



Clinical evaluation and management of endometriosis: guideline for Korean patients from Korean Society of Endometriosis

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Endometriosis is one of the most common diseases in reproductive ages, and it affects patients' quality of life and fertility. However, few Korean guidelines are available for the evaluation and management of endometriosis. Korean Society of Endometriosis reviewed various literatures and trials, and to provide seventy-one evidence-based recommendations. This review presents guidelines for the diagnosis and management of endometriosis with emphasis on: its role in infertility, treatment of recurrence, asymptomatic women, endometriosis in adolescents and menopausal women, and possible association of endometriosis with cancer.

Keywords: Endometriosis; Infertility; Pelvic pain; Dysmenorrhea

Introduction

Endometriosis is defined as the presence of endometrium-like tissue outside the uterus. Endometriosis causes severe pain, and/or infertility in reproductive women. The prevalence of endometriosis is known to be 2–10% in the reproductive age. While there are practice guidelines for endometriosis in Western countries, but none in Korea reflecting domestic epidemiology and condition. Thus, members of the Korean Society of Endometriosis (KSE) decided to develop guidelines for Korean clinicians.

To produce evidence based guideline, we reviewed published guidelines and literatures including international and domestic studies.

Recommendations are categorized into 4 grades (A–D) depending upon the strength of evidence. The grades of recommendation are:

- A: Meta-analysis or multiple randomized trials.
- B: Large non-randomized trials or case control/cohort studies.
- C: Non analytic studies or case reports/case series.
- D: Expert opinion.

Background

1. Prevalence

Prevalence of endometriosis is reported to be about 10% of reproductive age women, about 20–30% of infertility women, and about 40–82% of chronic pelvic pain women [1-3]. A study on Korean women reported that 1.03–6.7% of patients experiencing gynecologic surgery, 2.5–8.5% of patient who were operated for chronic pelvic pain, 2.5–45.4% of patient who were diagnosed with infertility, had endometriosis. The prevalence of

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endometriosis varies across studies (grade C) [4-6].

2. Risk factors

1) Clinical factors

Clinical risk factors for endometriosis include the following: null parity, short menstruation cycle, long menstruation duration, heavy menstruation bleeding, early menarche, family history of endometriosis, obstructive uterine anomaly, low body mass index, Asian, and diethylstilbestrol exposure *in utero* [7-9] (grade B).

2) Genetic factors

It is known that endometriosis is closely related to genetic factors. However, endometriosis follows multi-genetic foci with non-Mendelian heredity [10,11] (grade C).

3) Environmental factors

Although the relationship between endometriosis and exposure to endocrine disrupting chemicals has been reported recently, but the mechanism has not been revealed definitely, and further studies are needed [12,13] (grade C).

4) Dietary factors

Studies between endometriosis and diet have been conducted only on small scale studies or patient control studies. Consumption of alcohol, caffeine, fat and red meat, ham, and smoking can possibly elevate the risk of endometriosis, while consumption of green vegetables and fruits lower the risk. Meta-analysis, however, did not show any significance [7,14,15] (grade C).

Diagnosis

1. Symptoms

- Clinicians should suspect endometriosis when patients complain of following symptoms; gynecologic symptoms — such as dysmenorrhea, non-cyclic pelvic pain, dyspareunia, infertility and fatigue accompanied any symptom of above, or cyclic non-gynecologic symptoms such as — dyschezia, dysuria, hematuria and rectal bleeding, and shoulder pain in reproductive age (grade D).

Many studies reported endometriosis-related symptoms, as

dysmenorrhea, chronic pelvic pain, deep dyspareunia, cyclic bowel symptom, fatigue and infertility [16-18]. However, studies did not provide a predictive value of these symptoms. In addition to a history of ovarian cysts, irritable bowel syndrome or pelvic inflammatory disease, other symptoms, including dysmenorrhea in women with infertility, abdominopelvic pain, dysmenorrhea, heavy menstrual bleeding, infertility, dyspareunia, and post coital vaginal bleeding may indicate the possibility of endometriosis [16,19].

2. Clinical examination

- Clinicians should perform pelvic and abdominal examination to all suspected endometriosis patients. When vaginal exam is not appropriate, as for a patient with no sexual intercourse history, a rectal examination may be performed instead for diagnosis (grade D).
- Painful rectovaginal induration/nodule, and vaginal nodules in posterior vaginal fornix, may be due to deep endometriosis (grade C).
- Clinicians may regard palpable ovarian mass in pelvic examination as an ovarian endometrioma (grade C).
- Clinicians may consider endometriosis even if the patients have no abnormality in pelvic exam (grade C).

Endometriosis is diagnosed by past history, clinical examination based on sign and symptom, radiologic findings, and pathologic confirmation through laparoscopy [20,21]. Clinicians can definitively diagnose as endometriosis when endometrial glands and stromal tissue are found pathologically via laparoscopy. In many cases, clinicians regard typical endometriosis lesion in abdominal cavity as proof of endometriosis. Clinicians may prescribe pain relief medication for in invasive procedures.

3. Laparoscopy

- Histologic proof of endometriosis through laparoscopy is the gold standard of endometriosis diagnosis. Although laparoscopy without pathologic confirmation has limited value, the absence of histologic confirmation cannot exclude endometriosis (grade D).
- KSE recommends biopsy and histologic confirmation when patient have endometrioma and/or deep endometriosis to exclude malignancy (grade D).

Although there is an insufficient number of studies that suggest laparoscopy without biopsy has compatible accuracy

of diagnosis to histologic confirmation, clinicians may exclude endometriosis when the patient has no suspicious lesion on diagnostic laparoscopy [22-24]. It is only possible laparoscopy is performed appropriately and pre-operative evaluation is adequate. Laparoscopic endometriosis diagnosis without biopsy has limited value [25].

4. Ultrasound

- KSE recommends transvaginal or transrectal ultrasonography to confirm or exclude ovarian endometriomas (grade A).
- In premenopausal women, ovarian endometrioma has ultrasonographic findings, ground glass echogenicity, 1 to 4 compartments, absence of papillary structure, and blood flow (grade D).
- Transvaginal or transrectal ultrasonography may be helpful for patient with rectal endometriosis related signs and/or symptoms to confirm or exclude endometriosis (grade A).

KSE does not recommend the general use of transvaginal sonography for the diagnosis of rectal endometriosis, because diagnostic accuracy is low unless performed by a highly experienced expert [24,26,27].

5. Magnetic resonance imaging

- Clinicians should decide on follow-up assessment through additional imaging evaluation including magnetic resonance imaging (MRI), when deep endometriosis infiltrating ureter, bladder, or bowels is suspected in patients' history and clinical examination (grade D).
- It is not yet verified yet that MRI is useful for diagnosis of peritoneal endometriosis (grade D).

Clinicians should perform additional evaluation, such as cystoscopy, colonoscopy, barium enema, rectal sonography, or MRI, for suspected deep endometriosis [20,25].

6. Biomarkers

- It is not yet well verified yet the use of biomarker from endometrial tissue, menstrual bloods, and uterine fluids, or immunological biomarker such as CA125 from plasma, urine, or serum is helpful for the diagnosis of endometriosis (grade A).

Many researchers have studied various biomarkers, but clinical

application is still limited. If diagnostic value is revealed, clinicians may be able to correctly diagnose endometriosis less invasive [28-30].

Infertility

- KSE recommends the removal of adhesions by excision or ablation of endometriosis lesion to improve spontaneous pregnancy rates for laparoscopically diagnosed minimal endometriosis (American Society for Reproductive Medicine [ASRM] stage 1, 2) for infertile women (grade A).

As published literatures, operative laparoscopy is better than simple diagnostic laparoscopy for spontaneous pregnancy rate, in minimal or mild case of endometriosis [31-33]. There are only a few studies that compare the pregnancy rates among operation methods [34]. For minimal or mild endometriosis, CO₂ laser vaporization may improve pregnancy rate more than monopolar electro-coagulation [31].

- In infertile women with severe endometriosis (ASRM stage 3, 4), operative laparoscopy shows higher spontaneous pregnancy rate than expectant management (grade A).

Still now, the gap between surgical and expectant management is not well studied, but surgical methods, laparoscopic or laparotomy surgery demonstrate a superior pregnancy rate of, 45–69%, compared to expectant management [34]. However, clinicians should pay attention to normal ovarian tissue conservation when doing operation.

- KSE recommends ovarian cystectomy, instead of drainage and/or coagulation, because it may improve spontaneous pregnancy rate (grade A).
- Ovarian function may decline after an operation for ovarian endometrioma (grade D).

There is a study that claims cystectomy improves spontaneous pregnancy rate compared to drainage/coagulation of endometrioma (≥ 3 –4 cm) [35]. Clinicians should discuss about possible decline in ovarian function with patient sufficiently. Repeated operation had little influence on pregnancy rate improvement [36].

- When the patient wants to conceive naturally right after operation, clinicians should not prescribe adjuvant hor-

monal treatment (grade A).

- Clinicians should not suppress ovarian function by hormonal treatment to improve fertility, in infertile women having endometriosis (grade A).

Adjuvant medical treatment after surgery is for removing remnant endometriosis, and there is no evidence that states it raises pregnancy rates [36,37]. Ovarian suppression by oral contraceptive, progestin, gonadotropin-releasing hormone (GnRH) agonist, or danazol is not helpful in enhancing fertility [38].

- Clinicians should try assisted reproductive technology (ART) to infertile women with endometriosis, when causes of infertility are the compromised tubal function and/or male factor. It may be attempted, if patient has already failed to other infertility management (grade D).
- Clinicians may consider controlled ovarian stimulation followed by intrauterine insemination in infertile women with ASRM stage 1, 2 endometriosis women (grade C).
- In infertile women with severe endometriosis (ASRM stage 3, 4), *in vitro* fertilization-embryo transfer (IVF-ET) is an effective alternatives, if the patient have trouble conceiving after operation, or is of old age (grade C).

According to blind studies, regarding minimal or mild endometriosis women, controlled ovarian stimulation followed by intrauterine insemination showed 5 times higher pregnancy rate than observation. It is reported that intrauterine insemination combined with controlled ovarian stimulation improves pregnancy rate compared to IUI only method [31,34].

- KSE recommends the use of GnRH agonists for 3–6 months before ART to improve fertility in women with infertility diagnosed with endometriosis (grade B).

Cochrane review reported a 4-fold increase of pregnancy rate in GnRH agonist treatment prior to ART. However it is not well understood how this effect can be applied endometriosis, and the mechanism is not demonstrated convincingly [36].

- In infertile women with endometrioma (≥ 3 cm), there is lack of evidence to support whether cystectomy prior to ART increase pregnancy rate (grade A).

Many studies evaluated fertile influence of endometrioma excision, but there are no united results. Clinicians should be aware of the possibility of decrease in ovarian function by sur-

gical resection.

- KSE does not recommend supplying specific nutrients or applying alternative medicine to infertile women with endometriosis. However some women may feel that these treatments would be helpful (grade D).
- It is possible the there is an increased incidence of spontaneous abortion, preterm delivery, small for gestational age (SGA), or placenta previa, when the mother has endometriosis in pregnancy (grade B).

Endometriosis may increase the pregnancy related complication. It is reported to show 1.37 times higher in number of preterm delivery, 1.13 times placenta previa, 1.76 times in postpartum bleeding or placenta related complication, and 1.47 times for cesarean delivery ratio. SGA or fetal death in uterus, however, are not increased [37].

Medical treatment of endometriosis-associated pain

- There is no evidence that one medication has superior over any other medications, for endometriosis-associated pain treatment (grade A).

Clinicians should personalize the medication depending on side effects, compliance, and costs. Most randomized controlled trials about treatment of endometriosis-associated pain are aimed at surgically diagnosed endometriosis. Many studies mention unclearly whether operative or only diagnostic laparoscopy was done. In addition, researchers did not investigate the efficacy of long-term treatment (≥ 6 months). There is insufficient evidence to supports any medication is better than others.

1. Empirical treatment

Imaging modalities are increasing in accuracy for endometrioma and deep infiltrative endometriosis (DIE), though laparoscopy is an important method to diagnose endometriosis. Therefore, when endometriosis is suspected by clinical evidence or radiologic diagnosis, clinicians can begin medical treatment without operative confirmation [39-41].

2. Combined oral contraceptives

- Clinicians may prescribe combined oral contraceptives for

endometriosis related pain control (grade B).

- Continuous use of combined oral contraceptives has advantages for pain relief compare to cyclic medication (grade C).

There are rare randomized controlled trials which proved the effects of oral contraceptive for endometriosis-associated pain. In addition, it is not verified that a certain oral contraceptive is better than others [42]. However, most observational studies and guidelines recommend oral contraceptives as first line treatment for endometriosis-associated pain. KSE recommends continuous usage, because 20–40% of cyclic users experience pain during withdrawal bleeding, and 50% of women who have pain with cyclic use get better with continuous use. Moreover, both groups show similar safety and recurrence rates. Occasionally, women with continuous use may experience unexpected vaginal bleeding, so some clinicians recommend continuous use of 4–7 cycles with 4–7 days of withdrawal period; a so called pre-planned extended regimen. Individualization is most important for enhancing compliance [43,44].

3. Progestins

- KSE recommends progestin, such as medroxyprogesterone acetate (MPA), dienogest, or norethisterone acetate for endometriosis-associated pain (grade A).
- Clinicians may use levonorgestrel intrauterine system (LNG-IUS) for endometriosis-associated pain (grade B).

Clinicians have tried various types of progestins, those that are commonly used include norethindrone acetate (NETA), dienogest, and MPA. Patients may experience vaginal bleeding, weight gain, headache, mood change, and decreased libido. Clinicians should consider bone density loss for long-term use of progestin. Direct comparative study dealing with specific medication is superior to others in aspect of efficacy or side effect is rare [45]. Clinicians may prescribe progestins in consideration of side effects, costs, and compliance. For example, NETA and dienogest are both 19-nortestosterone derivatives, but dienogest has an anti-androgenic effect NETA (it is partially metabolized as estrogen, so theoretically it may prevent of loss of bone density) is not available domestically. Dienogest has advantages for compliance due to few side effects, but the effect of bone density has not been proved yet.

Clinicians can prescribe MPA for both oral and intramuscular route, and subcutaneous formulation was developed recently.

MPA has similar efficacy as GnRH agonist and decreases bone density temporarily. Although studies show recovery bone density after cessation of the medication, clinicians should be cautious on the long-term (≥ 2 years), and the use is not recommended in adolescents. Small scale studies reported that progestin has a similar pain relief effect as GnRH agonist, so clinicians may use progestin on patients with side effects from other medications or low compliance [40,43].

4. GnRH agonist

- KSE recommends GnRH agonist for treatment of endometriosis related pain (grade A).
- Clinicians should prescribe add back therapy for minimizing disadvantages of low estrogen symptom (grade A).
- Various medications, such as progestin, estrogen, estrogen+progestin, tibolone, etc. may use as add-back therapy. More studies are needed regarding which medication is most appropriate (grade C).

The effects of GnRH agonist for endometriosis related pain have been studied extensively. GnRH agonists are superior to placebo, but not to combined oral contraceptives. Clinicians should prescribe add-back for low estrogenic symptom and loss of bone density. Various medications may be used as add back, and no specific medication is better than others. Add-back treatment do not reduce effect of pain control. Low estrogen symptom is the most concerning matter, yet the duration of treatment is not identified. Most studies recommend less than six months only for women over 18 years of age [40,43,44].

5. Other medications

- Danazol, and gestrinone are effective for endometriosis related pain, but clinicians should be aware of the side effects (grade C).
- GnRH antagonists are not appropriate for common use (grade C).
- Clinicians may consider aromatase inhibitor merging with other medication; such as Combined oral contraceptive (COC), progestin, and GnRH agonist, when usual therapy is not satisfactory (grade B).

Danazol was the first medication approved by Food and Drug Administration (FDA), for endometriosis. It suppresses ovulation with powerful anti-estrogen effect and androgenic effect. However, clinicians prescribe restrictively nowadays

because of its side effects such as vasomotor symptoms, liver function abnormality, and dyslipidemia. GnRH antagonist has theoretical possibility, but only a few practical usages were reported. Aromatase inhibitor delayed recurrence with anastrozole-combined therapy compared to goserelin in sole. A literature reported combined treatment letrozole 2.5 mg and NETA 2.5 mg is effective for patients who are resistant to other endometriosis medication. If other medications are ineffective, aromatase inhibitor combined to other medication may be used [43,44].

Surgical treatment of endometriosis

1. Targets for surgical treatment of endometriosis

- Asymptomatic patients whose endometriosis was incidentally discovered during operation, do not need medical or surgical treatment (grade D).
- Surgical management of endometriosis for endometriosis-related pain may be done after failure of medical treatment (grade D).

Endometriosis patients who have pelvic pain or ovarian endometrioma need surgical management. Eligible candidates for surgical management are limited to patients who do not respond to medical treatment or are contraindicated for it, or have acute adnexal diseases such as torsion or rupture, or deep infiltrated endometriosis invading to bowel, bladder, ureter, or pelvic nerve [46,47].

2. Evaluation before operation

- Decision for surgical management of endometriosis should be based on clinical evaluation, imaging modality, and medical treatment response. Diagnostic laparoscopy should be restricted (grade D).
- Imaging evaluation should be based on symptoms and physical examination (grade D).
- Diagnostic value of preoperative serum CA125 is limited. Therefore, usual examination of serum CA125 is not recommended before operation. But, it may be done as a part of evaluation for undiagnosed adnexal mass (grade D).

Pelvic ultrasonography, especially transvaginal sonography, is recommended for suspicious adnexal mass. Transrectal sonography, colonoscopy, barium enema, and MRI are useful for detecting rectovaginal septum infiltrative endometriosis.

When patients have regular bladder symptoms, such as hematuria, cystoscopy is helpful [46]. Clinicians should discuss the risk of surgical management with the patient, and get informed consent.

3. Surgical approach

- Clinicians should not prescribe hormonal treatment for endometriosis pain control before surgery (grade A).
- Adjunctive hormonal therapy after surgery is divided into short-term (<6 months) and long-term (>6 months), and the latter is intended for secondary prevention (grade D).
- Clinicians are recommended not to prescribe adjunctive short-term hormonal therapy for endometriosis associated pain after surgery, because it does not add to the outcome of surgery (grade A).
- The selection of adjunctive treatment for prevention of recurrence and pain depends on patient preference, cost, efficacy and side effects (grade D).

Although clinicians prescribe GnRH agonists to reduce inflammation, blood flow, and adhesions in endometriosis, preoperative hormonal treatment did not reduce both endometriosis related pain and recurrence [40]. Therefore, KSE does not recommend preoperative hormone treatment for endometriosis related pain and/or prohibiting recurrence.

Adjuvant hormonal treatment has two purposes. In the short-term, it makes additional effect on pain relief effects of surgical treatment. Long-term treatments (≥ 6 months) may reduce recurrence [48].

Studies suggest that patients with post-operative hormonal therapy have lower degree of pain after 12 months. However in terms of pain recurrence, there is no significant difference with one year risk ratio of 0.76 (95% confidence interval [CI], 0.52–1.1), and 2 year risk ratio of 0.70 (95% CI, 0.47–1.03) [49].

4. Results of surgical treatment

- Surgical removal of laparoscopically diagnosed endometriosis can be helpful for pain relief (grade A).
- KSE recommends surgical resection of ovarian endometrioma, because it is more efficient to prevent pain recurrence than drainage or coagulation (grade A).
- If the patient has finished child bearing, and not responsive to conservative management, clinicians may operate total hysterectomy and both salpingo-oophorectomy, and surgical removal of endometriosis. However, clinicians

should explain that total hysterectomy is not essential for the treatment of endometriosis (grade D).

- KSE recommends continuously prescribing combined estrogen/progestogen or tibolone (grade C).
- Laparoscopy is preferred to laparotomy for surgical treatment of endometriosis (grade C).
- Clinicians may use anti adhesion agents during endometriosis-related operation (grade B).

When endometriosis lesion is resected surgically, 80% of patients are relieved of pain after operative laparoscopy compared to 32% of patients after diagnostic laparoscopy [35]. Cochrane review reported that the surgical resection of endometriosis reduces the endometriosis-related pain by 6.5 times less after 6 months and by 10 times lower after 12 months. Surgical resection of endometrioma is more effective than drainage or coagulation for dysmenorrhea, dyspareunia, or chronic pelvic pain [50]. It lowers the recurrence of endometriosis, and additional operation owing to recurrence, and enhances ovarian follicle response to gonadotropin. However, clinicians should be aware that cystectomy may damage the ovarian tissue and reduce the function of the ovary function. Drainage is not recommended because 80–100% of endometriosis will recur within 6 months. Total hysterectomy and both adnexectomy regress remnant endometriosis lesion and reduce recurrence rate of endometriosis-related pain as much as 6 times and as much as 8.1 times at re-operation [41]. Clinicians should consider hormone replacement therapy after both adnexectomy. KSE recommends estrogen-progesterone-combined therapy, because recurrence rate is lower than estrogen-only therapy or no adjuvant therapy.

Anti-adhesion agents are beneficial to patients who have no endometriosis. Clinicians can use oxidized regenerated cellulose on operative laparoscopy of endometriosis, but icodextrin has no proven effect [40].

- When patients have re operation for recurrent endometriosis, endometriosis is recurred in 20–40% of cases, similar to the recurrence rate after the first operation (grade A).
- Clinicians should carefully consider repeating the operation, for the degree of pain relief after operation is significantly decreased when operation is repeated (grade C).
- Although there is insufficient evidence, follicular phase may be beneficial for endometriosis operation (grade D).

About 83% of patients who had surgery still had endome-

triosis-related pain. After repeated operation, only 53% of patients experienced pain relief. Therefore, clinicians are advised to carefully consider repeating the operation [49].

Follicular phase is best for operating. During the luteal phase, clinicians may mistake corpus luteal cyst for endometrial cyst. In addition, endometrial tissue can be re-implanted by the following menstruation.

5. Deep infiltrative endometriosis

DIE operation should be based on a multidirectional approach and professional experience. Clinicians should give various and professional treatment, and also consider surgical excision of extragenital endometriosis for symptom relief.

6. Ovarian endometrioma

- Clinicians should consider the patient's future plans for children when deciding on the therapeutic range of ovarian endometrioma (grade D).
- Ovarian endometrioma may implicate the widespread endometriosis (grade D).
- In women with ovarian endometrioma, KSE recommends cystectomy compared to drainage or CO₂ laser vaporization. Ovarian cystectomy reduces pain and recurrence, and allows histological diagnosis (grade A).
- Clinicians should remove ovarian endometrioma (≥3 cm) in women with pelvic pain (grade A).
- Clinicians should prescribe post-operative hormone therapy for women who do not plan on pregnancy (grade A).
- Clinicians should prescribe LNG-IUS, COC, or progestin at least 18–24 months after operation (grade A).

Patients who received cystectomy have lower recurrence rate of dysmenorrhea, dyspareunia, and pelvic pain, than those who received drainage or coagulation for endometrial cyst. After the operation, patients who took COC during 6–24 months, experienced reduced dysmenorrhea, but no change in dyspareunia and pelvic pain. Combined oral contraceptive treatment within 6 months after operation also did not reduce endometriosis-related pain [18,36]. Both continuous and cyclic use of hormonal therapies is similarly effective, therefore the choice of medication should depend on patient preference, cost, and side effects. The more/longer the patient carried on therapy, the less amount of pain recurred. Women who were taking combined oral contraceptives showed lower rate of ultrasonographically-diagnosed ovarian

endometrioma.

Studies have reported that the use of LNG-IUS lowered dysmenorrhea in women with previous experience of endometriosis operation and severe dysmenorrhea. The use of GnRH agonist, danazol, MPA, and pentoxifylline after operation shows no additional advantage to reduce pain recurrence.

7. Additional treatment

- KSE does not recommend laparoscopic uterosacral nerve ablation (LUNA) as an additional step to conservative surgery for endometriosis associated pain (grade A).
- Clinicians can perform presacral neurectomy (PSN) for endometriosis associated midline pain as additional procedure to conservative surgery. It is effective, but risky and requires high degree skill (grade A).

Although it increases the risk of uterine prolapse and ureter damage, additional LUNA made no difference in symptom improvement after 6 months and 12 months, compared to established operations. PSN is effective for midline pain, but may have other complications such as bleeding, constipation, urinary retention, urgency, or insensibility to the first stage of labor, therefore requires a highly skilled expert to perform the surgery [40].

Recurred endometriosis

- Clinicians should avoid second line surgery in women who want to conceive when endometriosis is recurred after the first surgery (grade B).
- Clinicians may try empirical hormonal treatment for recurrent endometriosis-related pain between *in vitro* fertilization (IVF) procedure cycles (grade D).

There is a study about the effect of second line surgery for recurrent endometriosis. Out of 313 patients who attempt to conceive, and 81 patients (26%; 95% CI, 21–31%) were pregnant. There is no significant difference between laparoscopy (27%) and laparotomy (25%) [51,52]. In conclusion, pregnancy rates after IVF in recurrent endometriosis women is not inferior to that after second line surgery. Pregnancy after second line surgery is decreased compared to the first line surgery. Muzii et al. [53] reported that second line surgery to recurrent ovarian endometrioma may more severely damage ovarian tissue more, and decrease ovarian reserve compared

to first line surgery.

Therefore, if possible, clinicians should avoid second line surgery for recurrent endometriosis in women who plan on getting pregnant. Clinicians may try empirical hormonal treatment for recurrent endometriosis-related pain between IVF procedure cycles.

Asymptomatic endometriosis

- It is unnecessary to remove incidentally-diagnosed peritoneal, ovarian, deep endometriosis (grade D).

Asymptomatic endometriosis is defined as incidentally-diagnosed pelvic, ovarian, or deep endometriosis without pain, or infertility. Accurate incidence cannot be found, but 3–45% women who received laparoscopic tubal ligation have endometriosis [54].

There is no report that supports treatment of incidentally-diagnosed asymptomatic endometriosis. When researchers track the patient with asymptomatic endometriosis, the patient rarely experiences any symptoms [55,56]. Therefore, surgical treatment of endometriosis is not recommended.

Meanwhile, some researches recommend excision of endometrioma, for a type of ovarian cancer may be related to endometriosis. However, the risk of ovarian cancer is very low and a definite relation has not been verified [57,58]. Therefore, clinicians do not have to surgically remove asymptomatic endometrioma [41].

Endometriosis of adolescents

- Generally, treatment of adolescents' endometriosis is based remedy of adults (grade D).
- Clinicians should be aware of loss of bone density, when prescribing GnRH agonist to adolescents (grade D).

The guideline for adolescent endometriosis is based on studies for adults because the studies aimed at adolescents are extremely limited.

Clinicians may start medical treatment for suspicious endometriosis of adolescents and should take into account the patient's age and side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line treatment for dysmenorrhea. COC are the alternatives for resistant to NSAIDs. Many

luteal hormones reduce endometriosis-related pain, so it may substitute COC. However, there is risk of bone density loss. Clinicians may prescribe GnRH agonist for pain relief when patients are reluctant to surgery [59-61]. KSE does not recommend prescribe it for patients younger than 16 years old, because of possibility of bone density loss. Usually GnRH agonists are used on patients over 18 years of age. Clinicians should prescribe add back, and check the intake of calcium and vitamin D, as well as bone density [61].

Clinicians should be more careful when deciding on surgery when it comes to adolescent patients. Experts with copious experience on adolescent endometriosis should perform the surgery, because endometriosis of adolescents takes different aspects [60-63]. Studies on the effects of surgical treatment of adolescents are insufficient, though the treatment may effectively reduce pain. Clinicians should consider long-term medical treatment after operation for recurrence prevention. There is no consensus that adjuvant medical treatments are necessary for all adolescent patients nor that long-term problems such as recurrence or infertility may be prevented [64].

Endometriosis in menopausal women

- Endometriosis may exist after natural or surgical menopause, but symptoms usually disappear (grade D).

Clinicians should not hesitate to prescribe hormone replacement therapy in symptomatic menopausal women with endometriosis [65].

- KSE recommends the administration of continuous combined estrogen-progestin therapy or tibolone (grade C).

Endometriosis is able to recur after hormone therapy if the previous operation did not sufficiently remove endometriosis. Therefore, clinicians should closely watch the patient's symptoms [66,67].

Endometriosis and ovarian cancer

- Clinicians should confirm pathologic diagnosis after operative treatment.
- KSE does not recommend additional evaluation for ovarian cancer in women with endometriosis, because the

incidence of ovarian cancer is very low (grade A).

As meta-analysis of patient-control studies, women with endometriosis history have significantly higher risk of clear cell (odds ratio [OR], 3.05), low-grade serous (OR, 2.11), and endometrioid invasive ovarian cancer (OR, 2.04) [57]. Still, clinicians should recognize that the overall risk of ovarian cancer is extremely low.

Conclusion

This guideline is the first structured and evidence-based review for Korean endometriosis patients. There are some recommendations which are based on experts' opinions only, and actually many studies and clinical experiences are still in progress. Therefore, we expect that many answers will be provided with get high quality evidences in later guidelines.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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