatment algorithm. *J Minim Invasive Gynecol* 2011; 18: 483–488
- 178 Steege JF. Basic Philosophy of the integrated Approach: overcoming the Mind-Body-Split. In: Steege JF, Metzger DA, Levy BS, eds. *Chronic pelvic Pain: an integrated Approach*. Philadelphia: WB Saunders; 1998: 5–12
- 179 Stepienewska A, Pomini P, Bruni F et al. Laparoscopic treatment of bowel endometriosis in infertile women. *Hum Reprod* 2009; 24: 1619–1625
- 180 Strowitzki T, Marr J, Gerlinger C et al. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. *Hum Reprod* 2010; 25: 633–641
- 181 Swiersz LM. Role of endometriosis in cancer and tumor development. *Ann NY Acad Sci* 2002; 995: 281–292
- 182 Takamura M, Koga K, Osuga Y et al. Post-operative oral contraceptive use reduces the risk of ovarian endometrioma recurrence after laparoscopic excision. *Hum Reprod* 2009; 24: 3042–3048
- 183 Tietjen GE, Bushnell CD, Herial NA et al. Endometriosis is associated with prevalence of comorbid conditions in migraine. *Headache* 2007; 47: 1069–1078
- 184 Tsoumpou I, Kyrgiou M, Gelbaya TA et al. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. *Fertil Steril* 2009; 92: 75–87
- 185 Tummon IS, Asher LJ, Martin JS et al. Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis. *Fertil Steril* 1997; 68: 8–12

- 186 Tuttles F, Keckstein J, Ulrich U et al. ENZIAN-score. Eine Klassifikation der tiefen infiltrierenden Endometriose. Zentralbl Gynäkol 2005; 127: 275–281
- 187 Ulrich U, Rhiem K, Kaminski M et al. Parametrial and rectovaginal adenocarcinoma arising from endometriosis. Int J Gynecol Cancer 2005; 15: 1206–1209
- 188 Ulrich U, Nawroth F, Dorn C. Endometriose. Klinik, Diagnostik und Therapie. In: Ludwig M, Hrsg. Gynäkologische Endokrinologie und Reproduktionsmedizin. München: Hans Marseille Verlag; 2010: 219–227
- 189 Ulrich U, Drienko E, Müller F et al. Chirurgische Therapie der Endometriose: Möglichkeiten und Grenzen. Med Forsch/Exzellenzforschung in der Medizin 2012; 3: 56–62
- 190 Van Gorp T, Amant F, Neven P et al. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. Best Pract Res Clin Obstet Gynaecol 2004; 18: 349–371
- 191 Van Holsbeke C, Van Calster B, Guerriero S et al. Endometriomas: their ultrasound characteristics. Ultrasound Obstet Gynecol 2010; 35: 730–740
- 192 Vercellini P, Vendola N, Bocciolone L et al. Laparoscopic aspiration of ovarian endometriomas. Effect with postoperative gonadotropin releasing hormone agonist treatment. J Reprod Med 1992; 37: 577–580
- 193 Vercellini P, Trespidi L, Colombo A et al. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril 1993; 60: 75–79
- 194 Vercellini P, Trespidi L, De Giorgi O et al. Endometriosis and pelvic pain: relation to disease stage and localization. Fertil Steril 1996; 65: 299–304
- 195 Vercellini P, Frontino G, DeGiorgi O. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003; 80: 560–563
- 196 Vercellini P, Aimi G, Busacca M et al. Laparoscopic uterosacral ligament resection for dysmenorrhea associated with endometriosis: results of a randomized, controlled trial. Fertil Steril 2003; 80: 310–319
- 197 Victory R, Diamond MP, Johns DA. Villar's nodule: a case report and systematic literature review of endometriosis externa of the umbilicus. J Minim Invasive Gynecol 2007; 14: 23–32
- 198 Vlahos NF, Kalampokas T, Fotiou S. Endometriosis and ovarian cancer: a review. Gynecol Endocrinol 2009; 28: 1–7
- 199 Vlahos NF, Economopoulos KP, Fotiou S. Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. Best Pract Res Clin Obstet Gynaecol 2010; 24: 39–50
- 200 Volpi E, Peano E, Ferrero A et al. Association between ovarian endometriosis and malignancy in the peri-menopausal period: report of two cases and review of the literature. Gynecol Surg 2008; 7: 13–17
- 201 Wada S, Kudo M, Minakami H. Spontaneous uterine rupture of a twin pregnancy after a laparoscopic adenomyomectomy: a case report. J Minim Invasive Gynecol 2006; 13: 166–168
- 202 Walter AJ, Hentz JG, Magtibay PM et al. Endometriosis: correlation between histologic and visual findings at laparoscopy. Am J Obstet Gynecol 2001; 184: 1407–1411
- 203 Wiesender CCT. Pelvic Pain Clinic: a multidisciplinary Approach. In: Li TC, Ledger WL, ed. Chronic pelvic Pain. Abingdon-Oxford: Taylor & Francis; 2012: 197–210
- 204 Yeung P Jr., Sinervo K, Winer W et al. Complete laparoscopic excision of endometriosis in teenagers: is postoperative hormonal suppression necessary? Fertil Steril 2011; 95: 1909–1912
- 205 Yu HT, Huang HY, Soong YK et al. Laparoscopic ovarian cystectomy of endometriomas: surgeons' experience may affect ovarian reserve and live-born rate in infertile patients with in vitro fertilization-intracytoplasmic sperm injection. Eur J Obstet Gynecol Reprod Biol 2010; 152: 172–175
- 206 Zanetta GM, Webb MJ, Li H et al. Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis. Gynecol Oncol 2000; 79: 18–22
- 207 Zheng H, Gao Y. Serum HE4 as a useful biomarker in discriminating ovarian cancer from benign pelvic disease. Int J Gynecol Cancer 2012; 22: 1000–1005
- 208 Zhu X, Proctor M, Bensoussan A et al. Chinese herbal medicine for primary dysmenorrhoea. Cochrane Database Syst Rev 2008; 16: CD005288
- 209 Zhu X, Hamilton KD, McNicol ED. Acupuncture for pain in endometriosis. Cochrane Database Syst Rev 2011; 9: CD007864
- 210 Zilberman S, Ballester M, Touboul C et al. Partial colectomy is a risk factor for urologic complications of colorectal resection for endometriosis. J Minim Invasive Gynecol 2013; 20: 49–55
- 211 Zupi E, Marconi D, Sbracia M et al. Add-back therapy in the treatment of endometriosis-associated pain. Fertil Steril 2004; 82: 1303–1308

Note

Oral contraceptives and levonorgestrel-releasing intrauterine systems are not approved for the treatment of endometriosis in Germany. They can, therefore, only be used on an off-label basis.