

# DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS **2014**

TURKISH ENDOMETRIOSIS &  
ADENOMYOSIS SOCIETY  
GUIDELINES

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## **Abbreviations Used in the Guideline**

<b><i>BMI</i></b>	<i>Body mass index</i>
<b><i>CT</i></b>	<i>Computerized tomography</i>
<b><i>EOC</i></b>	<i>Epithelial ovarian cancer</i>
<b><i>GnRH</i></b>	<i>Gonadotropin releasing hormone</i>
<b><i>ICSI</i></b>	<i>Intracytoplasmic sperm injection</i>
<b><i>IUI</i></b>	<i>Intrauterine insemination</i>
<b><i>IVF</i></b>	<i>In vitro fertilization</i>
<b><i>IBS</i></b>	<i>Irritable bowel syndrome</i>
<b><i>IC</i></b>	<i>Interstitial cystitis</i>
<b><i>COC</i></b>	<i>Combined oral contraceptive</i>
<b><i>LNG-IUS</i></b>	<i>Levonorgestrel-releasing intrauterine system</i>
<b><i>MPA</i></b>	<i>Medroxyprogesterone acetate</i>
<b><i>MRI</i></b>	<i>Magnetic resonance imaging</i>
<b><i>NSAID</i></b>	<i>Non-steroidal anti-inflammatory drug</i>
<b><i>RCS</i></b>	<i>Randomized controlled study</i>
<b><i>SPRM</i></b>	<i>Selective progesterone receptor modulator</i>
<b><i>TAUS</i></b>	<i>Transabdominal ultrasonography</i>
<b><i>TVUS</i></b>	<i>Transvaginal ultrasonography</i>
<b><i>ART</i></b>	<i>Assisted reproductive techniques</i>
<b><i>3D USG</i></b>	<i>Three dimensional ultrasonography</i>

## **METHODOLOGY FOR PREPARATION OF THIS GUIDELINE**

*Available evidence was qualitatively assessed using the GRADE system ([www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)). Presenting recommendations whenever an intervention was concerned, we presented our opinion based on relevant literature for other descriptive questions. .*

*Quality of evidence and recommendations are two separate but related entities in the GRADE system. Regarding effectiveness, randomized controlled trials start as high-quality and observational studies start as low-quality evidence. However, each study is individually evaluated for methodological features, accuracy of effectiveness estimates, directness of selected outcome measures, consistency of findings across similar studies and possible publication bias. Consequently, randomized controlled trials can be downgraded whereas observational studies can be upgraded. Descriptions of evidence quality are shown in Table 1.*

*There are only two categories of recommendations for easiness of interpretation. Alongside quality of evidence, adverse effects, complication profile, cost, accessibility, and magnitude of effectiveness of an intervention are also taken into consideration during formulation of a recommendation. For instance, it is possible to make a strong recommendation in favour of a procedure supported by low-quality evidence; due to a modest magnitude of effect and limited number of studies, if the adverse effect profile is good, complication risk and cost is low. The GRADE system inevitably involves some subjectivity as the others, yet it is transparent and enables the reader to make his/her inference. Descriptions of recommendation level are shown in Table 2.*

<b>Table 1. Descriptions of Quality of Evidence</b>	
<b>High-quality</b>	<i>Further research is very unlikely to change our confidence in estimating the effect</i>
<b>Moderate-quality</b>	<i>Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate</i>
<b>Low-quality</b>	<i>Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate</i>
<b>Very low-quality</b>	<i>Any estimate of effect is very uncertain</i>

<b>Table 2. Descriptions of Strength of Evidence</b>		
<b>QUALITY of EVIDENCE</b>	<b>STRENGTH of EVIDENCE</b>	<b>DESCRIPTIONS of EVIDENCE</b>
<i>High</i>	<i>Strong</i>	<i>It is apparent that desired effect of the intervention is greater than its adverse effect</i>
<i>Moderate</i>		
<i>Low</i>	<i>Weak</i>	<i>Although quality of evidence is not high, it is possible that the desired effect to be greater than the adverse effects or in near-equilibrium</i>
<i>Very low</i>		

## CONTENTS

<i>Section 1</i>	<i>Endometriosis: Diagnosis and Assessment</i>	<b>7</b>
<i>Section 2</i>	<i>Endometriosis and Pain</i>	<b>16</b>
<i>Section 3</i>	<i>Endometriosis and Infertility</i>	<b>28</b>
<i>Section 4</i>	<i>Deep Endometriosis</i>	<b>43</b>
<i>Section 5</i>	<i>Extragenital Endometriosis</i>	<b>53</b>
<i>Section 6</i>	<i>Asymptomatic Endometriosis</i>	<b>56</b>
<i>Section 7</i>	<i>Adolescent Endometriosis</i>	<b>60</b>
<i>Section 8</i>	<i>Endometriosis in Perimenopausal and Menopausal Period</i>	<b>67</b>
<i>Section 9</i>	<i>Endometriosis and Pregnancy</i>	<b>72</b>
<i>Section 10</i>	<i>Recurrence of Endometriosis</i>	<b>76</b>
<i>Section 11</i>	<i>Endometriosis and Cancer</i>	<b>80</b>
<i>Section 12</i>	<i>Can Endometriosis be Prevented?</i>	<b>85</b>
<i>Section 13</i>	<i>Adenomyosis</i>	<b>98</b>
<i>Appendix</i>	<i>List of guidelines of the other countries and societies</i>	<b>100</b>

# ENDOMETRIOSIS: DIAGNOSIS and ASSESSMENT

Which and How often symptoms are seen in endometriosis?

Although dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclic intestinal complaints, tiredness/fatigue and infertility are often encountered symptoms in endometriosis, the value of any of the symptoms in the prediction of endometriosis is unknown (Kennedy et al., 2005; Nnoaham et al., 2011). Thus, there is no pathognomonic symptom for endometriosis. In general, the frequencies of the symptoms are reported as: dysmenorrhea; 60-80%, pelvic pain;30-50%, infertility; 30-40%, dyspareunia; 25-40%, menstrual irregularity; 10-20%, cyclic dysuria-hematuria; 1-2%, cyclic rectal bleeding: 1% (Eskenazi and Warner, 1997). Since it is reported that there may be 7-12 year delay from the onset of initial symptoms to the diagnosis of endometriosis, the possibility of endometriosis should be considered in the young women with pelvic pain (Ballard et al., 2006; Nnoaham et al., 2011; Hudelist et al., 2012). The severity and character of the endometriosis-related pain rarely shows correlation with extent of the disease. Abdominopelvic pain, dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia, postcoital bleeding, ovarian cyst in patients with or without previously diagnosed endometriosis, irritable bowel syndrome and history of pelvic inflammatory disease are the risk factors for endometriosis. Additionally, a significant number of cases of endometriosis may be completely asymptomatic.

*There is a wide spectrum of symptoms of endometriosis. Although none of the symptoms are specific for endometriosis; it is strongly recommended to consider endometriosis in the presence of dysmenorrhea, non-cyclic pelvic pain, deep dyspareunia, infertility, and chronic fatigue in addition to one of these complaints.*

Which diseases can be misdiagnosed as endometriosis?

Entry of different nerve fibers into the same spinal cord neurons due to overlapping of pain pathways of the visceral organs may cause difficulty in description and localization of visceral pain in terms of differential diagnosis. Perception of the pain in a different region away from the source of pain due to overlapping of somatic structures on the pain pathways can be perceived as skin or deep-tissue hyperalgesia. Therefore, complaint of pain may be derived from all systems that can cause chronic pain. Non-gynecological causes of pain that are frequently seen and can be misdiagnosed as endometriosis are: interstitial cystitis (IC) and irritable bowel syndrome (IBS). Among cases with the pre-diagnosis of IC, 38% had endometriosis and 28% had IBS whereas among cases with pre-diagnosis of IBS, 41% has endometriosis and 31% had IC (Ballard et al., 2008).

Non-gynecological causes of pain except IC and IBS should be investigated thoroughly by multidisciplinary approach by disciplines of Internal Medicine, Rheumatology, Urology, Gastroenterology, Physical Therapy & Rehabilitation and Psychiatry etc.

*Due to overlapping on the pain pathways, endometriosis-related pain can be misdiagnosed with the other causes of chronic pain. Pathologies that are frequently misdiagnosed as endometriosis are interstitial cystitis and irritable bowel syndrome. It is strongly recommended that the patient should be evaluated with an integrated approach and the other non-gynecological causes of pain should be considered in differential diagnosis.*

How should a patient with suspected endometriosis be examined?

Since the examination that is to be performed during or around menstruation will facilitate the palpation of the nodules, it is recommended to perform examination during menstrual or perimenstrual period in a patient considered to have endometriosis.

During the pelvic examination, presence of endometriotic lesion on the perineum, in the vagina and cervix should be sought, and position, size and mobility of uterus and adnexae should be assessed.

Pelvic tenderness, fixed retroverted uterus, tender and nodular uterosacral ligaments or adnexal enlargement are important diagnostic clues for endometriosis (Bazot et al., 2009). However, absence of these findings does not exclude the disease. When deep infiltrating nodules in uterosacral ligaments or Douglas space are present, and/or visible lesions in the vagina or cervix are present, probability of endometriosis increases considerably (Bazot et al., 2009).

In the presence of adnexal mass in women with the complaint of pelvic pain, possibility of endometrioma should be considered.

*It is strongly recommended to perform pelvic examination in patients with suspected endometriosis. If vaginal examination cannot be performed in the adolescents or in the individuals without previous sexual activity, rectal examination will be helpful in the diagnosis of endometriosis.*

*Since moderate-quality evidence suggests that the perimenstrual period is the period when the deep infiltrating nodules are felt most easily, performing pelvic examination in this period may increase the sensitivity of the examination.*

In the presence of adnexal mass in women with the complaint of pelvic pain, possibility of endometrioma should be considered.

*It is strongly recommended to consider the probability of deep endometriosis in cases with presence of vaginal nodule in the posterior vaginal fornix, and painful induration and/or nodule in the rectovaginal wall especially during perimenstrual period.*

*Normal physical examination does not exclude the presence of endometriosis.*

How much do examination findings give an idea about localization or natural course of endometriosis?

Although a fixed retroverted uterus could be due to presence of severe adhesion, it was observed that there had been no specific findings in 32% of the cases with stage 3-4 endometriosis. Endometriosis was not found in 19% of the patients with pre-diagnosis of endometriosis. The correlation between the extent of the endometriotic lesions and pelvic tenderness is weak.

The frequency and character of pain symptoms or pelvic examination findings are not sufficient to evaluate the localization or to predict the natural course of the endometriosis (Davis et al., 1993; Forman et al., 1993; Lemaire, 2004; Thomassin et al., 2004; Seracchioli et al., 2008; Luscombe et al., 2009; Bellelis et al., 2010).

What is the role of imaging methods in diagnosis of endometriosis? Ultrasonography:

Endometrioma is usually seen as a cystic structure comprising of one to four locules and in ground-glass echogenicity by ultrasonography (US). Despite the fact that avascular polypoid structures can be seen in approximately 10% of the cystic structures with confirmed histological diagnosis of endometrioma, presence of vascularization within polypoid structure makes the diagnosis of endometrioma suspicious. Sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of transvaginal (TVUS) and transabdominal USG (TAUS) for the diagnosis of endometrioma were reported as 64-89%; 89-100%; 7.6 - 29.8 and 0.1 - 0.4, respectively. Briefly, except small cysts, the diagnosis of endometrioma can be confirmed or excluded by TVUS using the described features (Moore et al., 2002).

The value of TVUS in the diagnosis of peritoneal endometriosis is fairly limited, compared to the laparoscopy.

Although sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of three dimensional (3D) US for the diagnosis of rectovaginal endometrioma were reported to be 89.5 (73.3-94.5)%, 94.7 (78.6-99.7)%, 17.2 (2.51-115) and 0.11 (0.03-0.41), respectively; there are limited number of cases, and the role of 3D US in the diagnosis of rectovaginal endometriosis has not been precisely defined (Pascual et al., 2010).

Extraperitoneal endometriosis and deep endometriosis can be determined using transrectal US (Hudelist et al., 2011). Contours and thickness of uterosacral ligaments, a common localization of pelvic endometriosis, can be evaluated with this method. When deep invasive (e.g. intestinal or urinary bladder invasion) endometriosis is suspected, although there aren't enough reliable data, additional tests such as TVUS or transrectal US, MRI, colonography with or without barium enema may be necessary in determining the extent of the disease.

For the urinary bladder, the following additional tests can be recommended: TVUS using the full-bladder technique, cystoscopy and biopsy. For the ureter, MRI or computerized tomography (CT) urogram can be recommended. It should be remembered that the success of the imaging methods is operator-dependent.

#### Magnetic Resonance Imaging (MRI):

Considering that the laparoscopic diagnosis is the gold standard, the sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for MRI in the diagnosis of endometriosis are reported as 86%, 75%, 2.76 and 0.41, respectively. Routine use of MRI in the diagnosis of endometriosis is not recommended due to its high cost (Stratton et al., 2003).

What is the place of biochemical markers and serum CA-125 in the diagnosis of endometriosis?

There are gynecological and non-gynecological causes of elevated CA-125. Gynecological causes include endometriosis, adenomyosis, functional ovarian cysts, leiomyoma, menstruation, pregnancy, pelvic inflammation, benign ovarian neoplasms, ovarian Sertoli-Leydig cell tumors, epithelial ovarian cancer, endometrial cancer, cervical adenocarcinomas, ovarian stimulation, Meig's syndrome, cancer of the fallopian tube and germ cell tumors. In a meta-analysis, the value of CA-125 testing in the diagnosis of the disease at any stage was found to be limited in patients with surgically confirmed endometriosis according to the results of 23 studies (Mol et al., 1998). In the review of 182 studies performed on this issue, it was shown that none of the markers was helpful in the confirmation of diagnosis, but the most promising ones were nerve fibers and the molecules that were playing a role in cell cycle control, adhesion and angiogenesis. (May and et al; 2011). It was reported that CA-125 measurements demonstrated a very limited value in the diagnosis of stage I/II endometriosis but it had better role in diagnosis of stage III/IV endometriosis. Investigation of suspected endometriosis includes history, physical examination and imaging methods. Routine CA-125 testing should not be performed as a part of the diagnostic investigation of endometriosis (Mol et al., 1998; May et al., 2010, 2011). Other markers have no place in daily clinical practice, either.

*Since the benefits of the biological marker including CA-125 measured in the serum, endometrial tissue, menstrual blood or other uterine fluids have not been proven in the diagnosis of endometriosis, Guideline Development Group strongly recommends against using these markers in routine clinical practice.*

What is the place of laparoscopy in the diagnosis of endometriosis?

Endometriosis is suspected based on the patient's history, symptoms and examination findings. The diagnosis is presumed by using general and pelvic examination and imaging methods. However, definitive diagnosis is made by histopathological investigation of the surgically obtained tissues. Typical appearances of endometriosis implants in the abdominal cavity are regarded as the evidence of the disease in many cases. Presence of endometrial glands and/or stroma in the tissue samples is considered to be the gold standard for the diagnosis of the disease (Kennedy et al., 2005).

Starting the empirical treatment based on the symptoms and examination/imaging methods without laparoscopy and/or histological verification -although it is controversial- gradually becomes more widely accepted (Ling, 1999; Jenkins et al., 2008). Especially in adolescents, empirical treatment can be initiated directly without performing laparoscopy just for demonstrating the presence of the disease (Chapron et al., 2011). However, there are no good quality studies evaluating the efficiency of this approach. Additionally, even though peritoneal endometriosis foci are observed in laparoscopy, it should be remembered that there may be a cause of pain other than endometriosis and the pain may not subside with treatment for endometriosis. Therefore, all patients considered to have intervention should be informed about all of the possibilities.

Clinical examination and imaging methods are used increasingly, especially in the diagnosis of deep endometriosis, whereas laparoscopy takes place as a therapeutic procedure rather than a diagnostic procedure.

It should be remembered that overuse of diagnostic laparoscopy does not only increase the cost alone but also poses the risks of complication. Laparoscopy has a mortality risk of 1:10000 and the risks of injury of bowel, urinary bladder or major blood vessels of 2.4:10000 (Xu et al., 2008). Diagnostic laparoscopy is an invasive procedure and it should not be performed by an inexperienced surgeon who is not capable of managing the complications.

Although diagnostic laparoscopy is a minor surgery, it should be kept in mind that its complications may require major surgery (Hassa H, 1987).

In brief, if concurrent therapeutic intervention is not planned, it is not necessary to make definitive diagnosis before medical treatment of the endometriosis-associated symptoms. In the presence of endometrioma and/or deep infiltrating disease –when the risk of malignancy is low-to reveal the rare cases with malignancy, laparoscopy may be recommended to take sample for pathological investigation when higher risk is suspected after reviewing all risk factors. It is strongly recommended to take a tissue sample for pathological investigation, when an “endometriotic” focus is observed in a patient during laparoscopy.

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## **ENDOMETRIOSIS and PAIN**

Chronic pelvic pain is present in 15-20% of women, and 40% of diagnostic laparoscopies are performed due to chronic pelvic pain (As-Sanie et al., 2012). Endometriosis was found in one-third of the women undergoing laparoscopy due to chronic pelvic pain (Howard 2000). Although it was generally stated that endometriosis was present in 33% of the women with chronic pelvic pain, it ranges 2-80% in the studies (Guo and Wang 2006). Fifty-five percent of the women with endometriosis have a complaint of chronic pelvic pain (Klein et al., 2014).

Endometriosis, with the most prominent symptom of pain, is a common, chronic inflammatory disease which is mostly in progressive nature. The etiology of the disease is not fully elucidated, and the frequency or the severity of the symptoms seems to be independent from the stage of endometriosis.

What are the medical treatment options in endometriosis-associated pain?

Medical treatment necessarily used in endometriosis is not specific, and is for relieving the pain. Absence of a definite cure for the disease, the need to use medical treatment until the menopause or time of desire for pregnancy necessitates the medical treatment to be efficient and safe.

Are non-steroidal anti-inflammatory drugs effective in relieving endometriosis-associated pain?

The efficacy of NSAIDs was shown in the treatment of primary dysmenorrhea but it could not be shown in relieving endometriosis-associated pain (Ailen et al., 2009). Due to easy access, NSAIDs can be tried as a first-line therapy of endometriosis-associated pain (Dunselman et al., 2014). While prescribing NSAIDs, side effect profile of the drugs (ovulation inhibition, gastric ulceration and cardiovascular disease) should be discussed with the patient.

*Guideline Development Group gives a weak recommendation for using NSAIDs and the other analgesics in the treatment of endometriosis-associated pain.*

Is hormonal therapy effective in relieving pain considered to be endometriosis-associated?

Hormonal therapy used for the treatment of endometriosis-associated pain includes the followings: contraceptives, progestins, selective progesterone receptor modulators (SPRM) and anti-progestins, GnRH analogues and aromatase inhibitors. A marked difference could not be shown between these drugs regarding the efficacy in relieving pain (Brown and Farquhar 2014; Cheong et al., 2014).

There is high-quality evidence indicating that hormonal contraceptives, progestins, selective progesterone receptor modulators and anti-progestins, GnRH analogues and aromatase inhibitors are effective in relieving endometriosis-associated pain.

Guideline Development Group recommends choosing the most appropriate agent in the hormonal treatment of endometriosis-associated pain by considering the adverse effects, efficiency, cost and accessibility in addition to patient preferences.

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### Combined Oral Contraceptives (COC)

Contraceptive drugs combining estrogen and progesterone are considered to be first-line treatment in endometriosis-associated pain. Despite the fact that they have been using them for a long time, the number of randomized controlled trials related to COCs is limited, compared to other medical treatment methods (Vercellini et al., 1993; Davis et al., 2007).

*There is moderate-quality evidence supporting the efficacy of combined oral contraceptives in reducing endometriosis-associated dysmenorrhea.*

*There is low-quality evidence supporting the efficacy of combined oral contraceptives in reducing endometriosis-associated dyspareunia and non-menstrual pelvic pain.*

*There is low-quality evidence regarding the use of the contraceptive vaginal ring or transdermal patch (estrogen/progesterone) in reducing endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain.*

*Guideline Development Group gives a strong recommendation for using hormonal contraceptives in the treatment of endometriosis-associated pain.*

### Progestins, selective progesterone receptor modulators and anti-progestins

Since estrogen may stimulate the development of endometriotic focus, and progestins show anti-proliferative and pro-apoptotic effects in both eutopic and ectopic endometrium, progestin-only drugs are widely used for treatment of endometriosis-associated pain in recent years (Brown et al., 2012). Thus, the drug group other than COCs, recommended as a first-line therapy in the treatment of endometriosis-associated pain is progestins (Leyland et al., 2010; Dunselman et al., 2014).

#### Norethindrone Acetate (NETA)

It was shown that low doses (5–20 mg/day) of NETA were effective in reducing the pain of the patients with chronic pelvic pain and endometriosis (Brown et al., 2012). Continuous use of NETA with this indication has been approved by American Food and Drug Administration (FDA).

#### Dienogest

Dienogest is a selective progestin having pharmacological properties of both 19-norprogesterone and progesterone derivatives. Therefore, along with showing potent progestational action in the endometrium, it has also systemic anti-androgenic activity.

There is a randomized placebo controlled study indicating that dienogest (2 mg/day) reduces pelvic pain and dysmenorrhea (Strowitzki et al., 2010a; Strowitzki et al., 2010b; Jeng et al., 2014). Its efficacy in relieving pelvic pain is equivalent to the efficacy of GnRH analogues. Additionally, there are case series indicating its efficacy in reducing both the size of lesion and the pain in deep endometriosis and extrapelvic endometriosis.

#### Depot medroxyprogesterone acetate (DMPA)

It was shown that DMPA was effective in reducing pain in the patients with chronic pelvic pain and endometriosis (Cheong et al., 2014). Its efficacy in reducing pain was found to be similar with that of leuprolide acetate. Use of DMPA with this indication has been approved by American Food and Drug Administration (FDA). However, its use is not common due to its side effects of irregular bleeding and negative effect on the bone mineral density.

#### Danazol

Danazol has been one of the most commonly used agents for medical treatment of endometriosis until the last two decades. Danazol that can be used orally is a weak androgen and it causes amenorrhea by inhibiting the gonadotropin release. In spite of its efficacy in reducing endometriosis-associated pain, danazol causes many androgenic side effects. Therefore, danazol regimens at lower doses or using vaginal route were tried. Use of danazol with this indication has been approved by American Food and Drug Administration (FDA).

#### Levonorgestrel-releasing intrauterine system (LNG-IUS)

Levonorgestrel which is a potent 19-nortestosterone-derivative progestin has a potent anti-estrogenic action in the endometrium. A commercially available LNG-IUS causes endometrial atrophy in 60% of the patients by locally releasing 20 mcg of levonorgestrel daily without inhibition of ovulation. There are studies indicating that LNG-IUS is effective in reducing endometriosis-associated pain (Petta et al., 2005; Abou-Setta et al., 2013; Brown and Farquhar 2014).

Since LNG is released locally and absorbed into the systemic circulation in minimal amounts, systemic side effects of LNG-IUS are low.

The LNG-IUS may be an effective therapy for rectovaginal endometriosis, decreasing dysmenorrhea and non-menstrual pelvic pain as well as reducing deep dyspareunia and dyschezia. There is moderate-quality evidence indicating the efficiency of LNG-IUS in the treatment of endometriosis-associated pain and adenomyosis (Petta et al., 2005; Abou-Setta et al., 2013; Cheong et al., 2014; Dunselman et al., 2014).

### SPRM and anti-progestins

There is a RCT indicating that gestrinone is effective in reducing endometriosis-associated pain. Since the trials using SPRM and anti-progestins (telapristone acetate, mifepristone and ulipristal acetate) are still ongoing, no recommendation is made for using them yet.

*There is moderate-quality evidence indicating the efficiency of progestins in reducing endometriosis-associated pain and their use is strongly recommended. Guideline Development Group strongly recommends considering the side effect profile in selection of progestins.*

*There is moderate-quality evidence indicating the efficiency of levonorgestrel-releasing intrauterine system in reducing endometriosis-associated pain and its use is strongly recommended.*

### GnRH analogues

There are many RCTs indicating that GnRH agonists are effective in reducing endometriosis-associated pain (Brown et al., 2010; Brown and Farquhar 2014; Cheong et al., 2014). However, use of a GnRH agonist alone causes many hypestrogenic side effects. Hot flashes, insomnia, vaginal dryness, loss of libido and decreased BMD, which is sometimes irreversible, are some of these side effects. Thus, GnRH agonist treatment is recommended as second-line treatment together with add-back therapy (estrogen and/or progestin or tibolone). Use of GnRH agonist with this indication has been approved by American Food and Drug Administration (FDA).

There is no evidence indicating the efficiency of GnRH antagonist in treatment of endometriosis-associated pain.

*There is high-quality evidence indicating the efficiency of GnRH agonists (nafarelin, leuprolide, buserelin, goserelin or triptorelin) in the treatment of endometriosis-associated pain. Guideline Development Group strongly recommends using GnRH agonists as second-line treatment in reducing endometriosis-associated pain.*

*It is strongly recommended to add an addback therapy from the commencement of GnRH agonist therapy to reduce the hypestrogenic symptoms and risk of bone mineral density decrease.*

## Aromatase Inhibitors

There is limited number of studies evaluating the efficiency of aromatase inhibitors in reducing endometriosis-associated pain (Nawathe et al., 2008; Ferrero et al., 2011). Due to their side effects, it is recommended to use them together with progestin or COC in premenopausal women with endometriosis (Ferrero et al., 2011). It may be an option for patients with rectovaginal endometriosis and for postmenopausal endometriosis. Additionally, its use can be considered in the women refractory to all other options of medical or surgical treatment.

*There is low-quality evidence supporting the efficacy of aromatase inhibitors in reducing endometriosis-associated pain.*

*Guideline Development Group gives a weak recommendation to use aromatase inhibitors in the women with rectovaginal endometriosis, and the patients' refractory to all other medical or surgical treatments.*

Does empirical treatment have a place in the management of endometriosis-associated pain?

Medical treatment can be prescribed for women suffering from pelvic pain with a high suspicion of endometriosis without performing a diagnostic laparoscopy. The aim of this approach is to avoid laparoscopy as an invasive and costly procedure. This empirical treatment method is widely used in adolescents and young women with complaints of pelvic pain and dysmenorrhea (Johnson et al., 2013; Cheong et al., 2014; Dunselman et al., 2014; Practice Committee of the American Society for Reproductive 2014). It is common practice to perform laparoscopy for definitive diagnosis if the patient does not respond to the empirical treatment. On the other hand, response of the patients to the empirical treatment is not accepted as the definitive evidence of the presence of endometriosis.

*Guideline Development Group strongly recommends trying the medical empirical treatment in the management of pelvic pain, considered to be associated with endometriosis.*

*Combined oral contraceptives or progestins are strongly recommended as first-line treatment in empirical treatment.*

*It is necessary to exclude the other causes of pelvic pain before commencement of the treatment.*

Is surgical treatment is effective in the management of endometriosis-associated pain?

A Cochrane meta-analysis of five randomized controlled trials comparing diagnostic laparoscopy alone and surgical treatment of endometriosis laparoscopically showed that the pain was improved considerably in the surgically-treated group (Jacobson, et al., 2010). If found during laparoscopy, it is recommended to treat endometriosis surgically (see and treat approach) as this approach has been shown to be effective for reducing endometriosis-associated pain.

Despite laparoscopy and laparotomy are equally effective in the treatment of endometriosis-associated pain; due to lower risk of adhesion formation, a shorter duration of hospitalization and better cosmetic results following laparoscopic surgery, and, currently it is accepted as standard approach.

*There is high-quality evidence supporting the efficacy of surgical treatment of endometriosis found during laparoscopy, and Guideline Development Group strongly recommends treating endometriotic lesions surgically.*

How should the surgical approach be for endometrioma?

Medical treatment for endometrioma may cause a transient reduction in size of cyst; but it cannot make a complete resolution. Therefore, surgical approach is considered for the symptomatic or large endometriomas. Conservative surgical options are excision of cyst wall, drainage and/or coagulation/ablation of the cyst.

Recurrence rates of endometrioma and pain after cyst excision are lower than ablation or fenestration of cyst wall (Hart et al., 2008). However, it should be remembered that surgical excision of the endometrioma wall may have negative impact on the ovarian reserve. In many studies, it was shown that surgical excision of the endometrioma has reduced the ovarian reserve (Biacchiardi et al., 2011; Celik et al., 2012; Raffi et al., 2012; Somigliana et al., 2012; Uncu et al., 2013; Alborzi et al., 2014).

In endometrioma surgery, no superiority of one energy modality to the others was shown.

*There is high-quality evidence indicating that after cystectomy, the recurrence rates are lower and the pain is better controlled compared to after drainage and coagulation. And Guideline Development Group strongly recommends preferring cystectomy; if the surgical treatment of endometrioma is planned.*

How should a surgical approach be in management of pain associated with deep infiltrating endometriosis?

There is moderate-quality evidence indicating that the surgical treatment reduces the pain and also improves the quality of life.

Guideline Development Group strongly recommends referring the patients with suspected or diagnosed deep endometriosis to a center of expertise that offers all available treatments in a multidisciplinary context; including urologist and colorectal surgeon.

Does hysterectomy have a place in the management of endometriosis-associated pain?

Hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO) can be preferred in women having failed to respond to the other treatments and having completed their family. Success of this approach is based on atrophy of endometriotic foci after surgical menopause. Hormonal treatment after surgical menopause may pose the risk of recurrence. Although it is considered that estrogen treatment alone may cause higher recurrence compared to combined estrogen plus progesterone regimens, there is no study comparing these two treatments directly. Continuous combined estrogen-progestogen therapy is recommended therapy regimen to treat the symptoms after surgical menopause in women with endometriosis.

*Guideline Development Group gives a weak recommendation to perform hysterectomy with bilateral salpingo-oophorectomy in women who have completed their family and failed to respond to the other conservative treatments, and to remove all of endometriotic foci observed.*

Is surgical destruction of pelvic nerve pathways effective in the treatment of endometriosis-associated pain?

There is high-quality evidence indicating that performing laparoscopic uterosacral nerve ablation, as an additional procedure to conservative surgery in reducing endometriosis-associated pain, is not effective. And Guideline Development Group strongly recommends not performing LUNA for the treatment of endometriosis-associated pain.

There is high-quality evidence indicating that performing presacral neurectomy is effective in reducing endometriosis-associated midline pain, but it requires a high degree of surgical skill and experience, and Guideline Development Group gives a weak recommendation to perform presacral neurectomy for the treatment of endometriosis-associated midline pain.

**Does preoperative hormonal therapy have a place in the treatment of endometriosis-associated pain?**

There is moderate-quality evidence indicating that preoperative hormonal therapy is not beneficial in the treatment of endometriosis-associated pain, and Guideline Development Group strongly recommends not prescribing preoperative hormonal therapy.

Does postoperative hormonal therapy have a place in the treatment of endometriosis-associated pain?

There is moderate-quality evidence indicating that postoperative hormonal therapy is not beneficial in the treatment of endometriosis-associated pain. Although Guideline Development Group strongly recommends not prescribing postoperative hormonal therapy, group gives a weak recommendation to prescribe long-term (> 6 months) postoperative hormonal therapy to reduce the risk of recurrence and to prolong the symptom-free interval.

Is secondary prevention against pain symptoms possible in women with surgically treated endometriosis?

Secondary prevention is the measures taken to prevent the recurrence of disease or pain symptoms in long-term (more than 6 months after surgery).

*There is high-quality evidence indicating that prescribing combined oral contraceptives in women performed **cystectomy for ovarian endometrioma** and not desiring the pregnancy in postoperative period reduces the recurrence rate, and it is strongly recommended*

*There is high-quality evidence indicating that prescribing postoperative use of combined oral contraceptives, progestin or a levonorgestrel-releasing intrauterine system in women operated for endometriosis for at least 18–24 months reduces the postoperative recurrence rate and symptoms; and it is strongly recommended to use them as one of the options for the secondary prevention.*

Are there alternative complementary therapy options in reducing endometriosis-associated pain?

Chronic pelvic pain, due to endometriosis, can lead to pain related to the musculoskeletal system by causing postural changes and muscle contractures. Referring the patients to the physiotherapists, specialized in pelvic floor rehabilitation can be useful for complaint of pain. Additionally, it can also be necessary to refer the patients to the psychiatrists to struggle with psychological stress and depression associated with chronic pelvic pain. It can be beneficial to incorporate algology specialist into the treatment for application of some other treatment modalities such as neuroleptic drugs and neural blockade as well as for harmonization of analgesic therapy.

Acupuncture can also be included in complementary therapies for chronic pelvic pain due to endometriosis. In two randomized blind studies designed specifically for the pain management in endometriosis, it was shown that pain was reduced more markedly with acupuncture (Wayne et al., 2008, Rubi-Klein et al., 2010).

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# ENDOMETRIOSIS AND INFERTILITY

## Does endometriosis cause infertility?

Although some old studies have reported the prevalence of endometriosis in women with infertility to be 50%, the actual prevalence is probably less (Williams and Pratt 1977).

Even though endometriosis is reported to be encountered in 1-7% of women during tubal ligation, the same studies have reported the presence of varying degrees of endometriosis in 17-20% of women operated laparoscopically for infertility (Strathy et al. 1982; Mahmood and Templeton 1991; Sang Haghpeykar and Poindexter 1995). The possibility of women diagnosed with endometriosis at a later stage of their lives to present with infertility is much higher than women without endometriosis (Odds ratio 8.2, 95% confidence interval 6.9-9.9) (Ballard et al 2008).

Clinical trials have shown the pregnancy rates in IUI cycles in women with endometriosis to be half of that of women without endometriosis (Jansen 1986; Toma et al. 1992, Omland et al 1998). Furthermore, pregnancy rates with IVF treatment have been reported to be lower in women with endometriosis than in women treated with IVF for tubal factor (Barnhart et al. 2002). One report on oocyte donation cycles has shown the presence of endometriosis in the donor to decrease implantation rates in the receiver (Simon et al 1994).

When all these observations are considered together, endometriosis and infertility seem to be related; however, the causal relationship and possible mechanisms have not been clearly demonstrated yet.

Distortion of pelvic anatomy; the harmful effects of increased inflammatory activity in the peritoneal cavity on tubal function, oocytes, sperm and/or embryos; progesterone resistance in eutopic endometrium; decreased expression of integrins and increased production of immunoglobulins are among the possible mechanisms (Shifren et al. 1996; Toya et al. 2000; Norenstedt et al 2001; Burney et al 2007).

## In which infertile patients should the diagnosis of endometriosis be considered?

The other main symptom of endometriosis besides infertility is pain. Although the predictive value of symptoms is not high, the possibility of endometriosis should be considered in women indicating infertility and symptoms of abdominopelvic pain, dysmenorrhea, deep dyspareunia, cyclic discharge and cyclic hematuria (Ballard et al. 2008).

The vaginal walls, posterior fornix and rectovaginal septum should be inspected thoroughly during physical examination and blue coloured areas suggestive of endometriosis should be sought for. The presence of a small external cervical os (pinpoint cervix), lateralized cervix, effaced fornices, painful nodules on the uterosacral ligaments or vaginal wall, a fixed retroverted uterus, and adnexal masses are suggestive of endometriosis. The absence of findings during physical examination does not rule out endometriosis. Ultrasonographic findings consistent with endometriomas and/or adenomyosis will support the diagnosis of endometriosis.

## **Should diagnostic laparoscopy be offered to women presenting with infertility to investigate the presence of endometriosis?**

The gold standard for the diagnosis of endometriosis is laparoscopy and histology. The benefit of performing diagnostic laparoscopy in women without painful symptoms or findings suggestive of endometriosis in physical examination or imaging studies, and the concomitant treatment of endometriosis when encountered in such patients is a matter of debate.

The findings of two randomized controlled trials investigating the effect of surgical treatment of mild endometriosis on spontaneous and ongoing pregnancies/live deliveries was homogeneously evaluated in a Cochrane meta-analysis, and surgical treatment was found to increase ongoing pregnancy rates significantly (Odds ratio:1.64,95% confidence interval:1.05–2.57)(Marcoux et al.1997; Parazzini 1999; Jacobson et al. 2010). However the impact of this positive effect is limited and the number of patients that need to be operated (the number in need of treatment) to achieve one more pregnancy following laparoscopic destruction of foci is 12, with a 95% confidence interval of 7-112. If the frequency of encountering endometriosis is estimated as 20-50% when performing laparoscopy in couples with unexplained infertility, the number of patients that need surgery to achieve one more pregnancy will be 24-60. On the other hand, the results of the Canadian and Italian studies included into the Cochrane meta-analysis contradict each other and may not be considered homogenous. In this case, the OR and 95% significance interval will be calculated as 1.45 and 0.65-3.21, respectively; leading to the assumption that surgical treatment does not have a significant effect on fertility. In another meta-analysis, the Italian study was excluded due to post-operative GnRH treatment and a small scale randomized controlled trial involving 41 patients was included (Duffy et al 2014). In this meta-analysis the Odds ratio to achieve ongoing pregnancies over 20 weeks/ live births was reported to be 1.94 (95% confidence interval 1.20-3.16). Taking these data into account, the number to treat will become 9 (95% confidence interval 4.9-30) and the recommendations for clinical practice will remain the same.

Taking the presence of contradictory findings, lack of a significant benefit of surgery, risk of complications, and less than 50% prevalence of endometriosis in patients with unexplained infertility into account, it does not seem appropriate to recommend laparoscopy for the detection and treatment of endometriosis in infertile women without symptoms suggestive of endometriosis.

*Guideline Development Group recommends **against** laparoscopy for the detection of endometriosis in the absence of symptoms suggestive of endometriosis or other indications for surgery in patients presenting with infertility.*

Does surgical treatment of early stage endometriosis increase fertility?

Endometriotic foci detected in infertile women receiving laparoscopic surgery for other reasons should be destroyed; since the destruction of endometriotic foci increases the probability of achieving spontaneous pregnancy.

There is no strong evidence that excision, cauterization or laser vaporization of endometriotic foci is more effective than the other in achieving fertility (Chang et al. 1997; Marcoux et al.1997).

***Moderate quality evidence suggests that destruction or excision of endometriotic foci in infertile women increases fertility, and the destruction or excision of endometriotic foci detected during surgery is strongly recommended.***

Does surgical treatment of advanced stage endometriosis increase fertility?

There is no high quality or randomized study investigating the effect of surgical treatment on fertility in infertile women with painful symptoms and/or physical/ultrasonographic findings suggestive of advanced stage endometriosis. The available non –controlled studies have reported cumulative spontaneous pregnancy rates of 46-77% over a three-year follow up period, however the reliability of these surgical studies are somewhat limited due to many factors (Nezhat et al 1989; Vercellini et al. 2009). The results of studies investigating the occurrence of spontaneous conception following surgical excision of rectovaginal lesions in women with deep infiltrating endometriosis are conflicting (Vercellini et al 2006b; Donnez and Squifflet 2010). This may be due to differences in the characteristics of the study populations and the possibility that unwanted outcomes were excluded from the studies. (Meuleman et al 2011). Surgery for deep infiltrative endometriosis is often complex and is associated with relatively high complication rates. Due to the complex nature of both endometriosis and infertility, it will not be appropriate to group these patients into a single one and recommend an algorithm that will be applicable to all.

Each patient must be evaluated individually taking into consideration the age, localization of endometriotic lesions, size, unilaterality/bilaterality and risk of malignancy of endometriotic cysts, presence of other factors associated with infertility, ovarian reserve and previous surgical treatment.

Except for the purpose of ruling out the malignancy, it is inappropriate to offer surgical treatment in order to increase fertility and await spontaneous pregnancy for patients who should have already been referred to ART due to other factors such as severe oligospermia, azospermia, bilateral tubal occlusion or low ovarian reserve.

***Evidence suggesting that surgical treatment of advanced stage endometriosis will improve fertility is very weak. The surgical treatment of advanced stage endometriosis requires expertise and complication rates are not low. Therefore, in the absence of other reasons for surgery, it is not recommended to offer surgery in advanced stage endometriosis for the sole purpose of improving fertility.***

**Does surgery for endometriomas increase the probability of spontaneous pregnancy?**

Endometriotic cysts negatively affect ovarian reserve (Uncu et al 2013). Nevertheless, there is strong evidence that excision of endometriomas leads to a further decrease in ovarian reserve. Furthermore, there is no evidence pointing to an increase in ovulation rates following endometrioma excision (Raffi et al 2012; Somigliana et al 2012; Uncu et al 2013). There are non-controlled case series suggesting increased spontaneous pregnancy rates following endometrioma surgery, however there are no randomized controlled trials (Vercellini et al 2006a; Dunselman et al 2014).

***There is low quality evidence suggesting that endometrioma excision improves fertility and the Guideline Development Group recommends the decision to operate on endometriomas to be individualized, having considered the other factors (bilaterality, ovarian reserve, etc.)***

Surgical removal of endometriomas may be recommended to rule out malignancy after evaluation of the age of the patient, size of endometrioma and other morphological characteristics suggestive of malignancy; management of cyst rupture or torsion or to render oocyte pickup possible in patients referred to ART who have endometriomas that will hamper oocyte pickup; because of their location.

<b><i>The excision of endometriomas is strongly recommended in infertile women with suspicions of</i></b>
<b><i>malignancy or for the management of acute events as cyst rupture or torsion</i></b>

*It is strongly recommended to avoid endometrioma surgery prior to ART cycles due to the presence of high quality evidence suggesting that endometrioma surgery does not increase pregnancy rates. Endometrioma surgery should be considered on an individual basis in cases when it will render oocyte pickup possible in “otherwise” inaccessible ovaries.*

Which approach should be chosen in the surgical treatment of endometriomas?

If endometrioma surgery is going to be carried out, cystectomy should be performed since spontaneous pregnancy rates by this approach are higher than those achieved after drainage or ablation (Hart et al 2008).

*If endometrioma surgery will be performed, there is high-quality evidence supporting that the recurrence rate of the endometrioma is lower and the probability of pregnancy is higher after cystectomy, compared to drainage and ablation; and cyst excision is strongly recommended. Cyst excision can be more difficult in small ovarian endometriotic cysts and there are concerns that blood supply to the ovary can be damaged. Therefore, in excision of small ovarian endometriotic cysts, ablation by leaving the floor of the cyst in situ can be considered.*

**Are alternative hemostatic methods more protective of ovarian reserve than bipolar cauterization after endometrioma excision?**

There are a small number of studies comparing the use of electrocautery with sutures for hemostasis following endometrioma excision (Fedele et al. 2004; Li et al 2009; Ferrero et al 2012; Li et al 2013; Takashima et al 2013) or hemostatic gel matrixes (Sonmezer et al 2013). Although there are conflicting data about hemostasis with suturing, the method adversely affecting ovarian reserve parameters most seems to be bipolar cautery. Even though rare, there are reports of small bowel obstruction requiring surgical treatment and thrombosis leading to morbidity and mortality after the application of hemostatic gels. The safety of these gels is limited in gynecological surgery and considering the extra cost, it does not seem appropriate to recommend their use in all patients. Irrespective of the method used for hemostasis, minimal use of electrocautery is important for the preservation of ovarian reserve. Studies suggest that some amount of loss in ovarian reserve is inevitable, independent of the hemostatic method used.

*There is moderate quality evidence indicating that bipolar cauterization following endometrioma excision leads to decreased ovarian reserve. Evidence suggesting that alternative hemostatic methods would be more advantageous is weak. It is strongly recommended to use as minimal cauterization as possible following endometrioma excision.*

*Due to the presence of limited data on the safety of hemostatic gels and lack of strong evidence indicating its superiority over cauterization regarding the preservation of ovarian reserve, the Guideline Development Group weakly recommends against the use of hemostatic gels.*

*There is low quality evidence indicating that suturization instead of bipolar cauterization for hemostasis after endometrioma excision leads to a lesser loss of ovarian reserve. It is recommended for the surgeon to choose the most suitable mode of hemostasis; according to his/her endoscopic suturing experience and the available equipment..*

Does the use of adhesion barriers surgery increase fertility after endometriosis?

There is no data on postoperative pregnancy rates and the use of adhesion barriers following endometriosis surgery.

The risk of postoperative adhesions and the probability of these adhesions to adversely affect fertility are dependent on the inherent characteristics of the surgical procedures themselves.

Adhesion barriers increase the cost of surgery and may lead to complications such as bowel obstruction.

*There is no evidence supporting the routine use of adhesion barrier gels following endometriosis surgery in infertile patients*

## **Does medical treatment increase fertility in endometriosis associated infertility?**

According to a Cochrane meta-analysis of more than 800 patients, inhibition of ovulation with GnRH analogues, oral contraceptives, progestins or danazol for the medical treatment of endometriosis does not increase pregnancy rates when used alone or following surgical treatment. Therefore, medications that inhibit ovulation should not be prescribed for patients with endometriosis desiring pregnancy (Hughes et al 2007).

*There is high-quality evidence indicating that medical treatments suppressing ovulation do not improve endometriosis-associated infertility and Guideline Development Group strongly rejects using these treatments.*

Do alternative and complementary therapies improve fertility in endometriosis-associated infertility?

There is no methodologically reliable evaluation of alternative medicine practices in infertile women with endometriosis. Consequently, since the possible adverse effects can not be ruled out, it will not be appropriate to practice such therapies except in controlled trials.

*There is very low-quality evidence regarding the efficiency of alternative and complementary therapies in endometriosis-associated infertility. Guideline Development Group weakly recommends against alternative and complementary therapy.*

Does tubal flushing with lipiodol increase fertility in a woman already known to have endometriosis and bilateral tubal patency?

In a subgroup analysis of a randomized controlled trial including women with unexplained infertility, a 4.4 fold increase in the probability of spontaneous pregnancy within 6 months after uterine lavage and tubal flushing with lipiodol was found (11% vs 48 %). This effect was found to be diminished in the two year follow up of the same study (Johnson et al 2004; Johnson et al 2007).

*There is moderate quality evidence indicating that tubal flushing with lipiodol increases the probability of spontaneous pregnancy in women with endometriosis and bilateral tubal patency. Guideline Development Group weakly recommends to await spontaneous pregnancy for 6 months following tubal flushing in ovulatory women with endometriosis and partners with normal semen parameters*

Does pentoxifylline increase fertility in women with endometriosis?

According to a Cochrane review including three small scale randomized controlled trials, pentoxifylline administration does not increase in pregnancy rates compared with placebo or untreated follow-up (Lu et al., 2012).

*There is moderate-quality evidence indicating that pentoxifylline treatment does not improve fertility in infertile women with endometriosis and Guideline Development Group strongly recommends against the use of pentoxifylline.*

Are assisted reproductive technologies effective in the treatment of endometriosis associated infertility?

In this section, the term assisted reproduction refers to ovulation induction, controlled ovarian stimulation, intravaginal, intracervical and intrauterine insemination and assisted reproductive technologies (ART). The term ART has been used to describe vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

Gonadotropin-Intrauterine insemination (IUI) leads to approximately 5 fold higher pregnancy and live birth rates, compared to those spontaneous follow up in patients with early stage endometriosis (Nulsen et al 1993, Tummen et al 1997). Gonadotropin -IUI provides better pregnancy rates than IUI alone or paracervical insemination (Nulsen et al 1993; Matorras et al 2010). Although higher pregnancy rates are achieved when compared with expectant management, the cumulative pregnancy/live birth rates after 4-6 cycles of Gonadotropin -IUI are in the range of 4-11%(Nulsen et al 1993; Tummon et al 1997; Matorras et al 20109).

*There is high-quality evidence indicating that pregnancy rate is increased in early stage endometriosis-associated infertility using gonadotropin + IUI. Since the cumulative pregnancy rates can be low with this treatment, it is recommended to take into consideration age, duration of infertility, ovarian reserve and semen analysis results in management.*

Are ART success rates lower in women with endometriosis than those with other causes of infertility?

There is disagreement about how endometriosis affects pregnancy rates in ART cycles. According to a meta-analysis published in 2002, although the pregnancy rates were lower in women with stage III-IV endometriosis than those with tubal factor (OR: 0.46, 95% CI: 0.28-0.74), there was no difference in those with stage I-II endometriosis (OR: 0.79, 95% CI: 0.6-1.03) (Barnhart et al 2002). However it is interesting to note that the results obtained from large national databases of women diagnosed with endometriosis are not worse.

*There is moderate-quality evidence indicating that pregnancy rates obtained after assisted reproductive technologies in women with endometriosis are lower than those with tubal factor infertility. However, because ARTs provide the highest pregnancy rates, Guideline Development Group strongly recommends ART as effective treatment of infertile women with endometriosis.*

What is the protocol of choice in assisted reproductive technology cycles in infertile women with endometriosis?

It appears that long term downregulation with GnRH agonists for 3-6 months in ART cycles increases pregnancy rates approximately 4 fold (Sallam et al 2006).

*There is high-quality evidence supporting that 3-6 months of GnRH agonist suppression increases pregnancy rates in infertile women with endometriosis undergoing ART treatment. Guideline Development Group strongly recommends using "ultralong" protocol including GnRH agonist suppression for 3–6 months as preferred therapy option before ovarian stimulation. Since long-term gonadal suppression may negatively affect ovarian response, alternative protocols can be considered in the patients with reduced ovarian reserve.*

Is routine antibiotic prophylaxis necessary during oocyte pickup in women with endometriosis?

Although there are case series reporting an increased risk of infection during oocyte pickup in women with endometriosis, the fact that no infection was reported in a prospective study of 214 patients not having received any antibiotic prophylaxis is relieving (Benaglia et al 2008; Seyhan et al 2014). Nevertheless, it may be appropriate to administer prophylactic antibiotics before the oocyte pickup procedure in women with endometriosis.

*There is low-quality evidence suggestive of routine antibiotic prophylaxis in women with endometriosis before oocyte retrieval procedure may decrease the risk of infection after the procedure. Infection is a rare event in these patients; therefore, Guideline Development Group gives a weak advice for administering routine antibiotic prophylaxis during oocyte retrieval procedure.*

Does surgical treatment of endometriomas prior to assisted reproductive technology cycles improve the pregnancy rate?

The management of endometriomas prior to ART cycles has been discussed above and due to the lack of data on the beneficial effects of endometrioma excision on ART results, it is not recommended to perform surgery solely for this purpose (Benschop et al 2010).

*There is high-quality evidence indicating that routine surgical treatment of endometriomas prior to assisted reproductive technology cycles does not increase pregnancy rate and Guideline Development Group strongly recommends against routine excision of endometriomas prior to the assisted reproductive technology cycles.*

Does ovarian stimulation for purpose of assisted reproductive technology increase the risk of recurrence of endometriosis?

Three retrospective studies evaluating the risk of recurrence of endometriosis after assisted reproductive technology cycles in the patients with endometriosis have consistently reported no increased recurrence rates (D'Hooghe et al., 2006; Benaglia et al., 2010; Coccia et al., 2010). A short-term estrogen rise, due to controlled ovarian hyperstimulation, does not seem to be an important risk factor for recurrence of endometriosis.

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# DEEP ENDOMETRIOSIS

What is deep endometriosis?

Deep endometriosis is defined as the involvement of the rectovaginal, vesicouterine cavities, intestinal or urinary system in endometriosis.

How often are the deep endometriosis, peritoneal endometriosis or endometrioma concurrent?

Women with deep endometriosis may also have other forms of endometriosis. In a case series with deep endometriosis consisting of ninety two patients, only 6.5% of women had deep endometriosis alone (Somigliana et al. 2004). Peritoneal endometriotic implants, endometrioma and pelvic adhesions were observed in 61%, 50% and 74% of the patients, respectively. In addition, when the endometrioma is concurrently present, the possibility of more than one nodule increases (Chapron et al. 2009).

What are the symptoms and findings of rectovaginal and intestinal endometriosis?

Chronic hypogastric-pelvic pain, dysmenorrhea necessitates the use of oral contraceptives, deep dyspareunia and pain during defecation are associated with deep endometriosis (Lafay Pillet et al. 2014). Menstrual diarrhea and rarely bloody stool may occur (Koninckx et al. 2012).

The vaginal nodules in the posterior vaginal fornix, fixed uterus and painful nodules during rectovaginal examination may suggest deep endometriosis. Only 50% of the patients show findings during examination (Koninckx et al. 2012).

What is the role of ultrasonography in the assessment of the patients with rectovaginal and intestinal endometriosis?

When transvaginal and transrectal ultrasonography is performed by qualified person, it has a sensitivity of >85% to diagnose deep endometriosis, and may also be beneficial to determine the depth of involvement (Hudelist et al. 2011;

Reid et al. 2014). However, its sensitivity to diagnose the lesions at or proximal to sigmoid colon is low (Hudelist et al. 2011). In a prospective study, it was reported that 3D ultrasonography provides a sensitivity and specificity of 95% and of 90%, respectively (Pascual et al. 2010). Success of ultrasonography in the diagnosis of deep endometriosis depends on the experience of the operator performing ultrasonography (Tammaa et al. 2014).

*It is strongly recommended that the patients suspected to have deep endometriosis should be assessed by an experienced operator using transvaginal and transrectal ultrasonography.*

What is the diagnostic role of other imaging methods in patients with rectovaginal or intestinal endometriosis?

MRI has high sensitivity to determine the location of deep endometriosis in rectum, sigmoid colon, Douglas cavity and anterior vaginal compartment in patients suspected to have deep endometriosis (Saba et al. 2014). There is no difference between standard and high resolution MRI, but the experience of the radiologist is utmost important (Scardapene et al. 2014). Double contrast radiography may be helpful in determination of the stenosis caused by lesions in sigmoid or rectosigmoid regions (Koninckx et al. 2012). Colonoscopy does not provide any additional benefit unless there is a significant occlusion, but it can be used in exclusion of primary intestinal cancer (Koninckx et al. 2012).

*When deep endometriosis is suspected, it is strongly recommended that MRI is evaluated by experienced radiologists.*

*It is strongly recommended that contrast colon radiography should be performed when stenosis, due to endometric lesions, is suspected in sigmoid or rectosigmoid areas.*

Is the medical treatment effective on pain, gastrointestinal complaints and fertility in patients with rectovaginal or intestinal endometriosis?

Administration of norethisterone acetate at 2.5 mg/day for 12 months was found to be as effective as surgery in treatment of dyspareunia in patients with rectovaginal endometriosis (Vercellini et al. 2012). The sexual function and improvements in quality of life were similar during 12-month follow-up (Vercellini et al. 2013).

The use of low-dose oral contraceptive pill for twelve months decreased both pain and the size of the rectovaginal nodules determined by imaging methods (Ferrari et al. 2012).

Further studies are needed to assess the improvement in gastrointestinal complaints and the effect on fertility in patients with intestinal involvement outside the pelvis (Vercellini et al. 2009a).

There is medium-quality evidence proving that the medical treatment is effective on pain in patients with rectovaginal or intestinal endometriosis and it is strongly recommended that medical treatment should be tried prior to offering a surgery.

Is the surgical treatment effective on pain, gastrointestinal complaints and fertility in patients with rectovaginal or intestinal endometriosis?

In a systematic review consisting of 49 studies, it was reported that the surgical treatment of deep endometriosis decreased pain and improved life quality regardless of the preferred surgical method (Meuleman et al. 2011). Decrease in pain was between 71% and 93% at the end of one year (De Cicco et al. 2011). The possibility of pain recurrence that requires repeated surgery differs based on the definitions used, but it varies between 0% and 34% after a follow-up period of 2-5 years (De Cicco et al. 2011).

A significant improvement was reported in the patients with gastrointestinal complaints, particularly constipation and pain during defecation (Ruffo et al. 2014). In terms of fertility, further studies are needed to see whether the surgical treatment of deep endometriosis is helpful in achieving pregnancy before assisted reproduction techniques or for spontaneous conception. In an uncontrolled prospective study, the cumulative spontaneous pregnancy rate was 44% at the end of one year (Meuleman et al. 2014). In a systematic review consisting of 11 studies, the cumulative pregnancy rate for one year was 24% in infertile women (Vercellini et al. 2012).

*There is medium quality evidence for surgical treatment providing improvement in pain and gastrointestinal symptoms in patients with rectovaginal and intestinal endometriosis.*

*It is strongly recommended that surgical treatment should be offered to patients with lumen obstruction or who do not respond to medical treatment.*

*There is no sufficient data on the efficacy of surgical treatment in fertility in patients with rectovaginal and intestinal endometriosis. It is strongly recommended that each patient should be assessed using a holistic approach considering other infertility factors, ovarian reserve, extent and possible progression of endometriosis, and accompanying symptoms, and the treatment should be individualized.*

What are the principles of surgical management of the patients with rectovaginal and intestinal endometriosis?

If the patient does not respond to the medical treatment, then the patient should be assessed using a multidisciplinary approach to plan the surgical management. Due to risks of the intraoperative and postoperative complication up to 2% and 14%, respectively during the surgery for deep endometriosis, it is important that the surgery should be performed by experienced surgeons (Kondo et al. 2011). The patients should be informed properly about surgical options, risks of recurrence, and possible complication rates prior to the operation.

The benefits of the preoperative colon cleansing should be discussed with the patient before the surgery for deep endometriosis, but administration of prophylactic antibiotic does not seem to be beneficial (Cohen and Einarsson 2011).

It may be impossible to remove all visible lesions in patients with deep endometriosis. No additional benefit of removing fibrotic tissues around the deep endometriotic implants was demonstrated. However, the remaining fibrotic tissue may be removed, if it significantly constricts the lumen. Although there are endometriotic cells in the lymph nodes in 10% of the patients, there is no data supporting lymphadenectomy.

*Administration of prophylactic antibiotic before the surgery for deep endometriosis is strongly recommended.*

What are the surgical options in the patients with rectovaginal or intestinal endometriosis?

In case of rectovaginal endometriosis, the conservative surgery includes dissection of the rectovaginal cavity and removal of the endometriotic nodules. At the same time, the lesion should be removed and repaired, if there is vaginal and rectal wall infiltration. Another surgical alternative, lower anterior rectal resection, may be more suitable if it is required to open the rectum widely and if there are intensive fibrotic bands. Rectal segmental resection does not provide better pain control and its complication rate is higher (Vercellini et al. 2009b). Thus, anastomotic leakage rate is 1% in rectal segmental resection, while it is up to 15% in lower rectal anastomosis (Ret Davalos et al. 2007).

In symptomatic cases with intestinal involvement except rectosigmoid colon, the type of surgery may vary depending on the depth and size of infiltration and the experience and preference of the surgeon (Meuleman et al. 2011). The depth of involvement in pathological specimens was reported as 1% serosa, 70% muscle, 23% sub-mucosa, and 6% mucosa in a systematic review (De Cicco et al. 2011).

Shaving or superficial excision is specifically suitable in cases without the involvement beyond the serosa (Donnez and Squifflet 2010). The integrity of the intestines should be checked and the damaged muscular layers should be repaired, if required.

In cases with the involvement beyond the serosa, during full-thickness discoid excision, the lesion and surrounding tissue are removed and the wall is closed in a double layer manner. The segmental intestinal resection may be preferred in patients with wide (> 3 cm) or multiple nodules and/or intestinal lumen narrowing >50% (Fanfani et al. 2010). However, as reported in a current systematic review, it is not clear when to perform the segmental resection (De Cicco et al. 2011). Thus, although there is no high-quality study that compares three methods stated above, the results of the retrospective studies show that improvement in pain is higher in case of segmental or discoid excision than shaving and superficial excision, but the complication rate is also higher (Mohr et al. 2005). The differences in definitions of recurrence and pain scores in the current studies prevail taking effective clinical messages (Meuleman et al. 2011).

It may be concluded that the most limited resection is the most proper approach based on the current data.

*The pain complaints are reduced and the complication rate is increased with radical surgery in the patients with rectovaginal and intestinal endometriosis. So, it is strongly recommended that each patient should be assessed individually and the size of surgery should be determined considering the benefit-risk balance.*

What is the approach for asymptomatic rectovaginal and intestinal endometriosis recognized during a surgery performed for another indication?

The need for surgery in women with asymptomatic deep endometriotic nodules found incidentally during a surgery is not clear. Due to low possibility of mucosal damage the nodules smaller than 2 cm can be removed. However, it will be better to decide on surgical treatment after obtaining the patient's informed consent in case of larger lesions or if mucosal damage is probable during surgery.

What are the symptoms and findings of urinary system endometriosis?

Of women with endometriosis, 1-2% may also have urinary system involvement (Kovoor et al. 2010). The most common area of involvement is bladder (85%) and ureter (10%). In general, endometrioma or deep infiltrative endometriosis in other anatomical regions accompany with the urinary endometriosis (Vercellini et al. 1998). The detrusor muscle should be infiltrated in order to speak of bladder involvement (Kovoor et al. 2010). Non-specific symptoms, such as pollakiuria, dysuria and urinary retention may be seen especially during menstruation. Although hematuria is not frequent, if present, it usually becomes significant during menstrual period.

And in case of ureter involvement, most of the patients are asymptomatic and the most common complaints include colic-type side pain and hematuria (Comiter 2002). Some of them may be found incidentally during surgery or can only be diagnosed after occurrence of hydronephrosis.

How should the patients suspected with urinary system endometriosis assessed?

In the presence of hydronephrosis, urinary system endometriosis should be considered in women diagnosed or suspected with endometriosis. Until definitive diagnosis, urinary tract infection, interstitial cystitis, calculus and malignancy should definitely be considered and assessed. The suspected patients should be assessed by urinary ultrasonography, IVP or MRI-IVP. If there is a suspicion of bladder involvement, then it should be assessed by cystoscopy, and the biopsy should be taken if there are visible lesions (Roman et al. 2014). In case of severe hydronephrosis, kidney perfusion scintigraphy may also be performed. If urinary involvement is suspected, insertion of preoperative or intraoperative double-J stent may help (Weingertner et al. 2008).

What is the role of medical treatment in patients with urinary system endometriosis?

Although there is no study comparing the surgical and medical methods in the management of urinary endometriosis medical approach may be preferred at the first step in order to prevent the surgical complications, if there is no hydronephrosis. However, its efficacy is temporary and the symptoms usually return after discontinuation of the treatment (Antonelli et al. 2006). Surgery may be preferred in patients, who do not respond to the medical treatment or do not want to use medications for years.

Medical treatment can be tried in patients with mild or intermittent hydronephrosis under close follow-up after implantation of ureteral stent.

What are the surgical principles for urinary system endometriosis?

The most commonly preferred method is the full-layer removal of the affected layers in cases of bladder involvement (Nezhat et al. 2002; Kjer et al. 2014). Superficial shaving without entering into the lumen may be preferred in the lesions that do not affect the bladder in full-thickness (Kovoor et al. 2010). If the lesion is in close proximity to the ureter less than 2 cm, the ureteral stent can be placed preoperatively. Postoperative bladder catheter remains for 7-10 days. Risk of postoperative recurrence is very low (Nezhat et al. 2002; Kjer et al. 2014).

Ureteral involvement may be extrinsic or intrinsic. In case of intrinsic involvement, proliferation and fibrosis of the muscle layer occur. A growth towards the lumen may rarely occur. In case of extrinsic involvement, there is an obstruction associated with peritoneal entanglement. Most commonly, the left side and the distal one-third area are involved (Bosev et al. 2009). The endometriotic lesions and the surrounding fibrotic tissues should be removed during surgery (Fedele et al. 2004). Even if it is possible to perform complete ureterolysis laparoscopically, laparotomy may be required in patients, who will undergo ureter resection followed by ureteroneocystostomy. Uretero-ureteral anastomosis is applied for proximal lesions. Ureteral stent may be inserted in all patients.

*Full-layer removal of the affected layers is strongly recommended in case of bladderinvolvement.*

*It is strongly recommended that a preference should be made among ureterolysis, ureterresection or ureteroneocystostomy based on the localization and the size of the ureteralinvolvement.*

What is the approach for asymptomatic urinary system endometriosis is found during a surgery performed for another reason?

If the urinary system endometriosis is found incidentally, then ureterolysis can be applied, if it is sufficient alone. If a more radical intervention is required, it will be appropriate to perform the surgical treatment after having patient's informed consent.

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# EXTRAGENITAL ENDOMETRIOSIS

What is the frequency of extragenital endometriosis?

The prevalence of extragenital involvement was reported as 8.9% in patients with endometriosis (Markham et al. 1989). The most common locations of involvement include intestines, urinary system, skin and thorax (Veeraswamy et al. 2010). Evaluation and management of intestinal and urinary endometriosis are discussed in the section of “*deep endometriosis*”.

What are the possible symptoms in diaphragmatic and thoracic endometriosis?

The catamenial symptoms that may vary depending on the location of involvement typically appear during menstrual period. However, in general, hormonal sensitivities decrease away from the uterus, and in almost half of the patients, the symptoms do not accompany menstruation (Veeraswamy et al. 2010). All of the malign transformations that develop from the endometrial foci except the uterus and ovary are originated from the pelvic organs (Veeraswamy et al. 2010).

The functional endometrial tissue may exist in the lungs, on the pleura, or in the respiratory tract and may exhibit clinical manifestations: (1) catamenial pneumothorax (the most common), (2) hemothorax, (3) hemoptysis and (4) lung nodules (Joseph and Sahn 1996). Such symptoms usually occur 5-7 years after the onset of pelvic symptoms. Of the women with extra genital endometriosis, 84% have pelvic involvement. The symptoms are seen more on the right side (Channabasavaiah and Joseph 2010).

How can diaphragmatic and thoracic endometriosis be diagnosed?

The catamenial symptoms should be investigated in case of clinical suspicion. BT and MRI can be used for definitive diagnosis (Rousset et al. 2014). Although the gold standard is video-thoracoscopic surgery (VATS), it may provide some false negative results in some patients (Veeraswamy et al. 2010). The response to hormonal suppression may also be used for diagnosis. Laparoscopy can be included to assess the pelvic disease (Nezhat et al. 1998).

What is the treatment for diaphragmatic and thoracic endometriosis?

Medical or surgical treatment can be used. The recurrence risk is lower in surgical (pleurodesis) compared to the medical treatment (Joseph and Sahn 1996). A combined treatment may also be effective (Duyos et al. 2014). Alternatively, vaporization or excision may also be used together by thoracoscopy. Resection can be used in cases with diaphragmatic involvement (Bagan et al. 2003).

*There is low-quality evidence about the treatment of thoracic endometriosis. The Guideline Development Group gives weak recommendation to carry out medical treatment as the first line.*

What are the risk factors for cutaneous endometriosis and how can it be diagnosed?

According to its definition, it includes the peritoneal lesions. It can also be referred to as scar endometriosis. Patient's history and clinical findings are sufficient for the diagnosis of cutaneous endometriosis. The most important risk factor is previous surgery for endometriosis. Any patient, who had cyclic or non-cyclic pain and/or mass in previous surgical scars, should be suspected. The average time to the occurrence of the symptoms after surgery is 2-4 years (Blanco et al. 2003; Chang et al. 2009). However, ultrasonography, BT, MRI and fine-needle biopsy may be used, if the lesion is large, the integrity of the fascia is suspicious or the diagnosis is not clear. Malign transformation was reported very rarely (Bats et al. 2008).

*Although cyclic pain and/or presence of mass at the surgical area are sufficient for the diagnosis, it is strongly recommended to use imaging methods or fine-needle biopsy for the confirmation of diagnosis*

How can cutaneous endometriosis be treated?

For treatment, the total excision with negative surgical margins is the most suitable approach, and its recurrence risk is low (Patterson and Winburn 1999). Repair using mesh may be preferred in patients with a risk of hernia. When needed, the general surgery consultation during or before surgery may be requested.

*It is strongly recommended to perform a total excision with negative surgical margins as an approach with the lowest recurrence risk.*

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# ASYMPTOMATIC ENDOMETRIOSIS

Asymptomatic endometriosis is defined as chancing upon of endometriotic foci and/or endometrioma during any medical investigation without any symptom and findings in an individual. Although the prevalence of asymptomatic endometriosis was reported as 2-30% in women at reproductive ages, the prevalence of asymptomatic endometriosis in women, who applied for tubal ligation, was reported as 6% in developed countries, whereas it was reported as 5% in the developing countries (Fuentes et al. 2014).

How can asymptomatic pelvic endometriosis be recognized?

Endometriotic lesions may be observed in perine, vulva, vagina and cervix during pelvic examination, or an ovarian mass related to endometrioma may be observed during ultrasonographic examination.

What are the risk factors for asymptomatic endometriosis?

In a cohort of 116,430 women monitored under English Nurses Health Study, the women, who were diagnosed as asymptomatic endometriosis by laparoscopy, were assessed and it was found that endometriosis was more frequent in women with low body-mass index (Shah et al. 2013). In accordance with this finding, the women with lower waist-hip ratio had a three times higher prevalence of asymptomatic endometriosis than those with higher waist-hip ratio (Shah et al. 2013).

Should women with asymptomatic endometriosis be treated to protect reproductive potential?

Asymptomatic endometriosis can be determined even in adolescence. How the treatment of women diagnosed as asymptomatic endometriosis will affect their reproductive potential in future is unclear and there is no consensus on this issue.

As late marriage due to industrialization, business life and education negatively affects the reproductive potential, although a treatment to slow/prevent progression asymptomatic endometriosis recognized in earlier period may sound logical, it is not clear if endometriosis is a progressive disease (Hans Evers 2013). All women diagnosed as asymptomatic endometriosis are not necessarily required treatment; the clinician may monitor the suitable women without giving treatment.

Completion of the number of children is the most important decisive factor in asymptomatic endometriosis. The “wait and see” approach may certainly be preferred.

As there is no evidence about the efficacy of medical treatment in asymptomatic women in reproductive period that completed family size, each woman should be assessed separately and the decision should be individualized considering their preferences (Rossmanith 2009).

What is the approach to asymptomatic endometrioma during pregnancy?

In 18 patients, operated for the ovarian mass and suspected malignancy with the histological diagnosis of endometrioma, 17 (94%) were asymptomatic (Mascilini et al. 2014). Although most of the patients (17/18) had vascularized polypoid protrusion in the cyst, finding endometrioma during the histological examination was interesting striking. On the other hand, in another case report, a 1 cm solid component was found in the cyst with increased vascularization and the mass had enlarged during pregnancy, although the case was followed up with the pre-diagnosis of endometrioma, in the end she was diagnosed with clear cell carcinoma (Chaudhry et al. 2013). Although this patient had multiple findings (vascularized solid component and expansion during pregnancy) that suggest malignancy, it should be discussed if the pre-diagnosis of endometrioma was correct.

*If an ovarian mass resembling endometrioma is incidentally determined during pregnancy, a conservative monitoring is strongly recommended, unless the possibility of malignancy is high.*

How can asymptomatic endometriosis be managed during perimenopausal period?

As the endometriosis is not expected to progress during perimenopausal period, no treatment may be required for asymptomatic endometrial foci, incidentally found during surgery. In this period, it is important to exclude malignancy of ovarian masses appearing as endometrioma.

How can asymptomatic endometriosis be managed during postmenopausal period?

Only 15.3% of 72 postmenopausal patients with endometriosis, who were diagnosed in Italy in 1998-2010, were diagnosed before. The most common lesion is endometrioma (Morotti et al. 2012).

Asymptomatic endometriosis can be determined as adnexal mass during postmenopausal period. In this period, even if the ultrasonographical appearance of adnexal mass suggests endometrioma, the preferred approach is usually excision and histological examination owing to the fact that the ovarian cancer risk proportionally increases, thus there is a need for differential diagnosis.

*Although the adnexal mass during the postmenopausal period resembles endometrioma, The Guideline Development Group gives weak recommendation to perform an excision and histological examination.*

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# ADOLESCENT ENDOMETRIOSIS

Is symptomatic endometriosis encountered in adolescence?

Although endometriosis is known as a disease of women of the reproductive age group, the disease process can start and become symptomatic in adolescence. According to The Endometriosis Association data, symptoms start before the age of 15 in 38% of patients (Ballweg 2003). It was reported that although 75% of patients were examined by a gynecologist at the beginning of their symptoms, it took a mean number of 4.2 doctor visits until a final diagnosis could be made (Ballweg 2003). As the age at the start of disease decreases, the time and number of doctor visits until diagnosis increase. The mean time from the appearance of the first symptom to the diagnosis of endometriosis reaches 9.3 years for symptomatic patients under 15 years of age (Ballweg 2003).

Chronic pain may adversely affect school attendance and participation in social activities, leading to potentially irreversible problems in adolescence (Ballweg 2003). Increasing the awareness about endometriosis in health professionals and patients and bearing in mind the possibility of endometriosis in young adolescents presenting with pelvic pain and dysmenorrhea might prevent delays in diagnosis and permanent adverse effects.

Although it is not possible to accurately determine the prevalence of endometriosis in adolescents, it has been reported to be found in 35-73% of adolescents who underwent laparoscopic evaluation for chronic pelvic pain refractory to NSAIDs or OCPs (Reese et al. 1996; Laufer et al 1997; Stravroulis et al. 2006). Macroscopic endometriosis-like lesions have been detected during laparoscopy for pelvic pain developing after telarche in premenarcheal girls without obstructive Müllerian anomalies (Marsh and Laufer 2005). The presence of endometriosis has been also documented histopathologically in some of these girls following menarche. These findings suggest that menstruation is not necessary for the development of the disease and its symptoms and that endometriosis must be considered in the differential diagnosis of pelvic pain in girls following telarche (Marsh and Laufer).

***There is high quality evidence that endometriosis can become symptomatic during adolescence and it is strongly recommended that endometriosis should be considered in the presence of painful symptoms during adolescence in order to prevent delay in diagnosis and treatment of the disease.***

What are the symptoms of endometriosis in adolescents?

The primary symptom in adolescent patients with endometriosis is dysmenorrhea with a prevalence of 65-90%. One of the reasons for a delay in diagnosis may be the assumption of menstrual pain as primary dysmenorrhea. In the presence of dysmenorrhea that starts right after menarche and gradually increases in intensity, asymmetrical obstructive Müllerian anomalies (i.e. obstructive hemivaginal septum, non-communicating functional horn) and endometriosis must be considered. In patients with endometriosis the prevalence of congenital anomalies of the reproductive system has been reported to be 11%, furthermore, the prevalence of endometriosis in women with Müllerian anomalies and menstrual flow obstruction has been reported to reach 76% (Sanfilippo et al.1986; Olive and Henderson 1987; Davis et al 1993). Another reason for a delay in diagnosis may be the fact that endometriosis frequently presents as non-cyclical pain in adolescents independently of dysmenorrhea (Laufer et al. 1997). The absence of infertility and dyspareunia complaints, because of a lack of desire for immediate fertility or sexual activity in adolescents, may be another factor that renders the consideration of endometriosis difficult. In the evaluation of adolescents, it has to be kept in mind that the second most common symptom of endometriosis in this age group is tiredness and listlessness, followed by painful defecation and gastrointestinal symptoms (Ballweg 2003).

### **How should an adolescent suspected of having endometriosis be evaluated?**

Medical history and physical examination appropriate for the patient's age are important in the evaluation of endometriosis in adolescents. The timing of the pain, its relation with menstruation and the presence of endometriosis in the family history must be questioned. A bimanual physical examination is not absolutely necessary; however an evaluation of the genital system anatomy is required. The external genitalia must be inspected and the presence of a vagina and its length must be evaluated by inserting a cotton swab through the hymenal ring. If a pelvic mass is suspected, a recto-abdominal examination may be carried out. A complete pelvic examination must be done in sexually active girls and the presence of other causes of pelvic pain such as pelvic inflammatory disease must be investigated. Findings associated with advanced stage endometriosis such as endometriomas presenting as adnexal masses or painful nodules in the uterosacral ligaments are rare in this age group and the absence of these findings does not rule out endometriosis (Vercellini et al 1989; Marsh and Laufer 2005). Müllerian anomalies and hematometra must be considered in adolescents presenting with pelvic pain and adnexal masses.

Pelvic ultrasonography and MRI are especially important tools in the evaluation of this age group when Müllerian anomalies are suspected.

*The Guideline Development Group strongly recommends the evaluation of the genital system anatomy for the presence of obstructive Müllerian anomalies; even if a vaginal examination is not performed. It must be kept in mind that a normal physical examination and negative imaging findings do not rule out the diagnosis of endometriosis.*

**Is laparoscopy absolutely necessary for the definitive diagnosis of endometriosis in adolescents?**

Administration of NSAIDs and OCPs in adolescents with dysmenorrhea seems to be an acceptable approach. If the symptoms do not subside with this approach, it should be kept in mind that endometriosis is the most common reason for secondary dysmenorrhea and a more detailed evaluation including laparoscopy should be considered.

*The guideline preparation committee recommends that empirical medical treatment be administered without the need for laparoscopic confirmation in adolescents if the history, symptoms and findings suggest the pain to be associated with endometriosis.*

**What are the three rules that need to be followed when performing laparoscopy in adolescents suspected of having endometriosis?**

Firstly the surgeon must have the experience to recognize these lesions and have the competency to surgically treat endometriosis and Müllerian anomalies since the treatment of obstructive Müllerian anomalies alleviates symptoms of endometriosis (Sanfilippo et al 1986). Secondly, it must be kept in mind that atypical white and/or red vesicular lesions are more prevalent than the classical powder burn lesions in this age group (Vercellini et al. 1989; Davis et al. 1993; Reese et al. 1996). The third important point is that a conservative and fertility sparing surgical approach must always be adopted when treating adolescents. Options like hysterectomy or oophorectomy must not be offered.

*If laparoscopy will be performed with the suspicion of endometriosis in adolescents:*

***It is strongly recommended that a surgeon capable of recognizing atypical lesions and surgically treating Müllerian anomalies performs the surgery.***

***It is strongly recommended to strictly perform fertility sparing surgery and spare the uterus and at least one ovary in the adolescent.***

**Should medical treatment be administered following surgery in the adolescent?**

Because surgical treatment of endometriosis does not annihilate the etiology except in the presence of congenital anomalies, postoperative recurrence rates are high. Consequently, all adolescents must continue taking medical treatment following surgery.

***Although there is no direct evidence of the benefits of medical treatment after surgery, considering the possible risk-benefit ratio, the guideline development committee strongly recommends administration of long term medical therapy following surgical treatment for all adolescents.***

## **What are the medical therapy options for endometriosis in adolescents?**

Data on the efficacy of various treatment options have been obtained from patients in the reproductive age group and the age of the patient must be considered when deciding on the type of medication to be administered. GnRH agonists and depot progestins lead to decreased bone mass and therefore are not appropriate for administration in adolescents below 18 who have not reached their maximal bone mass yet (American College of Obstetricians and Gynecologists 2005; Leyland et al. 2010). Nevertheless, these drugs may be administered along with add-back therapy in adolescents older than 16 years with laparoscopically confirmed endometriosis unresponsive to NSAID or OCP treatment.

***NSAIDs and/or OCPs are strongly recommended as first-line therapy in adolescents with suspected endometriosis. In adolescents with laparoscopically confirmed endometriosis oral contraceptives are recommended for medical therapy and secondary prevention.contraceptives.***

***It is strongly recommended that use of GnRH agonists should be avoided in adolescents up to 18 years old.***

***It is recommended to administer GnRH agonists with add back therapy in adolescents only as the last resort for symptoms refractory to treatment with first-line medications and progestins.***

## **How should add-back therapy be administered in case of treatment with GnRH agonists?**

Starting add-back therapy concomitantly with GnRHa protects bone mass better than when it is started 6 months later, without diminishing the effectiveness of the treatment; therefore, simultaneous initiation of add-back therapy and GnRHa treatment is appropriate (Al-Azemi et al.2009). OCPs are not appropriate for add-back therapy since their potent estrogen content will lead to supraphysiologic estrogen levels neutralizing the effects of GnRH agonists (DiVista and Laufer 2013). Noretisterone acetate and/or estrogens equivalent to 1mg of 17 beta estradiol can be used. Adolescents treated with GnRHa and add-back therapy must receive Vitamin D and calcium supplementation.

***The Guideline Development Committee strongly recommends the administration of noretisterone acetate or estrogens equivalent to 1mg of 17-beta estradiol as add-back therapy in adolescents treated with GnRH agonists..***

*It is strongly recommended that calcium and vitamin D should be administered to the adolescents during add-back treatment combined with GnRH agonist.*

Should bone density be measured in adolescents treated with GnRH<sub>a</sub>?

Measuring bone mineral density is not necessary in adolescents prior to GnRH<sub>a</sub> treatment unless other factors predisposing to bone loss as diabetes, chronic steroid treatment, anorexia etc. are present. Bone loss has been reported in the lumbar vertebrae of 31% of adolescents treated with GnRH<sub>a</sub> for twelve months, despite having received add-back therapy with noretisterone acetate (Divasta et al 2007). It may be appropriate to measure bone density every two years in those receiving long term GnRH<sub>a</sub> treatment.

*The guideline preparation committee does not recommend routine measurement and monitoring of bone density, in the absence of any other risk factor for bone loss in adolescents receiving GnRH agonist.*

For how long should adolescents receive medical treatment for endometriosis?

Because medical therapy does not annihilate the etiology of endometriosis, it is possible for symptoms to recur after cessation of therapy. Furthermore, the progression of disease may adversely affect fertility in the future years. Consequently, medical therapy should be continued until child-bearing has been completed.

*Although there is no high-quality evidence in this regard, considering the possible risk/benefit ratio, the guideline development committee recommends that adolescents should receive medical treatment until completion of child bearing, with breaks when they want to conceive.*

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# **ENDOMETRIOSIS in MENOPAUSAL and PERIMENOPAUSAL PERIOD**

Endometriosis, generally known to occur during reproductive years, may also occur during peri and postmenopausal period.

How often does endometriosis occur during postmenopausal period?

The answer is currently unknown. However, the studies revealed that 2-3% of women with endometriosis were in postmenopausal period (Punnonen et al. 1980; Haas et al. 2012).

Is endometriotic tissue active in terms of hormonal sensitivity and proliferation after the menopause?

Although postmenopausal endometriotic tissue is found to less hemorrhagic (Cumiskey et al. 2008), it was demonstrated that it has hormonal and proliferative tissue activity (Toki et al. 1996).

Is estrogen high in postmenopausal women with endometriosis?

As in other periods of female life, estrogen takes an important role in postmenopausal endometriosis, but there is no study showing high estrogen in such patients. Nevertheless, concomitant presence of estrogen-dependent conditions, such as myoma and adenomyosis (50% and 30%, respectively) suggests that estrogen has an important role (Sun et al. 2013).

What are the risk factors for postmenopausal endometriosis?

Some factors may increase the risk of development of postmenopausal endometriosis. These are:

*Obesity*: It is considered as a risk factor for postmenopausal endometriosis. In the related studies, most of the patients diagnosed with postmenopausal endometriosis were obese (Punnonen et al. 1980; Morotti et al. 2012). Obesity is considered to be one of the effective factors in postmenopausal endometriosis, especially owing to estrogen, produced in the fat tissue via aromatization.

*Remnant Ovarian syndrome (ROS)*: ROS, which is a rare condition in patients, who undergo total hysterectomy and bilateral salpingo-oophorectomy, may cause reactivation of endometriosis. In a retrospective analysis, of 153 patients with ROS, who were re-operated, 29% had endometriosis in the remnant ovarian tissue (Magtibay et al. 2005).

*Leaving ovaries in situ during surgery*: It was demonstrated that performing only hysterectomy during surgery for endometriosis had a 6.1 times higher recurrence risk than performing hysterectomy and bilateral oophorectomy (Namnoum et al. 1995). This recurrence may also occur during postmenopausal period.

Does HRT in the postmenopausal period have impact on endometriosis?

There is no sufficient data proving that HRT following surgery for endometriosis has impact on postmenopausal endometriosis. In addition, HRT has not been used as "low dose" in the literature. Even among those studies, there is no high-quality study showing the causal relationship between HRT and postmenopausal endometriosis.

The effect of the recently recommended low-dose or ultra low-dose estrogen alone or in combination has not been established yet. This is particularly important especially when "hypothesis of estrogen threshold" is considered (Barbieri 1992). Considering the estrogen threshold level at which the organs respond, it is known that endometrial tissue has a higher threshold level. Therefore, when a positive effect is desired -for instance, for the bone that is more sensitive to estradiol- the minimum level required does not show any impact on the endometrial tissue.

Under which conditions, HRT may increase the recurrence of endometriosis?

Two prospective randomized controlled studies on the impact of HRT use in women with endometriosis showed that the administration of HRT might increase the risk of recurrence especially in women with incomplete endometriosis surgery (leaving the uterus completely or partially) and in the presence of a severe peritoneal disease (>3cm), although these studies did not show the direct cause and effect relationship (Fedele et al. 1999; Matorras et al. 2002).

Can HRT be administered to the patients with surgical menopause due to endometriosis?

The occurrence risk of pain symptoms or the disease caused by the administration of HRT cannot be excluded. However, the combination of estrogen+progestin or tibolon can be used successfully in elimination of symptoms especially in surgically-induced "premature menopausal" patients with endometriosis.

In such patients, it is recommended that unopposed estrogen should be avoided and progestin should be added to the treatment against the risk of malignant transformation and recurrence of the disease (Al Kadri et al. 2009).

*The Guideline Development Group gives weak recommendation to avoid from administration of unopposed estrogen in HRT in surgically menopausal women with endometriosis.*

*In such patients, it is recommended that HRT should be continued until the expected age of menopause.*

Can HRT be administered after natural menopause in patients with endometriosis?

There are no data about the use of HRT in natural-menopausal-women with endometriosis (Hickman et al. 1998). However, the data on the surgically-menopausal-women may also be applicable to such patients. The treatment method should be decided on an individual basis considering the risk-benefit ratio.

There is no ideal time defined for commencing HRT following surgery in women, who underwent endometriosis surgery. However, the studies show that starting later did not offer the expected advantages (Stern et al. 2001).

What are the risk factors in terms of malignancy during postmenopausal period?

The malignant transformation was reported to be about 0.9% in patients with endometriosis (Zanetta et al. 2000). Although cancer associated with endometriosis was reported in postmenopausal patients, who were not on HRT, it is considered that residual disease and unopposed estrogen use pose a risk of malignant transformation especially in obese patients (BMI > 27 kg/m<sup>2</sup>) (Bese et al. 2003). Also, malignancy was reported in patients with endometriosis, who use tamoxifen due to postmenopausal breast cancer (Polyzos et al. 2011).

How can postmenopausal endometriosis be treated?

The postmenopausal endometriosis is most commonly detected by pain and/or ovarian mass. Due to the difficulty in distinguishing malignancy in masses, as the case especially in endometriomas, the primary treatment recommended in postmenopausal endometriosis is complete surgery. Here, the rational is to consider the risk of malignancy.

Is there a place for medical treatment in the treatment of postmenopausal endometriosis?

Medical treatment can be considered for patients with postmenopausal endometriosis, if there is a condition making the surgery inapplicable (presence of conditions that contraindicate surgery, very high risk of surgical complication due to previous operations, etc.). The aromatase inhibitors offer an important alternative in this regard.

Hot flashes do not usually occur in patients with postmenopausal endometriosis, who use aromatase inhibitor, the only case reported until today was treated with estradiol 0.5 mg/day without any recurrence (Moen et al. 2010). Annual bone density should be measured in patients, who use aromatase inhibitor and treatment with bisphosphonate is recommended in patients with high risk.

*The Guideline Development Group gives weak recommendation to perform measurement of annual bone mineral density in patients with postmenopausal endometriosis, who use aromatase inhibitor, and to administer bisphosphonate treatment in patients with high risk.*

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# ENDOMETRIOSIS AND PREGNANCY

Endometriosis is generally accepted as a problem in reproductive years. Therefore, the relation between endometriosis and pregnancy is important. However, studies on endometriosis and pregnancy are widely different in terms of various factors, such as the method of diagnosis, the presence of infertility before the pregnancy and administration of treatment modalities, if any.

Does endometriosis have negative impacts on obstetric results?

Based on the present data, endometriosis should be deemed as an obstetric risk factor considering the delivery and antenatal bleeding risks (Johnson et al. 2013).

What is the mechanism of the negative impact of endometriosis on obstetric outcome?

The possible the impact of endometriosis on pregnancy is attributed two underlying mechanisms; 1) Defective myometrial spiral artery remodelling (Brosens et al. 2010; Brosens et al. 2013), 2) Inflammation (Petraglia et al. 2012).

Is endometriosis related to sporadic or recurrent miscarriage?

While investigating the miscarriage risk in women with endometriosis, the infertility status, mother's age and role of the treatments administered should be considered. Inconsistent results have been reported in the studies on endometriosis and miscarriage risk (Matorras et al. 1998; Sinaii et al. 2008; Hjortd Hansen et al. 2014). In two cohort studies no association was found between spontaneous miscarriage and endometriosis and as well as recurrent miscarriage and endometriosis. The present data are not suggestive of any relationship between endometriosis and sporadic or recurrent miscarriage.

Does endometriosis increase the risk of ectopic pregnancy?

Some studies report that ectopic pregnancy risk does not change in the patients with endometriosis, while others report that the risk has increased. The recent study reports that the ectopic pregnancy risk has increased regardless of whether the pregnancy is spontaneous or achieved using assisted reproductive technology (Hjordt Hansen et al. 2014). It may be concluded that there is weak evidence pointing out the increased risk of ectopic pregnancy in cases with endometriosis.

Is endometriosis associated with obstetric bleeding?

It is reported that risk of placenta previa increases in women with endometriosis - especially with rectovaginal endometriosis (Vercellini et al. 2012; Takemura et al. 2013).

Endometriosis is a significant risk factor for *Spontaneous hemoperitoneum in pregnancy (SHIP)*, a special condition that is rare but has high maternal and fetal mortality (Brosens et al. 2012; Aggarwal et al. 2014).

Is endometriosis associated with the other pregnancy complications?

*Preeclampsia:* Preeclampsia, a condition specific to pregnancy, is considered to be arisen from defective transformation of spiral arteries in the endo-myometrial junction (Brosens et al. 2011). Regarding the endometriosis and the risk of preeclampsia, various data have been suggested an increased risk (Stephansson et al. 2009), unchanged risk (Hadfield et al. 2009; Carassou-Maillan et al. 2014) or decreased risk (Brosens et al. 2007). Although it is not expected in endometriosis due to the increased angiogenesis, nevertheless, the risk of preeclampsia is still unknown in the pregnant women with endometriosis.

*Preterm delivery and retarded intrauterine development:* Some studies reported that endometriosis did not cause any increased risk of preterm labor or intrauterine growth retardation (Kotelahti et al. 2003; Benaglia et al. 2012), whereas others reported that endometriosis caused 1.3-2 times increased risk of preterm delivery (Fernando et al. 2009; Falconer 2013). In the pregnant women with endometriosis, it was emphasized that there was a risk of preterm delivery regardless of whether the pregnancy was achieved using assisted reproduction technology (Stephansson et al. 2009).

Some of the observational studies show that the risk of intrauterine growth retardation has increased in the patients with endometrioma (Fernando et al. 2009). However, there are conflicting results for the risk of intrauterine growth retardation. It is especially asserted that inflammation is the common factor in both situations (Petraglia et al. 2012).

Does pregnancy have any impact on the course of endometriosis?

Although it is generally considered that pregnancy has positive impacts on endometriosis, there is no sufficient study with this regard. A significant reduction was reported in the endometriotic lesions during pregnancy in experimental endometriosis model in mice, (Cummings and Metcalf 1996). However, there are some studies showing either progression or regression of endometrioma during pregnancy (Benaglia et al. 2013). Those, who assert that endometriosis regress during pregnancy, suggest that the regression is caused by the desidualization in the endometrial tissue caused by increased progesterone, while others, who asset that it progresses, suggest that the increased angiogenesis causes a progression in the endometriosis focuses. In summary, the impact of endometriosis on pregnancy is currently unknown.

Is there a fetal anomaly risk in pregnant women with endometriosis?

Although it is known that the risk of endometriosis is increased in the presence of some fetal abnormalities (obstructive Müllerian abnormalities), the impact of endometriosis on fetal abnormality risk is unknown. However, some masculinization abnormalities in the female fetus have been reported when the pregnant woman exposed to danazol administered for the treatment of endometriosis (Duck and Katayama 1981, Shaw and Farquhar 1984, Kingsbury 1985)

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# RECURRENCE OF ENDOMETRIOSIS

What is the definition and frequency of recurrence of endometriosis?

The definition of recurrence following treatment of women with endometriosis differs among the studies. In addition to the gynecologic complaints, such as dysmenorrhea, dyspareunia and non-menstrual pelvic pain, inability to become pregnant has also been included in the definition of recurrence (Selçuk and Bozdag 2013). In addition, confirmation using ultrasonography and even laparoscopy was required for the confirmation in some studies (Selçuk and Bozdag 2013).

The reported recurrence rates are higher in the studies, which are based on recurrences of the symptoms/complaints rather than the surgical or radiological evidences, and have longer follow-up periods. Vignali et al. reported that recurrence rate for five years as 44% based on pain, whereas 28% based on surgical/radiological evidence (Vignali et al. 2005).

What are the risk factors for recurrence of endometriosis?

Several risk factors have been defined for the recurrence. Some of the main risk factors are young age during diagnosis or surgery, severe preoperative pain, previous medical treatment, nulliparity, bilateral endometrioma, large endometrioma and incomplete surgery (Guo 2009; Selçuk and Bozdag 2013). There is no consensus on which of the risk factors has a higher predictive value.

Can recurrence be prevented in endometriosis?

It seems that it is not possible to completely eliminate the recurrence risk of endometriosis in long term. However, the most effective strategy to minimize the symptomatic or clinical recurrence risk following surgery is to leave as little as possible residue during surgery. Cystectomy for endometrioma has lower risk of recurrence in both clinical (dysmenorrhea, dyspareunia and non-cyclic pain) and radiological terms compared to drainage and coagulation (Hart et al. 2008). Cystectomy instead of laser vaporization may be preferred due to lower recurrence rates (Carmona et al. 2011).

The symptoms may continue in 10-15% of patients, who underwent hysterectomy due to endometriosis (Berlanda et al. 2010). Including oophorectomy in the process may decrease the risk of recurrence (Namnoum et al. 1995) and the requirement for re-operation (Shakiba et al. 2008).

*There is high-quality evidence proving that cystectomy in endometrioma surgery poses lower recurrence risk compared to the drainage and coagulation and The Guideline Development Group strongly recommends that cystectomy should be preferred.*

Is medical treatment following endometriosis surgery beneficial?

The efficacy of the treatment may vary based on the type of medication and the duration of treatment. There is no data supporting the efficacy of NSAIDs on recurrence of the symptom following operation (Ailen et al. 2005).

Medroxyprogesterone acetate (MPA) and danazol may decrease postoperative pain scores compared to placebo, especially if used for six months or more (Telimaa et al. 1987; Morgante et al. 1999).

Use of GnRH agonist for more than six months may decrease postoperative pain scores at 12 and 24 (Jee et al. 2009), and may extend the time to recurrence compared to placebo (Vercellini et al. 1999).

Use of postoperative LNG-IUS or COCs for minimum 18-24 months is effective in prevention of recurrence of dysmenorrhea, but it is ineffective in dyspareunia or pelvic pain associated with endometriosis (Abou-Setta et al. 2006; Seracchioli et al. 2009). Particularly commencing COC immediately after endometrioma surgery significantly decreases the recurrence rates (Muzii et al. 2000; Vercellini et al. 2010, 2011).

*There is high quality evidence proving that hormonal suppression following endometrioma surgery decreases the risk of recurrence and The Guideline Development Group strongly recommends that hormonal suppression should be prescribed to the patients, who do not want to be pregnant, following endometrioma excision.*

*The Guideline Development Group strongly recommends oral contraceptives, in a continuous manner and at least for 18-24 months starting immediately after the surgery considering the ease of use and balance of side effects.*

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# ENDOMETRIOSIS AND CANCER

Does endometriosis increase the cancer risk?

It is not clear if the women with endometriosis are under the risk of various types of cancer (Melin et al. 2006; Somigliana et al. 2006). There is no increased risk of cancer in women with endometriosis (Standardized Incidence Rate (SIR):1.04 95% CI 1-1.07) (Melin et al. 2006). However, diagnosis of endometriosis was found to be associated with an increase in the risk of ovarian cancer (SIR 1.43, 95% CI 1.19-1.71). Van Gorp et al. calculated the ovarian malignant transformation as 2.5% in their review in 2004 (Van Gorp et al. 2004). Odds ratios (OR), relative risk (RR) or standardized incidence ratios were evaluated in six studies, including one case control and five cohort studies, and the risk of ovarian cancer was found to be increased by 1.3 to 1.9 times.

There is no significant association between the endometrium cancer and endometriosis. Endometriosis seems to be associated with the increased risk of cervical premalignant lesions and cervical cancer (Munksgaard and Blaakaer 2011).

Endometriosis was associated with endocrine tumors (SIR 1.36 95% CI 1.15-1.61), non-Hodgkin lymphoma (SIR 1.24 95% CI 1.02-1.49), brain tumors (SIR 1.22 95% CI 1.04-1.41) and malignant melanoma (SIR: 1.23, 95% CI: 1.07 - 1.40) (Melin et al. 2006). The association between endometriosis and breast cancer is unclear. The risk of breast cancer has increased in 3 of 8 cohort studies conducted on women with endometriosis, whereas increased risk was not observed in 4 of 5 case-control studies (Munksgaard and Blaakaer 2011).

A significant association was found between the self-reported history of endometriosis and epithelial ovarian cancer (EOC) in a meta-analysis in approximately 8000 women from the 13 case control studies selected. An increased risk was found in clear cell (OR 3.05, 95% CI 2.43-3.84), endometrioid (OR 2.04, 95% CI 1.67-2.48) and low grade serous (OR 2.11, 95% CI 1.39-3.20) EOC, while no increased risk was found in high grade serous (OR 1.13, 95% CI 0.97-1.32) or mucinous (OR 1.02, 95% CI 0.69-1.50) EOKs (Pearce et al. 2012). Even if SIR for ovarian cancer in patients with endometriosis has increased compared to the controls, the ovarian cancer incidence is low in both groups. For example, in a cohort study conducted by Melin et al., SIR was reported as 1.43 (95% CI 1, 19-1, 71) for the ovarian cancer (Melin et al. 2006). The mean follow-up period of the patients was 12.7 years; the cancer development risk was 0.027 in the patients with endometriosis and 0.019 in the controls. This means

that 3% patients with endometriosis developed ovarian cancer, whereas 2% control patients developed ovarian cancer during the follow-up period.

The risk of ovarian cancer is the highest in women with endometriosis and primary infertility (Brinton et al. 2004). It seems that this risk can be decreased significantly by using contraceptive drugs (Modugno et al. 2004).

On the other hand, hormonal treatment or administration of tamoxifen may increase the risk of cancer development in endometriotic foci, but there is no sufficient data (Modesitt et al. 2002; Bese et al. 2003).

What is the impact of the age of the patient with endometriosis on the cancer risk?

In a prospective cohort study conducted in Japan, ovarian cancer was determined in 46 of 6398 patients diagnosed with endometrioma during a follow-up period of 17 years and it was found that the ovarian cancer risk increased significantly in women with endometrioma (SIR 8.95, 95% CI 4.12-15.3) (Kobayashi et al. 2007). In this same study, the ovarian cancer risk was found to be associated with the age at the diagnosis of endometrioma but not with the follow-up period of the endometriosis. Based on the age at the diagnosis of endometrioma, SIR was 8.03 (95% CI 4.78-11.9) in women aged between 40 and 49 years and SIR was 13.2 (95% CI 6.90-20.9) in women over 50 years (Kobayashi et al. 2007). When the risk factors for cancer were investigated, tumor diameter >9 cm and postmenopausal period were found as independent risk factors (Kobayashi et al. 2008). In another study, of 18 patients that showed malignant transformation during follow-up for endometrioma, the average age of occurrence of malignant transformation was 45.2 years (age range:33-66) (Kawaguchi et al. 2008). 78% of the patients that showed malignant transformation were in their premenopausal period, and shorter latent period was observed in those over 45 years (Kawaguchi et al. 2008). In a review, it is reported that the ovarian cancer risk significantly increases in women with endometriosis over 40 years (Kobayashi 2009).

Is the size of endometrioma associated with the cancer risk?

In terms of size, endometrioma >9cm, was proposed as an independent risk factor for ovarian cancer (Kobayashi et al. 2008). It was found that the ovarian cancer risk increases by 5.5 times in masses with diameter  $\geq 9$  cm (HR, 5.5; 95% CI, 2.1 -9.2) (Kobayashi et al. 2008).

Should histopathological investigation of the suspected endometriotic lesions or endometrioma be recommended?

The histopathological investigation of the samples taken from the suspected endometriotic lesions and endometrioma helps to confirm the diagnosis and to exclude the underlying malignancy (Leyland et al. 2010).

*If the suspected endometriotic lesion and endometrioma are suspected by imaging methods, the malignancy risk should be assessed individually for each patient and it is recommended to take samples selectively for histological investigation.*

Are there any morphologic criteria that suggest malignancy?

The mural nodules taking up one or more contrast media in the cystic mass or the mural nodules with vascularization on color Doppler suggest malignancy (Tanaka et al. 2000). In addition to such criteria, loss of shadowing in the mass as determined by T2-weighted MRI images suggests malignancy (Takeuchi et al. 2006).

*A full oncologic assessment and pathologic investigation is strongly recommended because of the risk of malignancy in the ovarian masses, which take up contrast media, have vascularized polypoid protrusions or lost shadowing in the mass by MRI.*

What is the role of tumor markers, HE4 and CA 125, in differential diagnosis of endometrioma and ovarian malignancies?

There are some data suggesting that human epididymal antigen (HEA) 4 is a better indicator than Ca-125 to distinguish epithelial ovarian cancers from pelvic endometriosis and pelvic inflammatory diseases especially in premenopausal women (Takeuchi et al. 2006).

In a study in 1042 women with benign disease, HE4 increased in lesser extent than CA-125 (8% vs 29%,  $p<0.01$ ). The most significant difference was observed in patients with endometriosis, HE4 increased only 3% of the patients, whereas CA-125 increased in 67% of the patients ( $p<0.01$ ) (Moore et al. 2012). The difference was found to be 8% vs 26% in uterine fibroids ( $p<0.01$ ), 1% vs 21% in dermoid cysts ( $p<0.01$ ), 10% vs 37% in inflammatory diseases ( $p=0.01$ ), respectively (Moore et al. 2012). HE4 increases rarely compared to CA-125 especially in premenopausal patients. In a meta-analysis of 11 studies in a total of 3395 patients, the sensitivity of HE4 was 0.74 (95% CI 0.72-0.76), whereas the specificity was 0.87 (95% CI, 0.85-0.89). It was emphasized that measurement of HE4 was effective in distinguishing the benign diseases from the ovarian cancer (Lin et al. 2013).

Should the women with endometriosis scanned for ovarian cancer?

There seems to be causal relationship between endometriosis and specific types of ovarian cancer; however, the extent of this risk is very low and endometriosis is not deemed as a premalignant lesion. It is not recommended to scan the women with endometriosis for ovarian cancer due to its low incidence and the absence of effective scanning test. There is no data suggesting that the prophylactic excision of the endometriotic foci will help decreasing the risk of ovarian cancer. However, use of oral contraceptive pills decreases the risk of ovarian cancer in all users (Modugno et al. 2004).

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# CAN ENDOMETRIOSIS BE PREVENTED?

What are the risk factors for endometriosis?

First, it is required to determine the endometriosis risk factors to prevent endometriosis and associated autoimmune and atopic diseases. There are no classic risk factors specific to all women with endometriosis and the risk factors should be categorized in the patients with endometriosis classified into subgroups according to their clinical characteristics in future.

*Physical characteristics:* Some physical characteristics, such as having red hair, blue or green eyes, freckles have been associated with endometriosis (Woodworth et al. 1995; Somigliana et al. 2010).

*Family history:* Endometriosis is seen in women, whose first degree relatives have endometriosis, 4-10 times more than the general population (Moen and Magnus 1993). However, no specific gene was identified. Endometriosis is a polygenic/multifactorial disease, and develops as a result of genes and environmental factors (Matalliotakis et al. 2008; Layman 2013).

*Menstrual cycle characteristics:* Conditions that cause long term exposure to menstruation, such as early menarche ( $\leq 11$  years old), short cycle, long duration of menstruation, low parity, history of dysmenorrhea at younger ages are reported as risk factors (Eskenazi and Warner 1997; Missmer et al. 2004; Treloar et al. 2010; Nnoaham et al. 2012). However, the menstrual cycle characteristics can be used as a guide to the diagnosis and treatment strategies only if other symptoms suggest endometriosis (Peterson et al. 2013).

*Low BMI:* Low BMI is a risk factor during adolescence and early adulthood period (Ferrero et al. 2005; Peterson et al. 2013; Shah et al. 2013). It is suggested that an increase in BMI of one UNIT will decrease the possibility of endometriosis by 12-14% (Hediger et al. 2005). Endometriosis was observed 3 times more common in women with waist-hip ratio of 0.6 compared to those with waist-hip ratio of 0.7-0.79 (Shah et al. 2013).

*Environmental Factors:* The chemicals that damage the endocrine system either directly affect the gene expression or indirectly affect the function via metabolism, transportation, production, and release of the hormones and thus disrupt the reproduction in women. The consequent chromatin modifications can be transferred to the next generations and may cause the disease in the generations after (Edwards and Myers 2007; Jirtle and Skinner 2007).

Even if the role of such chemicals was not demonstrated clearly in the pathogenesis of endometriosis, it was observed that exposure to some chemicals, harmful to the endocrine system, was more common in patients with endometriosis (Simsa et al. 2010; Weuve et al. 2010).

Exposure to the chemicals that damage the endocrine system during embryogenesis increases the predisposition to endometriosis, whereas the hormonal and immune irregularities that occur during adulthood period trigger the onset of the disease (Cummings et al. 1996, 1999).

The risk of endometriosis and endometriosis-related infertility are higher in women working in agriculture, hostesses and healthcare professionals, who are exposed to the formaldehyde, chemical powders, and organic solvents (Marino et al. 2009).

*Smoking, Caffeine, Alcohol:* Smoking during adolescence and adulthood is associated with the decrease in the risk of endometriosis due to the antiestrogenic impact of the tobacco smoke. On the other hand, polycyclic-aromatic hydrocarbons and dioxin in the tobacco smoke increase the risk of endometriosis (Cramer et al. 1986; Sadeu et al. 2010; Zhang et al. 2011). In a study on the smoking habit in patients with endometriosis, no relationship was found between the types of endometriosis (superficial peritoneal endometriosis, endometrioma, deep infiltrated endometriosis) and the stages of endometriosis (Chapron et al. 2010).

Although it is considered that coffee and caffeine affect the immune system and increase the risk of endometriosis, no relationship was reported between caffeine consumption and the risk of endometriosis (Chiaffarino et al. 2014).

Alcohol can increase estrogen levels and damage the immune response. A relationship between alcohol consumption and endometriosis was reported, but the association with the severity of the disease was not clearly demonstrated (Parazzini et al. 2013).

*Allergic, Inflammatory and Autoimmune Disease History:* The inflammatory response and alterations in the cellular/humoral immunity cause overproduction of prostaglandins, metalloproteinases, cytokines, and chemokines, and thus create a suitable environment for the proliferation and maintenance of the endometriotic implants. This explains not only pain but also nervousness, tension, anxiety, headache, depression, fatigue, insomnia, dyspepsia, repeated vaginitis, repeated cystitis, autoimmune diseases, asthma and allergy may co-exist in patients with endometriosis (Kyama et al. 2003; Matarese et al. 2003; Olovsson 2011).

The epidemiological studies show that there is an association between endometriosis and autoimmune and atopic diseases (Sinaii et al. 2002). The drug allergies, allergic rhinitis, asthma, family history of allergic diseases are seen more in patients with endometriosis (Mabrayveark. 1982; Sinaii et al.2002; Matalliotakis et al. 2012). In clinical view, the autoimmune diseases, such as SLE, rheumatoid arthritis, Sjögren syndrome, are seen more often in the patients with endometriosis (Sinaii et al. 2002; Tietjen et al. 2007; Seaman et al. 2008; Keller et al. 2013). Again, the epidemiological studies showed that there was an association between endometriosis and pain syndromes (fibromyalgia, chronic fatigue syndrome, interstitial cystitis, IBS) (Sinaii et al. 2002). The prevalence of endometriosis was also found higher in patients with migraine. The risk of migraine has increased by 30% in the patients with endometriosis (Tietjen et al. 2007).

*Obstructive Müllerian anomalies:* Obstructive Müllerian anomalies that cause retrograde menstruation such as absence of the cervix, narrowing or blockage due to a malformation, vaginal agenesis, hymen imperforated are accompanied with endometriosis in adolescence, and treatment of such anomalies allow resolution of endometriosis (Ugur et al. 1995; Laufer et al. 2003; Bricou et al. 2008).

*Contraception:* The risk of endometriosis increases by the increasing number of ovulatory cycles (Missmer et al. 2004). COCs do not only suppress the ovulation but also increase apoptotic activity of the endometrium. Progestin component in COCs prevents implantation of regurgitated endometrial cells; inhibits expression of angiogenesis and matrix metalloproteinase, decreases inflammation of endometriotic implants and consequent immune response (Meresman et al. 2002; Vercellini et al. 2003a). On the other hand, estrogen component may play a role to ensure survival of the regurgitated endometrial tissue (Di Zerega et al. 1980). There was no study on the impact of any other oral contraceptives, except for monophasic COCs, on development or treatment of endometriosis in the literature, while this guideline was being drafted.

Do the combined oral contraceptives play a role in primary prevention of endometriosis?

The findings of the studies to determine the relationship between COCs and endometriosis are inconsistent in the literature. A protective effect was reported for those, who use COCs, but it was reported that the risk of endometriosis was 60% higher in those, who previously used COCs (Vercellini et al. 2011). However, this relation might not be casual. There might be non-diagnosed endometriosis in women, who did not respond to NSAIDs for dysmenorrhea and administered with COCs. And diagnosis of endometriosis might be delayed due to use of COCs for dysmenorrhea.

COCs do not significantly affect the risk of endometriosis. Recommending use of COCs for primary prevention of endometriosis has not been validated sufficiently.

Does the use of progesterone-only hormonal contraceptives play a role in the prevention of endometriosis?

Therapeutic amenorrhea achieved by progestin use is a useful method in the management of endometriosis (Fraser 2007; Belaisch 2009). As endometriosis is a chronic and recurrent disease, administration of a long-term hormonal treatment is recommended for patients with endometriosis (Belaisch 2009).

LNG-IUS, local, intrauterine progestin, which is a form of long-acting gestagen treatment, is a useful method for the management of endometriosis (Muzii 2006; Fraser 2007). LNG-IUS is very effective in the treatment of the complaints associated with endometriosis, providing endometrial atrophy and increasing apoptotic activity (ESHRE Capri Workshop Group 2008; Lan et al. 2013). LNG-IUS decreases the risk of recurrence of dysmenorrhea following conservative surgery of endometriosis (Vercellini et al. 2003b).

Do the methods that support immune system and decrease inflammation affect the development of endometriosis?

Stress affects the immunological health of the individual. The cellular immunity is damaged in endometriosis, facilitating development of ectopic endometrial implants (Christodoulakos et al. 2007). The duration of cycle is shorter in women with stressful job, and this is a risk factor for endometriosis (Fenster et al. 1999; Wang et al. 2004). Although it is not clear whether the impact of stress is causal or aggravating in development of endometriosis, some psychological, behavioral methods should be included in the multidisciplinary approach to prevent endometriosis.

Do the anti-inflammatory, antioxidant; anti-angiogenic agents have a role in primary prevention of endometriosis?

It is suggested that retinoic acid, COX-2 inhibitors, TNF-alpha inhibitors, vitamin D, Magnesium, Calcium, Simvastatin, Pentoxifylline, Curcuma (a yellow colored natural polyphenolic substance, used as a flavoring and colorant in curry, mustard, etc.) affect the levels of inflammatory markers and show anti-inflammatory activity and may potentially be used in prevention and treatment of endometriosis in experimental trials (D'Angelo et al. 1992; Balasch et al. 1997; Matsuzaki et al. 2004; Agic et al. 2007; Somigliana et al. 2007; Bruner-Tran et al. 2009; Swarnakar and Paul 2009, Altan et al. 2010; Jana et al. 2012; Lu et al. 2012; Mariani et al. 2012; Wieser et al. 2012; Harris et al. 2013).

It is suggested that melatonin, statins, and curcuma might be effective in prevention and regression of endometriotic lesions, and might be protective against endometriosis via inhibition of implantation and growth of endometriotic implants in the experimental trials (Paul et al. 2008; Bruner-Tran et al. 2009; Swarnakar and Paul 2009, Jana et al. 2012).

Endometriosis is an angiogenesis-depended disease. In the experimental models, it was demonstrated that sorafenib, an anti-angiogenic agent, and green tea inhibit development, growth and angiogenesis of endometriotic implants (Hull et al. 2009; Xu et al. 2009; Moggio et al. 2012; Wang et al. 2013). Resveratrol is a phytochemical compound that prevents proliferation, apoptosis and radical formation of oxygen radicals, which exists in grape, red wine, nut, and various fruits. It suppresses development of new microvascular development (Chen and Tseng 2007, Rudzitis-Auth et al. 2013). Such natural substances may potentially be used as preventive agents in endometriosis.

Use of anti-inflammatory, antioxidant and anti-angiogenic agents in endometriosis is still at experimental level, but they may have potential for use in future.

Pregnancy, Delivery, Lactation; Do nutrition and environmental factors play a role in primary prevention of endometriosis?

Infertility is an important risk factor for endometriosis (Peterson et al. 2013). Endometriosis is found in infertile women 6-8 times more than fertile women (Verkauf 1987). Pregnancy suppresses growth and inflammation of endometriotic lesions by increased progesterone level. The parity and lactation period in multiparous women are associated with the low risk of endometriosis (Missmer et al. 2004). In multiparous women, the risk is decreased by the number of children born alive and the duration of lactation period (Missmer et al. 2004). The recurrence rate of endometriosis was lower in women, who delivered vaginally, compared to nullipars and those, who delivered abdominally (Bulletti et al. 2010).

The toxic chemicals are discharged from the maternal reservoirs during lactation; the longer the time of lactation, the more toxins will be released, possibly the lower the risk of breast cancer will be.

One of the benefits of breastfeeding is a decrease in the risk of breast cancer and the other is recurrence of endometriosis. The risk of recurrence in the patients with endometriosis, who gave birth and breastfed within the last 5 years, decreases (Missmer et al. 2004).

When the literature about nutrition during pregnancy or exposure to chemicals is summarized, exposure to chemicals that harm endocrine system during embryogenesis increases susceptibility to endometriosis but for the initiation of the disease, hormones, immune disarrangements or exposure to chemicals that damage endocrine system is required in the adult life (Cummings et al. 1999).

According to Barker hypothesis, during early development phases, especially during intrauterine life, the exposure to harmful agents increases the risk of disease in adulthood leading to some permanent changes in the physiology and metabolism (Dexinger and Whitelaw 2012). As to endometriosis, it was reported that the sensitivity to estrogen develops if exposure to bisphenol-A occurs. As an example, the teeth fillings include bisphenol-A (Taylor 2008).

There is no clear data about prevention of endometriosis during intrauterine period.

Does diet play a role in primary prevention of endometriosis?

The consumption of a diet abundant in vegetables and fruits increases the immune system function, and prevents damages caused by free radicals, as they are rich in antioxidants (Parazzini et al. 2004). Some studies report that a diet abundant in plants and fibers increases estrogen excretion and decreases the risk of endometriosis (Armstrong et al. 1981; Kaneda et al. 1997). A high-fat diet increases the levels of estradiol (Longcope et al. 1987; Kaneda et al. 1997). Therefore, it is suggested that low-fat diet rich in fibers may affect the risk of endometriosis. Also, the benefit of consuming fish oil in the prevention of endometriosis has also been supported scientifically. Cabbage, cauliflower, broccoli, Brussels sprouts decrease estrogen level and they should be consumed abundantly (Zeligs 1998).

Data obtained from the studies show that the association of dietary fat intake with the risk of endometriosis is not clinically significant (Missmer et al. 2010; Trabert et al. 2011).

Even if it is known that a low-fat diet rich in plants and fibers decreases the risk of endometriosis, the strategies related to the modifications in diet to prevent endometriosis should be adopted after assessment of efficacy by future studies.

Does the physical activity play a role in primary prevention of endometriosis?

The regular physical activity increases the levels of sex hormone-binding globulin (SHBG), decreases the level of estrogen, and increases the levels of anti-inflammatory/antioxidant cytokine levels; and thereby demonstrates a protective affect for endometriosis, a diseases dependent upon estrogen (Dhillon and Holt 2003; Missmer and Cramer 2003). It is suggested that regular exercise decreases endometriosis risk by 40-80% (Cramer et al. 1986; Dhillon and Holt 2003). It was reported that doing exercise 3 or more times per week or for 30 minutes or more per day, 10 months or more per year for 2 years decreases the risk of endometrioma by 70% (Dhillon and Holt 2003). There is an inverse relationship between regular physical activity and risk of endometriosis, even if it is not strong (Vitonis et al. 2010). On the other hand, during ages between 12 and 21 years, it is suggested that intensive physical activity especially during early adolescence may increase the risk of endometriosis (Vitonis et al. 2009).

Does endometriosis regress spontaneously?

It was reported that pregnancy has a positive impact on endometriosis and endometrioma and the endometriotic cysts regress to such an extent that it cannot even be detected in postpartum (Benaglia et al. 2013).

There is no clear data on primary prevention of endometriosis in the literature. However, there is abundant clinical and scientific information that can be used to prevent endometriosis, if it is accepted as a systemic inflammatory, endocrine, immunological disease.

**Table. Risk Factors Associated with Endometriosis**

<b>High-Quality Evidence</b>	<b>Medium-Quality Evidence</b>	<b>Low-Quality Evidence</b>
<i>Müllerian Anomalies (obstructive anomalies that cause retrograde menstruation)</i>	<i>Family History</i>	<i>Physical characteristics (red hair, blue or green eyes, freckles)</i>
<i>Infertility</i>	<i>Characteristics of menstrual cycle (premature menarche, history of dysmenorrhea during early ages, short cycle, long duration of menstruation)</i>	<i>Low-fat diet rich in plants and fibers</i>
<i>Low Parity</i>	<i>Low BMI, low waist-hip ratio</i>	<i>Smoking</i>
	<i>Exposure to chemicals</i>	<i>Caffeine</i>
	<i>Alcohol</i>	<i>Anti-inflammatory agents</i>
	<i>COCs</i>	<i>Antioxidant agents</i>
	<i>Progestines, LNG-IUS</i>	<i>Anti-angiogenic agents</i>
	<i>Lactation time</i>	<i>Presence of myoma</i>
	<i>History of allergic, inflammatory or autoimmune diseases</i>	
	<i>Physical activity</i>	

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# ADENOMYOSIS

## **What is adenomyosis and how frequent is it?**

Adenomyosis is a benign pathological condition in which the ectopic endometrial stroma and glands are present at various depths in the myometrium (Benagiano ve Brosens 2006).

Adenomyosis is reported in 1-20% of women of reproductive age (Garcia ve Isaacson 2011). It is seen in 50% of patients with deep pelvic endometriosis (Lazzeri et al. 2014), and about 20% of endometriosis cases (Di Donato et al. 2014). The diagnosis of adenomyosis is conventionally based on the histologic examination of the hysterectomy specimen.

What are the risk factors associated with adenomyosis?

Being between 40-50 years-of-age, multiparity, previous uterine surgery, tamoxifen treatment, irregular menses, long-term tobacco use (>10 years) are risk factors for adenomyosis (Parazzini et al. 1997; Shrestha 2012).

## **What are the typical symptoms for adenomyosis?**

Dysmenorrhea, menorrhagia, chronic pelvic pain is typical but non-specific symptoms of adenomyosis (Shrestha ve Sedai 2012). Irregular and heavy menses along with dysmenorrhea without dyspareunia are highly suggestive of adenomyosis (Shrestha and Sedai 2012; Li et al. 2014).

## **How is adenomyosis recognized?**

Adenomyosis is usually asymptomatic. Since its symptoms, pain (dysmenorrhea, dyspareunia, chronic pelvic pain) and menometrorrhagia (mostly menorrhagia), are non-specific, its clinical diagnosis is difficult. Pelvic pain, dysmenorrhea and menorrhagia refractory to medical treatment presenting after 35 years of age should suggest adenomyosis. A homogeneously large uterus may indicate adenomyosis; however, leiomyomas are seen in 35-50% of the adenomyosis cases (Azziz 1989; Bazot et al. 2002). Imaging modalities for diagnosis are MRI, transvaginal ultrasound (TVUSG), and 3D-TVUSG.

What is the role of MRI in the diagnosis of adenomyosis?

The most reliable imaging modality for adenomyosis is MRI. Yet, MRI is not indicated for diagnosing adenomyosis and should be used only if another uterine pathology is to be investigated concurrently. MRI shows uterine zonal anatomy clearly, and a thick junctional zone (normal thickness is 2-8 mm) is suggestive of adenomyosis. Junctional zone thickness can vary during the menstrual cycle.

Moreover, hormonal therapies and myometrial contractions may distort the MRI findings. A junctional zone  $\geq 12$ mm is highly significant for adenomyosis (Reinhold et al. 1998; Bazot et al. 2001; Novellas et al. 2011). Likewise, MRI is reliable for the diagnosis of focal adenomyomas. The accuracy of MRI for adenomyosis diagnosis is 85-90% (Reinhold et al. 1996; Novellas et al. 2011).

What is the role of transvaginal sonography in diagnosis of adenomyosis?

TVUSG can be safely used for the diagnosis of adenomyosis. The sonographic findings for adenomyosis are irregular cystic areas in the myometrium (especially in the posterior wall), an enlarged uterus with a relatively thicker posterior wall, a displaced uterine cavity, echogenic linear stripes, border abnormalities and the presence of a mass effect (Reinhold et al. 1995; Kepkep et al. 2007). TVUSG has a high sensitivity but low specificity for adenomyosis (Meredith et al. 2009). The accuracy of TVUSG is reported to be 71% (Hanafi 2013).

3D TVUSG is especially useful in evaluating the junctional zone. It has an accuracy of 90% for the diagnosis of adenomyosis (Luciano et al. 2013).

## **Can a leiomyoma and a focal adenomyoma be differentiated preoperatively?**

MRI is useful in differential diagnosis of leiomyoma and adenomyosis (Byun et al. 1999). Although TVUSG has a high specificity and low specificity for adenomyosis, it is highly accurate for combined leiomyoma and adenomyosis. (Hanafi 2013)

Does adenomyosis cause pain?

## **Does adenomyosis cause pain?**

One of the most common symptoms of adenomyosis is dysmenorrhea, seen in 70-80% of patients (Li et al. 2014). However, coexisting endometriosis can complicate the situation. When dysmenorrhea and chronic pelvic pain are present in a patient with an enlarged uterus, adenomyosis should be suspected. If pain is the prominent symptom in a patient with a myomatous uterus, concomitant adenomyosis may be present. Dysmenorrhea is seen more frequently as the number of adenomyotic foci and depth of myometrial involvement increase (Levgur et al. 2000). Dysmenorrhea without dyspareunia is highly suggestive of adenomyosis.

Does adenomyosis cause menorrhagia?

Coexisting leiomyoma is reported to interfere with the evaluation of menorrhagia in patients with adenomyosis (Naftalin et al. 2014). The severity rather than the presence of adenomyosis is associated with menorrhagia (Naftalin et al. 2014). The depth of myometrial invasion is found to be associated with menorrhagia (Levgur et al. 2000). In conclusion, there is no consensus on the adenomyosis-menorrhagia association (Naftalin et al. 2014).

## **Does adenomyosis cause infertility? Should it be investigated in infertile patients?**

Since a significant number of patients with adenomyosis also suffer from endometriosis, the role of adenomyosis in infertile patients is debatable. Nevertheless, adenomyosis is thought to contribute to the problem (Gordts et al. 2008; Campo et al. 2012; Tomassetti et al. 2013). Others have suggested that diagnosing or treating adenomyosis is not necessary in infertility investigations (Maheshwari et al. 2012). In summary, a consensus is not reached on the subject.

### **Does adenomyosis affect IVF outcomes?**

The effect of adenomyosis on IVF outcomes has been a matter of debate; however a recent meta-analysis demonstrated it to have negative effects (Vercellini et al. 2014). Adenomyosis decreases implantation and clinical pregnancy rates and increases the risk of first trimester abortions (Thalluri ve Tremellen 2012; Vercellini et al. 2014; Yan et al. 2014). Therefore, evaluating for adenomyosis before proceeding with ART is recommended (Vercellini et al. 2014). Moreover, long term down-regulation is suggested to be of benefit in patients with adenomyosis who will undergo ART (Vercellini et al. 2014). Improved IVF success is reported in patients who are down-regulated using GnRH agonists for at least 3 months (Mijatovic et al. 2010). Coexisting endometriosis is again an important factor.

On the other hand, it has been suggested that implantation rates are not affected in women who are asymptomatic but found to have adenomyosis in TVUSG (Benaglia et al. 2014).

### **Does treating adenomyosis improve IVF outcomes?**

Adenomyomectomy is a uterus-sparing adenomyosis surgery, and when myometrium is spared as much as possible, it is found to decrease dysmenorrhea and menorrhagia while improving pregnancy rates (Wang et al. 2009; Osada et al. 2011; Grimbizis et al. 2014). It can increase fertility in adenomyosis patients with subfertility or multiple IVF failures (Pepas et al. 2012; Kishi et al. 2014).

Laparoscopic adenomyomectomy can improve pregnancy rates in patients  $\leq 39$  years old who had multiple IVF failures (Kishi et al. 2014).

## **Which treatment options are available for adenomyosis?**

The treatment method for adenomyosis depends on the symptoms and severity of adenomyosis and the patient's desire for pregnancy. Follow-up or treatment is not indicated in asymptomatic patients.

### **Surgery**

Hysterectomy is the preferred treatment for symptomatic patients who do not desire pregnancy.

Uterine artery embolization can be a minimally invasive option for symptomatic patients (Liang et al. 2012). MRI-focused ultrasonographic surgery is a minimally invasive procedure with thermal ablative effects (Fukunishi et al. 2008). Hysteroscopic endometrial resection/destruction/ablation techniques are short term minimally invasive treatment options for patients with menorrhagia. These techniques can be alternatives to hysterectomy for patients who do not plan to conceive and complain only from menorrhagia (Preutthipan and Herabutya 2010).

Uterus sparing (laparoscopic) adenomyomectomy can increase fertility in infertile patients below 39 years of age (Pepas et al. 2012; Kishi et al. 2014).

Uterus sparing surgery options are defined as either complete adenomyomectomy or cytoreductive/incomplete adenomyoma resection. Both are found to reduce dysmenorrhea and menorrhagia and increase pregnancy rates (Grimbizis et al. 2014).

### **Medical Treatment**

Medical treatment options in symptomatic patients are non-steroid anti-inflammatory agents, levonorgestrel intrauterine systems (LNG-IUS), GnRH agonists, aromatase inhibitors, and progestions (Cho et al. 2008; Schweppe 2009; Badawy et al. 2012). LNG-IUS are found to be the most successful medical treatment option. They decrease uterine volume and reduce dysmenorrhea and menorrhagia significantly (Cho et al. 2008).

*There is moderate quality evidence supporting the efficacy of medical treatment options, especially LNG-IUS, for adenomyosis-related dysmenorrhea and menorrhagia. Guideline Development Groupd strongly recommends their use for treatment of adenomyosis.*

### **Is adenomyosis associated with cancer?**

In the pathological specimens of malignant cases, adenomyosis is found to be most commonly associated with endometriod adenocarcinoma (Musa et al. 2012). Endometrial cancer coexisting with adenomyosis is associated with low grade disease, a history of hormonal therapy, negative lymph nodes and a good prognosis (Musa et al. 2012). Malignant transformation of adenomyosis is extremely rare.

### **Does adenomyosis increase pregnancy complications?**

Pregnancy complications such as early pregnancy loss, preterm birth, intrauterine growth retardation, hypertension, and placental insertion anomalies are reported in up to 70% of adenomyosis cases (Minegishi et al. 2014). Pregnancy complications are more common in the presence of diffuse adenomyosis than in focal adenomyosis. Pregnancy complications seem to decrease after adenomyosis surgery, especially in the diffuse type. (Minegishi et al. 2014). However, all pregnancies following adenomyosis surgery should be monitored closely. Although the risk for uterine rupture is not very high (0.4%), the possibility should be considered (Nikolaou et al. 2013).

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# APPENDIX: OTHER GUIDELINES

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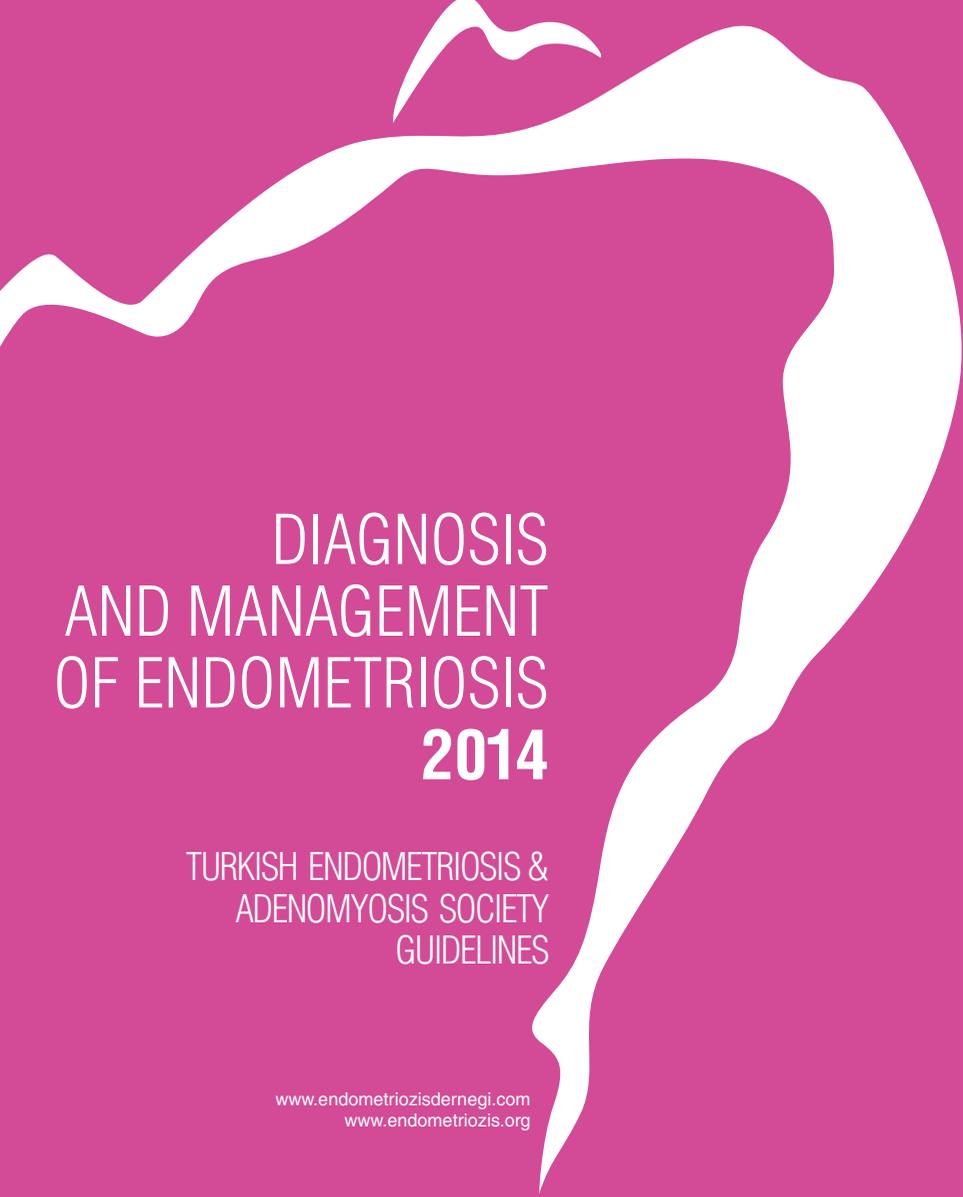
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