Clinical Guidelines for the **Management of Endometriosis** 2016

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Obstetrical and Gynaecological Society of Malaysia

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1.0 Introduction

What is endometriosis

Endometriosis is a common but debilitating disease that affects between 5 – 10% of women of reproductive age.[1] Clinically, endometriosis is defined as the presence of endometrial glands and stromal tissue outside the uterus. This causes an estrogen-dependent chronic inflammatory process which results in substantial morbidity, severe pelvic pain, multiple surgeries and impaired fertility [2,3]

At present, there is no consensus on what is the cause of this disease. Healthcare professionals need to be aware that there are a number of possible factors that would increase the chances an individual would suffer from endometriosis. Studies have indicated that genetics may increase the risk of endometriosis by 3 to 10 times, particularly among first-degree relatives of women with endometriosis.[2]

Why is it important?

Endometriosis is not merely a disease that affects the reproductive system of a woman. Studies have shown that regardless of age, endometriosis negatively affects a woman's life in terms of marital/sexual relationships, social life, physically and psychologically.[3]

Purpose of this proposed guideline

The purpose of this guideline is to provide healthcare providers with practical advice on the care of women with endometriosis. This guideline will highlight diagnosis, classification, and treatment for endometriosis-related pain and infertility. This guideline serves to address the limitations that are faced in the treatment of this condition in Malaysia. The areas that we need to address are the expertise in advanced laparoscopy as well as the availability of assisted reproductive techniques in Malaysia.

For further reading and levels of evidence, kindly refer to the 2014 European Society of Human Reproduction and Embryology (ESHRE) Guidelines: Management of women with endometriosis.

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2.0 Endometriosis

2.1 The basic science of endometriosis

At present, the pathogenesis of endometriosis is still unclear. However, there are several theories behind the cause of this disease.

On a cellular level, the failure of immune mechanisms to destroy ectopic tissue and prevent abnormal differentiation of endometriotic tissue has been suggested to be the cause of the stromal-cell defects associated with the increased estrogen and prostaglandin production, along with resistance to progesterone.[1]

The failure of immune mechanisms to destroy ectopic tissue and prevent abnormal differentiation of endometriotic tissue has been suggested as the cause of stromal-cells defects.

The theory of retrograde menstruation, whereby the menstrual tissue refluxes into the fallopian tubes and implants on the pelvic structures has been credited to Dr Sampson.[2] However, retrograde menstruation occurs in most women but the disease only occurs in 10 – 15% of women.

Increased estrogen sensitivity along with an increase in progesterone resistance have been found in women with endometriosis. Endometriotic lesions may also develop when coelomic mesothelial cells of the peritoneum undergo metaplasia. There are also theories that postulate the circulation and implantation of ectopic menstrual tissue via the venous or lymphatic system, or both.[3]

Endometriotic cell survival and growth and associated inflammation are responsible for the clinical symptoms of infertility and pain. Inflammation, the main feature of endometriotic lesions, is characterised by the overproduction of cytokines, prostaglandins, and other inflammatory substances that cause pain and is associated with infertility. Additionally, estrogen promotes the survival and persistence of endometrial lesions.[3]

Key message:
Clinicians need to be aware of the various factors that increase the likelihood of endometriosis.

Types of endometriosis

There are several types of endometriosis:

Peritoneal endometriosis: Peritoneal implants that consist of glandular and stromal tissue and respond to hormonal changes associated with the menstrual cycle showing cyclic changes similar but not identical to the normal endometrium. These implants heal by fibrosis.[4]

Ovarian endometriomas: Benign, estrogen-dependent cyst also known as "chocolate cyst" that contains thick, old blood that appears as a brown fluid.[5] This results from recurrent chronic bleeding from the endometriotic implants. In long-standing endometriomas, the endometriotic tissue is gradually replaced by fibrotic tissue.[4]

Deep endometriosis (DE): This form of endometriosis is characterised by proliferative fibromuscular tissue with sparse endometrial grandular and stromal tissue (akin to adenomyosis), with no surface epithelium. DE does not show significant changes during the menstrual cycle. Growth of endometriotic nodules are usually found in the uterosacral ligaments, the rectovaginal space, the upper third of the posterior vaginal wall, the bowel, and the urinary tract.[4,6]

Adenomyosis: Uterine endometriosis presents as asymmetrical uterine enlargement.

Disseminated endometriosis: Growth of endometriotic tissue in various organs in the body including at the scar site.

2.0 Endometriosis

Clinical manifestations

Box 2.1: Common presenting symptoms for endometriosis[4,7]

Pain in endometriosis presents as any of the following:

- Painful menstruation (dysmenorrhoea)
- Painful intercourse (dyspareunia)
- Painful defecation (dyschezia) that may be cyclic or semi-cyclic.
- Painful micturition (dysuria)
- Lower back or abdominal discomfort
- Chronic pelvic pain (non-cyclic abdominal pelvic pain of at least 6 months duration)

Atypical presentations include cyclic leg pain or sciatica (nerve involvement), cyclic rectal bleeding or haematuria (bowel or bladder invasion), and cyclic dyspnoea secondary to catamenial pneumothorax. These presentations are indicative of a more significant disease involvement.[3]

Physical examinations may present with the following[3]:

- Painful induration and/or nodules of the rectovaginal wall or visible vaginal nodules in the posterior vaginal fornix (DE)
- Detection of adnexal masses (ovarian endometrioma)
- Fixed, retroverted uterus (severe adhesive disease).

Complications

Endometriosis can be a cause of subfertility and pain. Epidemiological and laboratory evidence have linked endometriosis with epithelial ovarian carcinoma.

Key message:
The primary focus of investigation and treatment of endometriosis should be the resolution of presenting symptoms.

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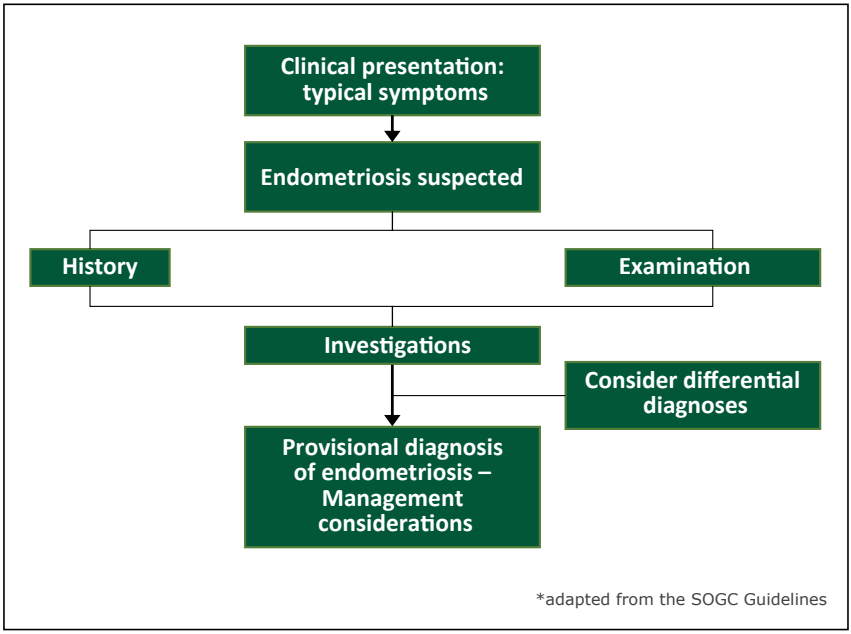
3.0 Diagnosis – Laparoscopy versus clinical

Figure 1: Diagnostic pathway[1]*



Generally, diagnosis of endometriosis is based on the history, the symptoms and signs, physical examination and imaging techniques. Physical examinations should include an assessment to determine the position, size, and mobility of the uterus. Rectovaginal examinations are useful in determining presence of DE. Other than the examination of the pelvic region, inspection and palpation of the abdomen is also advised.[2]

Key message:
When deeply infiltrating endometriosis is suspected, a pelvic examination, including rectovaginal examination, is essential.

3.0 Diagnosis – Laparoscopy versus clinical

Ultrasonography is the first-line investigational tool for suspected endometriosis. It allows detection of ovarian cysts and other pelvic disorders such as uterine fibroids. There is little support for the routine use of blood works, or other imaging studies in the primary investigation of these cases.[1]

The serum level of cancer antigen 125 (CA-125) may be elevated in some cases of endometriosis. However, there is no value of CA-125 in diagnosis or follow-up. However, if the appearance of the ovarian cyst is suggestive of an origin other than endometriosis, CA-125 and other tumour markers are recommended.[3]

It has been traditionally believed that laparoscopy must be performed to definitely diagnose endometriosis. Direct visualisation with laparoscopy and histology has been regarded as the gold standard for diagnosis. However, this view has been recently challenged as nonsurgical diagnosis of endometriosis have proven to be highly reliable.[4]

Diagnostic laparoscopy should be done by an experienced laparoscopic surgeon and preceded by appropriate preoperative assessment.[5] The severity of endometriosis is best described by the appearance and location of the endometriotic lesions and the involvement of any organs.[1]

Diagnostic laparoscopy is not required before treatment of all patients with pelvic pain. Despite being considered a minimally invasive procedure, there are still surgical risks including bowel and bladder perforation and vascular injury. The overall risk of any complication with laparoscopy, minor or major, varies with publications and in this reference, is 8.9%.[6] Diagnostic laparoscopy carries a lower risk than operative laparoscopy.[7]

3.0 Diagnosis – Laparoscopy versus clinical

When endometriosis is thought to be of the DE variety, ancillary tests such as colonoscopy, cystoscopy, rectal ultrasonography, and MRI may be required.[1,2]

Key messages:

1. Investigation of the suspected endometriosis should include history, physical examination and imaging assessments.
2. The role of CA-125 in the diagnosis and follow-up of endometriosis has not been shown to have any proven value.
3. The role of laparoscopy for the definitive diagnosis of endometriosis is not thought to be essential in all cases.

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1. Leyland N, et al. *J Obstet Gynaecol Can*. 2010;32(7 Suppl 2):S1–S32.
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3.0 Diagnosis – Laparoscopy versus clinical

3.1 Classifications*

At present, there are several types of classification staging of endometriosis. The two scoring systems most commonly used are stated below.

* Scores can be assessed in the Appendix section of this booklet.

3.1.1 The revised American Society for Reproductive Medicine score

This scheme is based on the total 3-dimensional volume of endometriosis. Aspects that are noted include size, depth of invasion, bilaterality, ovarian involvement, extent of cul-de-sac involvement, as well as density of associated adhesions.

Scoring system

Point scores are assigned and tallied. Scores ranging from 1 – 15 indicate minimal or mild disease, 16 – 40 moderate, and >40 severe.

3.1.2 The ENZIAN Staging System

Published in 2005, the ENZIAN score was designed to take into account deep infiltrating endometriosis (DIE) and act as a supplement to the rAFS (revised American Fertility and Sterility) score with regards to the description of DIE, retroperitoneal structures and involvement of other organs (intestinal, uterine, intrinsic ureteral bladder, other).[1]

Scoring system[2]

This scoring system encompasses 3 axes in compartments *a*, *b*, and *c*, and also classifies the severity of endometriosis (except for 'other'). The prefix '*E*' is used to indicate the presence of an endometriotic tumour. The number that follows it describes the size of the lesion and subsequent lowercase letter indicates the location or affected compartment. Two letters would indicate bilateral disease.

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4.0 Treatment options for pain

Endometriosis is a chronic and usually progressive inflammatory condition of the pelvis, predominantly presenting as pain. The degree of endometriosis does not correlate with the severity of symptoms. By necessity, medical therapy is non-specific and is aimed at alleviating symptoms. Due to its chronic condition, medical treatments must be effective and safe to use until menopause or until pregnancy is desired.

4.1. Laparoscopy before commencement of treatment

It is not necessary for laparoscopy before medical management of pelvic pain begins. In women with severe dysmenorrhoea or chronic pelvic pain that affects their quality of life, pain management is vital, whether endometriosis related or not.

Laparoscopy should only be done if the surgeon is prepared to remove the lesions when endometriosis is discovered. There is good evidence that surgical intervention provides long-term relief for patients with endometriosis.[1]

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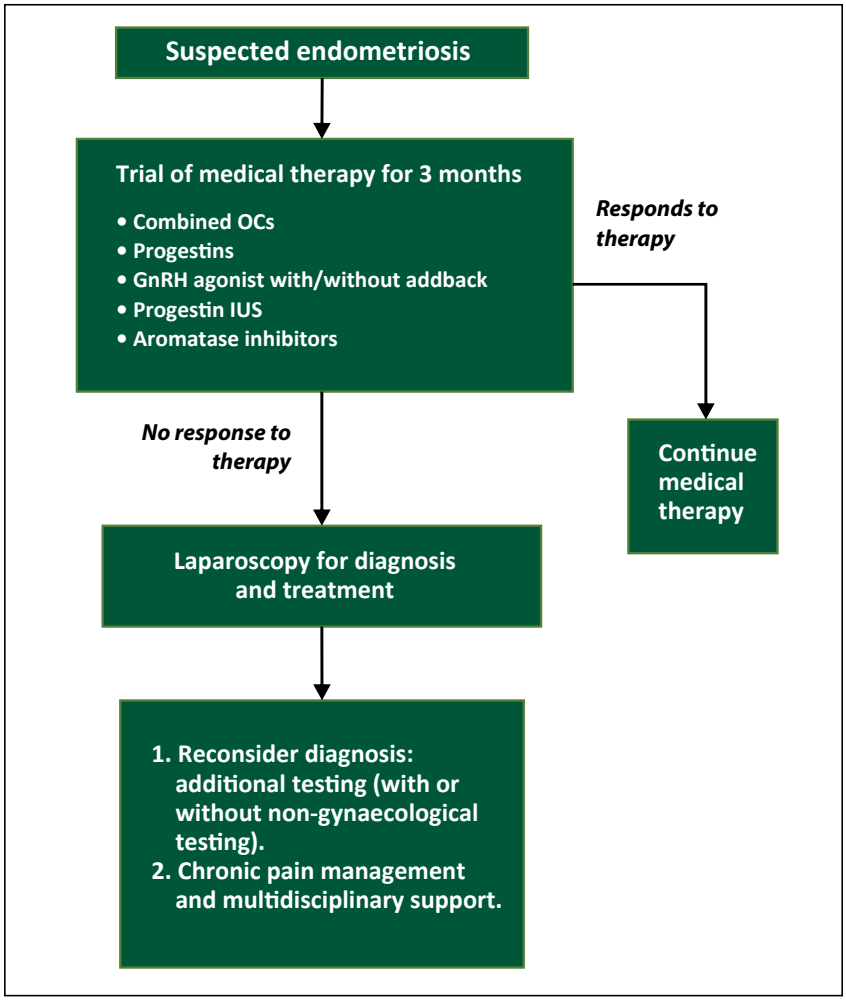
4.0 Treatment options for pain

4.2 Medical treatment

Figure 4.1: Management of pain associated with suspected endometriosis



4.2.1 Combined estrogen and progestin therapy

Oral contraceptives (OCs) that combine estrogen and progestin are considered as first-line treatment for pelvic pain associated with endometriosis.

Harada et al found that although estrogen-progestin OCs were able to significantly relieve dysmenorrhoea, there was no difference in non-menstrual pelvic pain relief when compared to placebo.[1] Cyclic treatment with combination OCs for 3 months has also been shown to only reduce or completely relieve pain in less than 50% (42%) of patients.[2]

Data suggests that the continuous administration of OCs, without a 7-day break, may be more beneficial in terms of pain relief.[3,4] This takes into account the retrograde menstruation theory. By preventing the withdrawal bleeding, the efficacy of OCs in providing pain relief associated with endometriosis may be improved.

Despite their potential, combined OCs may not be a universal option in managing patients with endometriosis-associated pain due to the status of estrogen and progestin receptors in the ectopic endometrial implants. These implants have normal estrogen receptors, however the progesterone receptor isoforms PRA and PRB are reduced or absent. The endometriotic lesions thus may not recognise progestins and the enzyme 17-β-hydroxysteroid dehydrogenase, which converts estradiol to estrone, may not be activated by progestin.[5,6] The pharmacologic dose of progestin in OCs are then not recognised and there may not be any estrogen-antagonistic effect from the medication.

4.2.2 Oral progestin therapy

Estrogen stimulates endometriotic growth. OCs contain both estrogen and progestin. Various progestins in appropriate doses can effectively treat endometriosis related pain.

4.2.2.1 Dienogest

Dienogest is a progestin with selective 19-nortestosterone and progesterone activity.[7] Pelvic pain and dysmenorrhoea was significantly relieved when 2 mg of dienogest was administered once daily. This dose is as effective as GnRH agonist therapy in relieving endometriotic pain.[8,9] Data has shown that dienogest, 2 mg daily, was as effective as leuprolide acetate, 3.75 mg delivered intramuscularly every 4 weeks over a period of 24 weeks, in relieving dysmenorrhoea, dyspareunia, and pelvic pain.[10]

Quality of life has been reported to be improved in women receiving dienogest compared with those receiving leuprolide acetate, although no addback was used in the latter. There were no side effects related to low levels of estrogen reported.[10]

Overall, studies have shown that deinogest is non-inferior to GnRH agonists and may be effective as a long-term treatment option for endometriosis.[11]

Common side effects that may be experienced include irregular bleeding, amenorrhoea, headaches, and constipation.[12]

4.2.2.2 Norethindrone acetate

Norethindrone acetate, 5 to 20 mg daily, has been effective in most patients for relieving dysmenorrhoea and chronic pelvic pain.[13] This treatment results in breakthrough bleeding in about half of the patients but seems to have a positive effect on calcium metabolism, resulting in relatively good maintenance of bone mineral density (BMD). There may be negative effects on serum levels of high-density lipoprotein cholesterol. Continuous use of medication is approved by the US FDA for the treatment of endometriosis.

Some side effects commonly associated with this treatment includes bloating, weight gain and depression.

4.2.3 Depot progestin therapy

Depot medroxyprogesterone acetate (DMPA) is widely used as a method of contraception. It has also be studied as a form of treatment against pain due to endometriosis. Two randomised controlled trials (RCTs) have found that subcutaneous DMPA (DMPA-SC) over a period of 6 months and 12 months, was equivalent to leuprolide acetate in relieving pain. There was less loss of BMD in the DMPA group as compared to leuprolide acetate without addback.[14,15]

Up to 75% of patients find DMPA-SC effective in relieving pelvic pain and is an economical alternative to the treatment of symptomatic endometriosis. It is not recommended for women wanting a pregnancy in the near future as there is a prolonged delay in the resumption of ovulation. Breakthrough bleeding may also be prolonged, heavy and difficult to correct as the progestin effect takes a long time to reverse. Long-term use of DMPA may have adverse effects on BMD.[11]

4.2.4 Interuterine progestin-releasing system

Levonorgestrel (LNG) causes atrophic endometrium and amenorrhoea in up to 60% patients without inhibiting ovulation.[16] Studies have indicated that LNG-IUS may be useful in reducing pain.[17,18]

Disadvantages include an expulsion rate of approximately 5% with a risk of pelvic infection of around 1.5%.[19] Treatment with LNG-IUS may be effective as therapy in adenomyosis.[20,21] Irregular menstrual bleeding and amenorrhea are common side effects though bone density is preserved.[22]

4.2.5 Danazol

More than 20 years ago, danazol was considered the main medical treatment for endometriosis. It works by suppressing gonadotropin secretion and inducing amenorrhoea.[23] It is currently rarely used due to side effects such as acne, weight gain, hirsutism, breast atrophy, and rarely, virilisation[24]. There is evidence that danazol has an adverse reaction on blood lipid levels[25] and increases the risk of ovarian cancer in endometriosis patients.[26] In view of this, danazol is not advised for long term use and is preferably prescribed in low-dose regimens or via vaginal administration.[27]

4.2.6 GnRH agonists

GnRH agonists should be considered as first line treatment for endometriosis and particularly in women who are unresponsive to combined OCs or progestins or have a recurrence of symptoms after initial improvement. If used for more than 6 months or if severe vasomotor symptoms are present, addback hormone therapy (HT) should be used. HT regimen options are as shown in **Box 4.1**.

GnRH agonist treatment coupled with induced hyperestrogenism is effective in managing endometriosis.

GnRH therapy helps in the inactivation of pelvic lesions and resolving the pain. Unfortunately, symptoms of estrogen deficiency such as breakthrough bleeding during the first month of therapy, vaginal dryness, irritability, fatigue, headaches, depression, skin problems and BMD depletion may occur.[28]

Box 4.1: List of HT addback therapy available in Malaysia[29-31]

Progynova	1 mg/ 2 mg daily
Conjugated equine estrogen	0.625 mg daily
Norethisterone	5 mg daily
MPA	100 mg daily
Tibolone	2.5 mg daily

4.2.7 Aromatase inhibitors (AI)

This form of treatment for endometriosis is still experimental. The basis for this treatment is that endometriotic lesions express aromatase and are able to make their own estrogen even in the absence of gonadotropin stimulation.[32] Pilot studies found that 6 months of daily treatment combined with high-dose norethindrone acetate[33] or OCs[34] significantly reduced pelvic pain in women with endometriosis, who did not respond to first-line treatment.

In pre-menopausal women, a progestin or combined OC should be added to aromatase inhibitors to prevent ovarian stimulation and cyst formation due to the increased gonadotropin secretion which occurs once the estrogen negative feedback is removed.[35] The BMD was found to be stable over 6 months in one study.[36] At present, there still is insufficient evidence and more research needs to be done for the efficacy and safety of aromatase inhibitors in long-term treatment for endometriotic pain. The ESHRE 2014 Guidelines recommends the use of AIs with OCs, progestogens, or GnRH analogues as they reduce pain in rectovaginal endometriosis, refractory to medical or surgical treatment.[37]

AI treatment is associated with long- and short-term effects. Some of the symptoms include hot flushes, vaginal dryness, arthralgia and decrease in BMD.

4.2.8 Analgesia

Analgesic agents are a useful adjunct in the management of pain related to endometriosis. These agents include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-depressants, and in some cases, opioids.

Box 4.2: Practice points for treatent[38]

- Careful assessment of the pattern of chronic pelvic pain and a trial of medical treatment should be started empirically if endometriosis is suspected. If pain persists, proceed with laparoscopy for definitive diagnosis.
- Treatment should be tailored to the patient, taking age, disease severity and extent, fertility requirements, contraception, and patient's wishes into account.
- In adolescents with symptoms of endometriosis, empirical treatment with analgesics and/or medical treatment is recommended before resorting to laparoscopy.
- GnRH agonists may adversely affect the final bone density formation in adolescents, particularly those under 17 years of age.

4.0 Treatment options for pain

Key message:

1. Medical management is an important option in the treatment of endometriosis. If surgical intervention is necessary, medical intervention can be used before or after the surgery.
2. If a GnRH agonist is used for more than 6 months or if there are severe vasomotor symptoms, an addback HT must be considered.
3. Analgesic agents are a useful adjunct in the management of pain related to endometriosis.

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4.3 Surgical management of endometriosis

Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximising the use of medical treatment and avoiding repeat surgical procedures.[1] However, it is important to note that surgery is more effective in reducing pain in patients with more advanced endometriosis.[2] Surgical management of endometriosis requires careful consideration of the indications of surgery, preoperative evaluation, surgical techniques, surgeon's experience, and ancillary techniques and procedures.[3]

The decision to move to surgery in women in pain and suspected endometriosis should be based on clinical evaluation, imaging, and effectiveness of medical treatment. The role of laparoscopy as first line for diagnosis is not recommended.

4.3.1 Indications

Surgical intervention for endometriotic pain is indicated when the patient[2]:

1. Does not respond to, declines, or has contraindication to medical therapy
2. Has an acute adnexal event (adnexal torsion or ovarian cyst rupture)
3. Has severe invasive disease involving the bowel, bladder, ureters, or pelvic nerves
4. Has or is suspected to have an ovarian endometrioma >3 cm, especially in patients for whom the uncertainty of the diagnosis affects the management (as with chronic pelvic pain)
5. Patients with infertility and associated factors (i.e. pain or a pelvic mass) caused by endometriosis

Key message:
An asymptomatic patient with an incidental finding of endometriosis at the time of surgery may not always require any medical or surgical intervention.

4.3.2 Preoperative evaluation

A complete preoperative evaluation will assist in planning the surgical approach, intraoperative timing and the need for additional procedures and consultations.

There is limited value for the serum CA-125 test in preoperative detection of endometriosis.[4] Thus, the test is not recommended as part of preoperative routine. Rather, it may be done to evaluate the presence of an undiagnosed adnexal mass.

Pelvic ultrasonography, particularly transvaginal is recommended when an adnexal mass is suspected from physical examination. Transrectal sonography, colonoscopy, barium enema radiography, and MRI may be useful in detecting the presence of deeply invasive endometriosis of the bowel and rectovaginal septum in patients with dyschezia and in those with deep dyspareunia with nodularity upon examination. Cystoscopy should also be performed if there are cyclic bladder symptoms (e.g. haematuria).

Any risks associated with the surgery should be thoroughly discussed with the patient. Informed consent should be obtained and documented.

4.3.3 Surgical approach

Surgery can be classified as either "conservative" or "definitive". The goal of conservative surgical management of endometriosis is to relieve pain while restoring normal anatomy. This approach is usually applied to women of reproductive age and those who wish to conceive in the future or to avoid induction of menopause at an early age. This may involve ablation, lysis, or excision of lesions, interruption of nerve pathways, removal of ovarian endometriomas and excision of lesions invading adjacent organs (bowel, bladder, appendix or ureter).

Conversely, in definitive surgery to induce menopause will include removal of the uterus, fallopian tubes and both ovaries and excision of all visible endometriotic nodules and lesions. This form of surgery should only be considered in women who have had significant pain and symptoms despite conservative treatment, has severe disease and does not wish to have future pregnancies or are undergoing a hysterectomy due to other pelvic conditions (e.g. fibroids or menorrhagia).

Laparoscopy is the preferred route for surgical management of endometriosis, regardless of the severity of the disease. Patient recovery and return to normal is faster than when compared to laparotomy.[5] Patients with invasive endometriosis including bowel and bladder involvement should be referred to a multidisciplinary team with more experience or advanced training in managing this form of endometriosis.[6]

Adhesion-prevention adjuncts

Adhesions can still form with laparoscopic procedures and the adhesion-related complications of open and laparoscopic gynaecological surgery are similar.[7] Use of antibiotics, NSAIDs, corticosteroids, and fibrinolytics have proven to be ineffective in preventing adhesions. The use of physical separators (e.g. gel barriers) have shown reduction in adhesion formation.[8] However, more research is required for the use of other preventive agents as there has been no evidence on improvement of fertility.

4.3.4 Deeply Infiltrating Endometriosis (DIE)

DIE refers to lesions that penetrate 5mm or more (rectovaginal nodules, bowel invasion and constriction, bladder invasion, ureteric invasion or compression, nerve involvement). The lesions are more often than not, multifocal and are much deeper than perceived. Lesions deeper than 10 mm are usually associated with pain.[9] From the limited evidence available, it has been shown that excision of these lesions are able to provide pain relief.[10,11]

Rectovaginal infiltration

Surgery for rectovaginal infiltration requires a multidisciplinary approach with gynaecologists experienced in minimally invasive surgery, along with a general surgeon or urologist. For pain relief, bowel surgery may be required[12,13] and should be done by an experienced surgeon or gynaecological oncologist.

If DIE is identified during diagnostic laparoscopy, immediate excision is not advised. An informed consent should be obtained along with a proper preoperative evaluation due to the complexity of the disease.

Key message:
Surgical treatment of deeply infiltrating endometriosis requires a multidisciplinary approach.

4.3.5 Ovarian Endometriosis

Ovarian endometriomas are indicative of severe disease and can be a challenge to manage surgically.[14] One of the most important considerations is the patient's desire for fertility when determining the level of intervention needed to preserve the ovaries and their function. In this case, the surgical options available include excision of the cyst wall or drainage, and coagulation of the cyst bed.

In terms of pain, evidence suggests that laparoscopic excision of the endometriomas is more beneficial than simple laparoscopic ablation. Excision results in lower rates of recurrence, dysmenorrhoea, dyspareunia, non-menstrual pelvic pain, and requirement for additional surgery. The cumulative pregnancy rate in this group of patients is also higher than those that underwent cystectomy.[15]

Despite the benefits of laparoscopic excision of ovarian endometriomas, it usually involves the unintentional removal of normal ovarian tissue.[16] During the excision, it is important preserve as much normal ovarian tissue as possible. Decisions to treat endometriomas surgically needs to be based on clinical presentation, particularly after the risks of unintentional removal of normal ovarian tissue has been considered. Excisions may be more suitable for larger endometriomas (>3 cm in diameter) in the presence of pelvic pain. For smaller cysts, a simple drainage and ablation or expectant management may suffice.

Ovarian endometriomas tend to recur in 30% of patients after laparoscopic excision.[17] It has been observed that lower recurrence rate and better management of symptoms can be achieved through postoperative hormonal suppression.[18,19] In patients that do not wish to conceive, combined OCs (cyclic or continuous), should be considered after surgery. As risk of malignancy is low and there is no evidence on fertility improvement, the decision for repeat surgery should be based on the symptoms and size of the cyst.

4.3.6 Additional surgical interventions

During laparoscopy, the appendix and other peritoneal organs should be visualised. In addition to ablation or excisions of endometriotic lesions, there are other surgical interventions available to help relieve pelvic pain. In large randomised trials, uterosacral nerve ablation has not proven to be effective in providing chronic pain relif.[20]

Key message:

1. In the case of ovarian endometriomas, it is crucial that the patient's desire for fertility be considered when determining the degree of intervention needed to preserve the ovaries and their function.
2. Ovarian endometriomas are usually indicative of more extensive endometriosis.
3. Ovarian endometriomas larger than 3 cm in diameter in women with pelvic pain should be excised as soon as possible.
4. In patients that do not wish to conceive, therapy with combined OCs (cyclic or continuous) should be considered after surgical management of ovarian endometriomas.

References:

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11. Chapron C, et al. *Hum Reprod*. 1996;11:868–873.
12. Darai E, et al. *Curr opin Obstet Gynecol*. 2007;19:308–313.
13. Mereu T, et al. *J Minim Invasive Gynecol*. 2007;14:463–469.
14. Chapron C, et al. *Fertil Steril*. 2009;92:453–457.
15. Hart RJ, et al. *Cochrane Database Syst Rev*. 2008;16(2):CD004992.
16. Matsuzaki S, et al. *Hum Reprod*. 2009;24:1402–1406.
17. Koga K, et al. *Hum Reprod*. 2006;21:2171–2174.
18. Seracchioli R, et al. *Hum Reprod*. 2009;24:2729–2735.
19. Seracchioli R, et al. *Fertil Steril*. 2010;94(2):464–471.
20. Daniels J, et al. *JAMA*. 2009;302:955–961.

5.0 Fertility Issues

Endometriosis is common in women with infertility. However, the clinical management of the infertility in these patients is difficult because many clinical decision end-points have not been evaluated in randomized controlled trials. Furthermore, existing data is often conflicting. Therefore, its management is often controversial and varied.

It has been suggested that 25% to 50% of infertile women have endometriosis, while 30% to 50% of women with endometriosis are infertile.[1] However, the true prevalence of endometriosis is difficult to quantify. Some studies suggest that the prevalence of endometriosis among the fertile population may be 1% to 7%.[1]

The exact reason why endometriosis causes infertility is still unknown. Possible reasons include distorted pelvic anatomy, altered peritoneal function, altered hormonal and cell-mediated function, abnormalities in endocrine and ovulation, and impaired implantation. Abnormalities in oocyte and embryo quality as well as abnormal utero-tubal transport have also been suggested as possible mechanisms.

5.1 Diagnosis

The combination of laparoscopy and the histological confirmation of endometrial glands and/or stroma is considered the **gold standard** for the diagnosis of the disease.

It is therefore required for a definitive diagnosis of endometriosis to be made. However, in patients with infertility but who are otherwise asymptomatic, laparoscopy **merely to confirm** or exclude the diagnosis is not warranted. This is largely because the therapeutic benefit of laparoscopy to increase fecundity in women with minimal or mild disease is minimal.[2,3]

References:
1. Missmer MA, et al. *AM J Epidemiology*. 2004;160:784–796.
2. Marcoux S, et al. *NEJM*. 1997;337:217–222.
3. Parazzini F. *Hum Reprod*. 1998;14(5):1332–1334.

5.2 Medical therapy

A. Before fertility treatment (without surgery)

Medical therapy does not improve fertility.

B. Before surgery

In infertile women with endometriosis, adjunctive hormonal therapy before surgery should not be prescribed as it has not been shown to improve pregnancy rates.

However, in symptomatic women, medical treatment is reasonable while waiting for surgery or assisted reproductive treatment.

C. Medical treatment after surgical treatment

There is no evidence that post-surgical adjuvant therapy significantly improves fertility but may instead unnecessarily delay further fertility treatment.[1]

D. Medical treatment before assisted reproductive treatments

Down-regulation with GnRH agonists for a period of 3-6 months prior to treatment with assisted reproductive treatment may improve clinical pregnancy rates in infertile women with endometriosis[2,3]

References:

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2. Sallam HN, et al. *Cochrane Database Syst Rev*. 2006;(1):CD004635.
3. Rickes D, et al. *Fertil Steril.* 2002;78:757–762.

5.3 Surgical treatment

5.3.1: Indications for surgery

A. For diagnosis only

Laparoscopy in **asymptomatic** women merely to confirm or exclude the diagnosis is **not warranted**.

The therapeutic benefit of laparoscopy to increase fecundity in women with minimal or mild disease is negligible. Therefore, it may be of value only in **symptomatic** women.

B. In mild endometriosis

In stage 1/11 endometriosis, laparoscopic ablation of endometrial implants may improve spontaneous pregnancy rates and has also been associated with a small but significant improvement in live birth rates.

C. In severe endometriosis

In infertile women with AFS/ ASRM stage III/IV endometriosis, operative laparoscopy instead of expectant management increases spontaneous pregnancy rates.[1,2]

D. In women already planned for IVF/ICSI

In women planned for IVF/ICSI, there is insufficient data to suggest that the removal of the endometrioma would improve IVF success rates.[3-5]

However removal may be considered for the following reasons:

a) To confirm the diagnosis histologically
b) To improve access to follicles during the oocyte retrieval
c) Possibly to improve ovarian response

E. Treatment of endometriomas and deeply infiltrating endometriosis and infertility

There is no evidence that surgical excision of deep nodular lesions prior to ART will improve reproductive outcome.[6,7]

5.3.2 Laparotomy versus laparoscopy

The preferred surgical approach for treatment of infertility related to endometriosis is laparoscopy. This is because laparoscopy is usually associated with less pain, shorter hospital stay, quicker recovery and a better cosmetic outcome.[8]

5.3.3 Surgical principles, procedures and techniques

A. The purpose of surgery is:

1. To determine the severity of the disease by staging and looking at other areas, such as the appendix, bowel, and diaphragm.
2. The removal of the endometriotic lesions as much as possible.
3. To restore the normal anatomy with adhesiolysis.
4. To optimise ovarian and tubal preservation and integrity by using the principles of microsurgery (magnification, diligent haemostasis, reduced fulguration, avoidance of tissue drying, and limited use of sutures).
5. To evaluate (if there is suspicion) the adnexa, through peritoneal cytology and frozen section in case of doubt.
6. Performing a blue dye test to evaluate tubal patency. The further management options of a blocked tube and/or hydrosalphinx **should have been discussed** prior to the surgery.

B. Surgical techniques

The surgical procedure of choice in women with an ovarian endometrioma should be excision of the endometrioma capsule, instead of drainage and coagulation, to increase spontaneous pregnancy rates.

In addition, there was a decreased rate of recurrence and no difference in response to gonadotrophin stimulation.[4,9]

A cystectomy is also preferred to a CO_2 laser vaporization as it is associated with a lower rate of recurrence.[10]

C. Issues to discuss with patients prior to surgery:

A detailed discussion is warranted prior to surgery, especially with regards to:

a) Reduced ovarian reserve: Ovarian reserve may already be reduced in the presence of an endometrioma. Ovarian surgery if extensive may also compromise ovarian function and reserve, hence causing diminished ovarian response to stimulation.

b) Management of a hydrosalphinx: the need to assess tubal patency during surgery and if a hydrosalphinx is discovered, the possible need to either remove or clip the relevant tube / tubes. The possibility of tubal surgery should also be discussed.
c) Recurrence rates: the endometriotic cyst is likely to recur and therefore the **window of opportunity** for fertility must be optimized.

5.3.4 Recurrent surgery

Additional surgery after the first fertility operation rarely increases fecundability, and in these patients, it may be better to refer them for ART.

Pregnancy rates have been shown to be halved after repeat surgery when compared to first line surgery.[11]

Therefore, it is imperative that the initial surgery is well planned, with future reproductive treatment options discussed and referred to the appropriate expertise.

The decision to undertake repeat surgery should depend on:
1. Presence of symptoms
2. Presence of complex cysts requiring histological diagnosis
3. Age
4. Ovarian reserve
5. Presence of male factor infertility
6. Surgical skill
7. Costs
8. Time to conception considerations

References:
1. Nezhat C, et al. *Fertil Steril*. 1989;51(2):237 – 240.
2. Vercellini P, et al. *Am J Obstet Gynecol*. 2006;195(5):1303–1310.
3. Donnez J, et al. *Fertil Steril*. 2001;76(4):662–665.
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5. Benschop L, et al. *Cochrane Database Syst Rev*. 2010;10:CD008571.
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5.4 Options after surgery

In women with **stage I/II endometriosis** the following options may be offered:

1. Expectant management
2. Superovulation with IUI (SO/IUI)
3. IVF

A key determining factor when deciding between the three options is female age. It is well documented that there is significantly decreased fecundity after age 35 years.

Fecundity may be decreased further due to endometriosis. Therefore, in older women more aggressive options (SO/IUI or IVF) should be offered.

In women with **stage III/IV endometriosis**:

The initial surgical intervention may restore fertility in these patients. If this fails, IVF is an effective alternative.

In women with advancing reproductive age, consider IVF sooner.

In women with stage III/IV endometriosis and have had previous fertility surgery (once or more), IVF is likely a better therapeutic option than another surgical intervention.

5.5 Assisted reproduction

5.5.1 Super-ovulation and intrauterine insemination (SO/IUI)

In infertile women with AFS/ASRM stage I/II endometriosis, IUI with controlled stimulation instead of expectant management increases live birth rates.[1]

Controlled ovarian stimulation is better than IUI alone as it increases pregnancy rates.[2]

IUI with controlled stimulation may commence within six months after surgical treatment.[3]

However, women with endometriosis have a lower clinical pregnancy rate following controlled ovarian hyperstimulation-IUI (COH-IUI) compared to women having COH-IUI for other indications

5.5.2 In vitro fertilisation (IVF)

IVF may maximise cycle fecundity for those with endometriosis especially where there is distortion of pelvic anatomy due to moderate or severe disease.

In women who fail to conceive after surgery or because of advancing reproductive age, IVF should be considered.

However, it is likely that endometriosis affects IVF results.

Women with endometriosis have lower clinical pregnancy rates following in vitro fertilization compared to women with other aetiologies. This effect is even greater with the increasing severity of the disease.

The clinical pregnancy rate per woman was found to be significantly higher in women receiving GnRH agonist down regulation for 3 to 6 months prior to IVF – than compared to those that did not.[4]

References:
1. Tummon IS, et al. *Fertil Steril*. 1997;68(1):8–12.
2. Nulsen JC, et al. *Obstet Gynecol*. 1993;82(5):780–786.
3. Werbrouck E, et al. *Fertil Steril*. 2006;86(3):566–571.
4. Sallam HN, et al. *Cochrane Database Syst Rev*. 2006 Jan 25;1:CD04635.

6.0 Post-menopausal management of endometriosis

Generally, post-menopausal endometriosis is rare as estrogenic-hormone production should have ceased. The estimated incidence of post-menopausal endometriosis is between 2–4%, a bulk of which is generally recurrence due to hormone therapy.[1]

6.2 Pathogenesis of post-menopausal endometriosis

The ovaries are the main source of estrogen. In post-menopausal women, estrogen is derived from either exogenous administration or from endogenous extra ovarian production. Exogenous administration is usually in the form of hormone therapy (HT)[2] while endogenous extra ovarian production arises from the skin and adipose tissue. Obese post-menopausal women tend to produce more endogenous estrogen than non-obese women.[3]

6.3 Treatment options of post-menopausal endometriosis

In the treatment of post-menopausal endometriosis, surgery is the first-line management as any post-menopausal mass carries the risk of developing into a malignancy.[2] Young women who have had a hysterectomy with removal of the ovaries requiring hormone therapy should receive combined hormone therapy (estrogen and progestin) or tibolone.[4-6] The addition of a progestin may be unnecessary after a hysterectomy but protects against the unopposed action of the estrogen on any lesion.

Key messages:

1. HT may cause a recurrence of endometriosis in post-menopausal women. It is crucial to consider the risks and benefits of administering HT to patients with previous endometriosis.
2. Surgery should be considered as first-line treatment for post-menopausal endometriosis with follow-up to monitor for recurrence.
3. If HT is required, combined hormone therapy or tibolone can be used.

References:

1. Sasson IE and Taylor HS. *Fertil Steril*. 2009;92(3):1170e1–1170e4.
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7.0 Endometriosis and the risk of cancer

Endometriosis is generally a benign disease that shares traits similar to malignancy: invasive and unrestricted growth, tendency to metastasize and recur. There are epidemiological and laboratory evidence that link endometriosis to epithelial ovarian carcinoma.

7.1 Epidemiology

Scott[1] added a fourth criterion in 1953 for the malignancy originating from endometriosis (**Box 7.1**) to the three other criteria added by Sampson.[2] Since then, there has been numerous studies that have supported the relationship between endometriosis and epithelial ovarian carcinoma, especially in clear cell and endometroid subtypes.[3]

Box 7.1: Criteria for malignancy originating from endometrosis

1. The presence of both endometriosis and malignancy within the same ovary must be demonstrated.
2. The carcinoma must arise from the endometriosis and not invade it from another source
3. The specimen must contain histological characteristics of endometriosis, including stroma and glands.
4. Malignant transformation or transition occurring in benign ovarian endometriosis.

A retrospective cohort study of >20,000 women with endometriosis found an overall increased cancer risk and a greater increase in risk of ovarian cancer.[4] A recent study found that the hazard ratio associated with endometriosis was 12.4 for ovarian cancer and 5.5 for borderline ovarian tumours. The study concluded that there is an estimate of 3- to 8-fold increase risk of ovarian tumours associated with endometriosis.[5]

7.2 Pathophysiology

While the evidence that shows the link between endometriosis and ovarian cancer is strong, little is known of the mechanism that causes the malignant transformation. In a review by Somigliana et al,[6] it was suggested that endometriotic cells may undergo malignant transformation, and the coexistence of endometriosis and ovarian cancer may be due to shared risk factors and preceding mechanisms.

It is suggested that endometriosis is the precursor lesion to ovarian cancer. This theory is derived from histologic evidence of malignant transformation of the endometriosis to clear cell or endometrioid carcinoma.[7] Molecular genetic alteration studies have also provided evidence that endometriosis is the precursor lesion to carcinoma; however, more research is needed to fully define this progression.[8,9]

Somigliana also suggested that endometriosis and ovarian cancer are two separate biological entities that are bound by an indirect link as the two diseases share similar risk factors. For instance, nulliparity, early menarche, late menopause[3] and other similar risk factors (e.g. genetic predisposition, immune dysregulation, and environmental factors).[6]

While there seems to be a link between endometriosis and ovarian cancer, this does not prove causality.

7.0 Endometriosis and the risk of cancer

7.3 Management

If there is suspicion of ovarian malignancy in an endometriotic cyst, the management will follow the standard guidelines for this condition.

Key message:

1. While there is a link between endometriosis and certain cancers, there is no conclusive evidence that indicates that endometriosis causes cancer.
2. Some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.[6]

References:

1. Scott RB. *Obstet Gynecol*. 1953;2:283–289.
2. Sampson JA. *Arch Surg*. 1925;10:1–72.
3. Nezhat F, et al. *Fertil Steril*. 2008;90:1559–1570.
4. Brinton LA, et al. *Am J Obstet Gynecol*. 1997;176:572–579. 5 Buis CC, et al. Hum Reprod. 2013;28(12):3358–3369.
6. Somigliana E, et al. *Gynecol Oncol*. 2006;101:331–341.
7. Feeley KM and Wells M. *Histopathology*. 2001;38:87–95.
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9. Otsuka J, et al. *Med Electron Microsc*. 2004;37:188–192.

American Society of Reproductive Medicine Score

Classification of Endometriosis

Name:_____Date:_____

Procedure performed:_____

ENDOMETRIOSIS		<1cm	1-3cm	>3cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	Right Superficial	1	2	4
	Deep	4	16	20
	Left Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CUL-DE-SAC OBLITERATION		Partial	Complete	
		4	40	
ADHESIONS		<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
Ovary	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
Tube	R Filmy	1	2	4
	Dense	4[1]	8[1]	16
	L Filmy	1	2	4
	Dense	4[1]	8[1]	16

1. If the fimbriated end of the Fallopian tube is completely enclosed, change the point assignment to 16.
Staging: stage I (minimal): 1-5; stageII (mild): 6-15; stage III (moderate): 16-40; stage IV (severe): >40.
Revised ASRM Classification. *Fertil Steril 1997*;67:819.

Appendix

Additional Endometiosis: _____

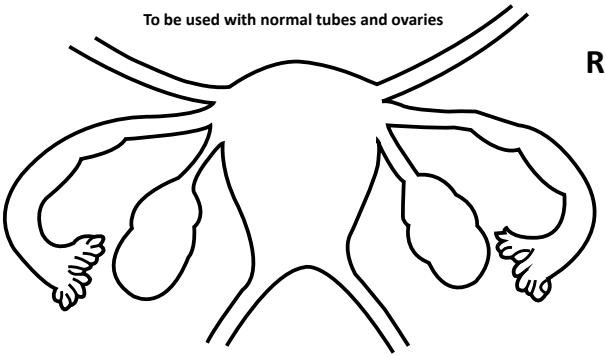
_____

_____

_____

To be used with normal tubes and ovaries

L R



_____

Associated Pathology: _____

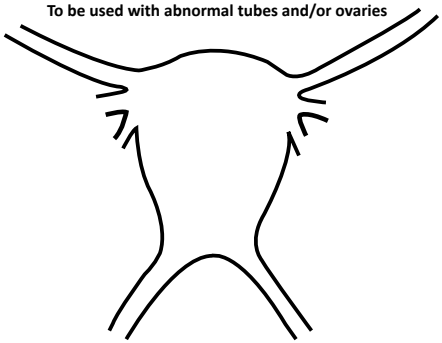
_____

_____

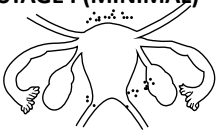
_____

To be used with abnormal tubes and/or ovaries

L R



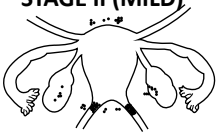
STAGE I (MINIMAL)



PERITONEUM
Superficial Endo 1-3cm 2
Right OVARY
Superficial Endo <1cm 1
Filmy Adhesions 1/3 1

TOTAL POINTS 4

STAGE II (MILD)



PERITONEUM
Deep Endo >3cm 6
Right OVARY
Superficial Endo <1cm 1
Filmy Adhesions <1/3 1
Left OVARY
Superficial Endo <1cm 1

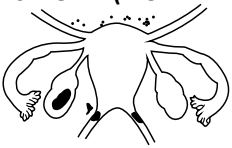
TOTAL POINTS 9

STAGE III (MODERATE)

PERITONEUM
Deep Endo >3cm 2
CULDESAC
Partial Obliteration 4
Left OVARY
Deep Endo 1-3cm 16

TOTAL POINTS 26

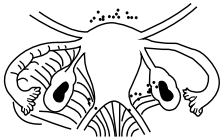
STAGE III (MODERATE)



PERITONEUM
Superficial Endo >3cm 4
Right TUBE
Filmy Adhesions <1/3 1
Right OVARY
Filmy Adhesions <1/3 1
Left TUBE
Dense Adhesions <1/3 16*
Left OVARY
Deep Endo 1-3cm 4
Dense Adhesions <1/3 4

TOTAL POINTS 30

STAGE IV (SEVERE)

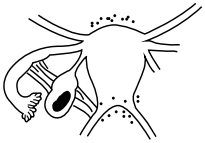


PERITONEUM
Deep Endo >3cm 6
CULDESAC
Complete Obliteration 40
Right OVARY
Deep Endo 1-3cm 16
Dense Adhesions <1/3cm 4
Left TUBE
Dense Adhesions >2/3cm 16
Left OVARY
Deep Endo 1-3cm 16
Dense Adhesions >2/3cm 16

TOTAL POINTS 114

***Point assignment changed to 16**

STAGE IV (SEVERE)



PERITONEUM
Superficial Endo >3cm 4
Left OVARY
Deep Endo <1cm 32**
Deep Adhesions <1/3 8**
Left TUBE
Dense Adhesions >3cm 8**

TOTAL POINTS 52

****Point assignment doubled**

Appendix

Enzian Staging System

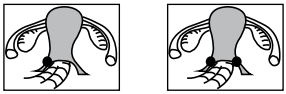
Enzian Score

a
* cul-de-sac
* vagina

b
* uterosacral ligament
* cardinal ligament

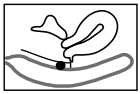
c
* bowel, rectum
* rectosigmoid

E1a = isolated nodule the pouch of Douglas



E1b = isolated nodule <1 cm from the uterine sacral ligament (USL)

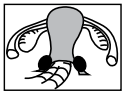
E1bb = bilateral infiltration of the USL



E1c = isolated nodule in the rectovaginal space

E2a = infiltration of the upper third of the vagina

E2b = infiltration of the USL >1 cm

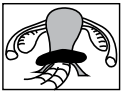


E2bb = bilateral

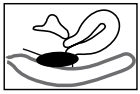
E2b = infiltration of rectum <1 cm

E3a = infiltration of the middle part of the vagina

E3b = infiltration of the cardinal ligament (without ureterohydronephrosis)



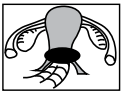
E3bb = bilateral



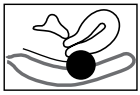
E3c = infiltration of the rectum 1-3 cm without stenosis

E4a = infiltration of uterus and/or lower third of the vagina

E4b = infiltration of the cardinal ligament to pelvic side wall and/or ureterohydronephrosis



E4bb = bilateral



E4c = infiltration of the rectum >3 cm and/or rectal stenosis

FA = adenomyosis uteri

FO = other locations

FB = deep infiltration of the bladder

FU = ureteral infiltration (intrinsic)

FI = intestinal infiltration (other side than rectum or sigmoid)

Notes

Notes