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EXcellence in PCOS & Expertise in Reproductive Technology

MODULE 2:
POLYCYSTIC OVARY SYNDROME AND ENDOMETRIOSIS

Brought to you by

THE PCOS SOCIETY

An Initiative of PCOS Society (India)

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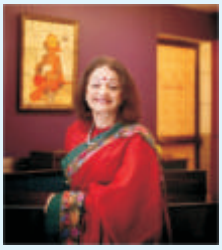
Foreword



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PCOS is quite often associated with infertility, especially in women with irregular periods and hyperandrogenemia. It is one of the most treatable forms of infertility, if ovulation induction is optimal. Unfortunately, many PCOS women, both lean and obese, behave erratically during ovulation induction sometimes leading to ovarian hyperstimulation syndrome which can become a serious iatrogenic complication. Keeping in mind that many PCOS women approach us for management for their infertility issues, it is important for us to understand the principles of management. Which when applied correctly, they can give us great success in making PCOS women pregnant. Of course experience counts, and as we continue treating women, we learn how to tweak our stimulation protocols to avoid complications and give us the best results!

After initiating the Basic Course on Infertility in 2018, we are delighted to introduce to you the Advanced Course called **"EXPERT"- (Excellence in PCOS and Expertise in Reproductive Technology")** a Certificate Course brought to you by the PCOS Society of India, through an unrestricted educational grant by Sun Pharma, Inca Life Sciences.

"EXPERT" will be presented to you in a set of 6 Modules which will update you on various aspects of the management. Infertility in PCOS, from minimal intervention to Assisted Reproduction.

Once you complete the 6 Modules, you could participate in an Online Exam, Assessment and on clearing it, you will be eligible to receive a beautiful certificate from the PCOS Society of India, which you will be extremely proud to display! To own this Certificate, you need to be a member of the PCOS Society, India!

To become a member, please log on to http://www.pcosindia.org/ to download your form and become a Life Member or Patron Member of the PCOS Society of India

If you have any queries, please write to us at thepcossociety@gmail.com

Both Madhuri and myself have worked hard on creating this program and we thank the team at Sun Pharma for their support in making this program a reality !

Enjoy reading.

With warm regards,

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Contents

POLYCYSTIC OVARY SYNDROME AND ENDOMETRIOSIS

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POLYCYSTIC OVARY SYNDROME AND ENDOMETRIOSIS

Endometriosis: An Overview

Is Endometriosis a Gynaecological Enigma?

Endometriosis is a chronic estrogen-dependent inflammatory, intermittent condition in which the functional endometrial glands and stroma proliferate and grow outside the uterine cavity, in other parts of the reproductive system. The most frequent sites include the ovaries, anterior/posterior cul-de-sac, broad ligaments, uterosacral ligaments, fallopian tubes, sigmoid colon, and appendix.[1]

Commonly, endometriosis manifests as severe pain; however, it can be asymptomatic, impacting reproductive potential. Endometriosis is difficult to diagnose, manage, and treat in view of the fact that the pathophysiology of endometriosis remains ill-defined. Thus, owing to the absence of an established etiology and owing to the existence of a large number of methodological nuances that challenge its understanding at a clinical level, endometriosis is frequently described as a 'gynaecological enigma.'[1]

Prevalence of Endometriosis

Although the accurate prevalence of endometriosis is difficult to estimate, endometriosis still remains one of the most commonly seen conditions in clinical practice. This is primarily attributed to the variations seen among patients, diversity of symptoms, difference in severity of symptoms, higher chance of misclassification, lack of valid and reliable non-invasive biomarkers and diagnostic tools and most important it may be asymptomatic.[1,2] Correct diagnosis can be established only by surgery.

Studies suggest the mean age at time of diagnosis of endometriosis is 25–35 years. The prevalence of endometriosis ranges between 25% and 50% in infertile women; 30%–50% of women with endometriosis are infertile. In addition, 45%–82% of women with chronic pelvic pain are diagnosed with endometriosis. Alarming statistics suggests that the prevalence of endometriosis is 6–21-fold higher in infertile women when compared to fertile women.

Among infertile women, the incidence ranges from 4% to 43%.[1,2] The condition is rare in pre menarche girls, with most of the cases <17 years are associated with Mullerian anomalies and vaginal obstruction. Endometriosis represents a major cause of hysterectomy and hospitalization in the United States, with total annual healthcare costs estimated at $69.4 billion in 2009.[3,4]

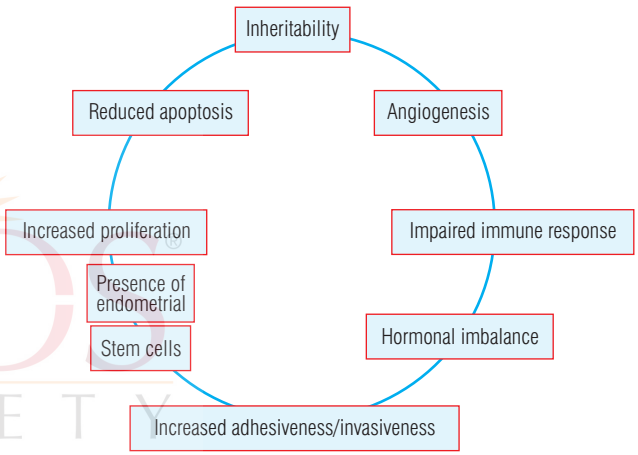
Endometriosis has polygenic, multifactorial mode of inheritance and occurrence rate among first degree relatives is 6.9% as compared to 1% non-blood related control group.

Pathogenesis of Endometriosis

As suggested, although endometriosis is strongly correlated with infertility, the pathophysiology still remains controversial. However, a few theories of the pathogenesis have been proposed, such as retrograde menstruation, coelomic metaplasia, altered immunity and association with stem cells, and genetics.[5]

Possible mechanisms of development of endometriosis are given in Figure 1.

Figure 1: Possible mechanisms of development of endometriosis.



Retrograde Menstruation

This theory was proposed by Sampson in the 1920s and is the best-acknowledged and oldest theory on the pathogenesis of endometriosis. The theory suggests that endometriosis occurs due to the retrograde flow of sloughed endometrial cells/debris via the fallopian tubes into the peritoneal cavity during menstruation. Further, the theory proposes that these endometrial cells attach themselves to the peritoneal mesothelial cells, establish a blood supply, proliferate, and produce endometrial implants. Thus, it is postulated that endometrial epithelial progenitor cells and endometrial mesenchymal stem-like cells together with their niche cells are shed into the peritoneal cavity via retrograde menstruation where they establish ectopic endometriotic lesions in women who develop endometriosis. This theory can explain the fact that the incidence of endometriosis is much higher in young girls.[5,6] However, researchers found that most women have retrograde flow and do not develop endometriosis, hence suggesting the possibility of a multifactorial pathogenesis of endometriosis. In addition; the theory also does not explain how endometriosis develops in women who have undergone hysterectomy or a tubal ligation.[5]

Coelomic Metaplasia

This theory was proposed by Ferguson in the 1960s; it suggests that endometriosis may develop from the metaplastic transition of the cells lining the pelvic peritoneum. This theory explains the occurrence of endometriosis in non-menstruating situations.[5]

Altered Immunity

This theory suggests that endometriosis occurs due to altered and defective immune responses that are unable to clear up retrograde endometrial cells that were probably produced during menstruation. This theory implicates the following in the causation of endometriosis: faulty functioning of cell-mediated immunity, inability of leukocytes to recognize the incorrect location of the endometrial tissue, and impaired natural killer (NK) cell activity. In fact, there is an increase in the number of leukocytes and macrophages in and around endometrial implants, secreting cytokines and growth factors that facilitate the recruitment of capillaries and leukocytes. Thus, the immune system itself facilitates the growth, proliferation and vascularization and increases the severity of endometriosis.[5]

Stem Cells

Studies have indicated the possibility of bone marrow-derived cells differentiating into endometrial cells and developing into ectopic endometrial implants. This also explains the possibility of the presence of ectopic tissue in extra-reproductive organs.[5]

Genetics

Genetic predisposition is a known causative factor in endometriosis. Women with a familial history of the disease have a 7-fold higher risk of developing endometriosis when compared to women without a familial history of the disease. Specific genetic alterations may allow the detection of endometriosis sub-types, thereby supporting risk stratification, individualized therapy, and personalized care for endometriosis.

Risk Factors for Endometriosis

Endometriosis is said to be higher in Asians and blacks when compared to Caucasians. Reports suggest that women with early menarche, short menstrual cycles are more prone and its occurrence is inversely related to BMI. The relationship between occurrence of endometriosis and volume and duration of menses is less consistent. Positive association was also found between smoking, alcohol consumption, high consumption of red meat, palmate acid and trans-fats. Negative association was found between endometriosis and fruits and vegetables and the risk reduced with consumption of omega 3 fatty acids.

Presence of cyclic gastrointestinal/urinary symptoms, dyschezia, dysmenorrhea, dyspareunia, dysuria, early menarche and pelvic pain should prompt you for early diagnostic test to rule out endometriosis.

Features such as red hair, blue or green eyes, and freckles have been implicated as risk factors; however, their association still remains debatable.[7,8]

Summary

- Endometriosis is a chronic, inflammatory, intermittent condition in which the functional endometrial glands and stroma proliferate and grow outside the uterine cavity, in other parts of the reproductive system.
- Affect 6–10 % women in reproductive age
- Studies suggest that the prevalence of endometriosis ranges between 25% and 50% in women with pelvic pain and infertility.
- In presence of dysmenorrhoea - Incidence is 40–60%
- Infertile women x 10 risk - 20–40%
- Multiparous women
  - During Laparoscopic sterilization - 6–43%
  - Fertile women - 5.2%
- 45% of women with chronic pelvic pain are diagnosed with endometriosis.
- Pathogenic theories of endometriosis include retrograde menstruation, coelomic metaplasia, altered immunity, retrograde menstruation of endometrial stem/progenitor cells and genetic predisposition.

Endometriosis and Infertility

Implications of Endometriosis on Fertility

Table 1 gives the cause of infertility in women with endometriosis.

Table 1: Cause of infertility in women with endometriosis

- Distorted pelvic anatomy
- Altered tubal milieu and transport
- Altered peritoneal fluid
- Hormonal dysfunction
  - LH surge
  - Hyperprolactinemia
- Ovarian dysfunction
  - Follicular growth
  - Anovulation
  - LUF syndrome
  - CL insufficiency
- Altered follicular function
- Oxidative stress
- Altered endometrial function
- Autoimmune/Immune dysfunction

Effect of Endometriosis on Fertility Mechanisms

Distorted Pelvic Anatomy due to major pelvic adhesions that result from endometriosis impair oocyte release from the ovary or inhibit ovum capture or transport. There is abnormal utero tubal transport due to reduction in physiologic utero tubal transport capacity which can affect the oocyte as well as sperm transport.[5]

Altered Peritoneal Function

During endometriosis there is an increased volume of peritoneal fluid with increase in concentration of prostaglandins, proteases and inflammatory cytokines - IL-1, IL-6,TNFα, and angiogenic cytokines - IL-8 and VEGF

produced by macrophages. Elevated concentrations of inflammatory cytokines in serum imply that endometriosis may lead to systemic inflammation. An ovum capture inhibitor that prevents normal cumulus-fimbria interaction has been reported in the peritoneal fluid of hamsters with induced endometriosis.

The concentration of transferrin, iron & alpha 2-HS glycoprotein is also elevated in peritoneal fluid, which is detrimental to oocyte quality and adversely affect sperm motility and survival. Transferrin attenuates FSH induced differentiation of granulosa cells contributing to ovarian dysfunction.

Endocrine and Ovulatory Abnormalities

Following endocrine and ovulatory abnormalities have been observed in women with endometriosis

- Luteinized unruptured follicle syndrome
- LH receptor disorder
- Luteal phase dysfunction
- Abnormal follicular growth
- Premature and multiple LH surges
- Longer follicular phase
- Lower serum estradiol levels and lower LH-dependent progesterone secretion during the luteal phase
- Increased levels of prolactin

Moreover, increased concentrations of interleukin-1b (IL-1b), IL-8, IL-10, and tumor necrosis factor-alpha in follicles adjacent to endometriomas are associated with reduced ovarian response.

Endometriosis and Granulosa Cell Dysfunction

Granulosa cell dysfunction resulting in abnormal folliculogenesis is common and may be due to any of the factors highlighted below.[9]

- Lower level of LH receptors with decreased sensitivity to LH stimulation
- Impaired steroid production (lower aromatase activity)
- Higher apoptosis of granulosa cells
- Lower VEGF gene expression
- Alteration in cell cycle
- Increase of oxidative stress markers
- Higher expression of STS mRNA expression
- *In vitro* granulosa cells secrete higher levels of IL-1 beta, IL- 6,IL-8, and TNF alpha

Follicular Environment and Endometriosis - Potential Effects on Oocyte Quality

Folliculogenesis is regulated by endocrine factors (FSH, LH), peritoneal factors, vascularization of the follicles and intrafollicular paracrine control, which plays a key role. Altered progesterone and cytokine concentrations are seen in the follicular fluid of women with endometriosis. Table 2 gives the effects of the altered cytokine concentrations.

Table 2: Effect of altered intra-follicular cytokine concentrations

↓ATP	Reduced oocyte viability
↑VEGF	Decreased embryo development
↑TNF alpha	Regulates apoptosis
↑Endothelin-I	Inhibition of granulosa cell steroidogenesis
↑IL-10	Causes arrest in GO Phase of GC
↑RANTES	Increased inflammation, cytotoxic effects and OS

Endometriosis and Oxidative Stress

Oxidative stress (OS) in women with endometriosis results in reduced antioxidant capacity[10], OS is increased in granulosa cells[11] and follicular fluid[12], increased ROS in Peritoneal Fluid[13,14] and antioxidant-oxidant imbalance.[15] In the presence of high OS there is meiotic spindle damage and poor oocyte quality and increased intra follicular high concentration of ROS can be associated with a high rate of degenerated oocytes .

Oxidative stress has a significant role in infertility through multiple mechanisms with significant impact on fertility outcome of ART as seen in Table 3.

Table 3: Effect of oxidative stress associated with endometriosis on fertility

Effects of OS	Impairment of
Local inflammation	Granulosa cell function
Degradation of cell membrane	Oocyte quality and function
Inactivation of enzymes	Sperm integrity and function
Genomic and mitochondria DNA damage	Embryo integrity and development
Ultimately cell death	Implantation

Effect on Gametes and Embryo

Endometriosis can result in poor response with low oocyte quality, incomplete maturation of ovarian follicle, decreased fertilization and implantation rates, poor quality early embryonic development. Abnormal embryonic development is seen in the form of abnormal phenotype on day 2, which is 3.5 to 15 times more frequent, presence of large peripheral regions of organelle depletion with or without darkened central cytoplasm at the 2 PN stage, arrested 2 PN with halo and anucleated fragments which can result in abnormal cleavage. Bad embryo quality as a result of poor oocyte quality with increased rate of nuclear and/or cytoplasmic aberration, less number of blastomeres on day 3 and a low blastocyst formation rate.[5]

Moreover, if endometriotic fluid gets inadvertently incorporated into oocyte-cumulus complex at oocyte retrieval may have a negative effect on fertilization & implantation potential of the oocyte and resultant embryo.

Reduced Implantation Rate With Low Pregnancy Rates

Low implantation rates (IR) are related to poor embryo quality, disorders of endometrial function, reduced endometrial expression of avb3 integrin (a cell adhesion molecule) during the time of implantation, very low levels of an enzyme involved in the synthesis of the endometrial ligand for L-selectin. Aberrant genes expressed in endometriosis reduce IR by affecting endometrial receptivity as HoxA-10 and HoxA-11 not up regulated during implantation window, there is persistent expression of Matrix metalloproteinase 7 and 11 during secretory phase with reduced alpha, beta integrin expression and is also associated with up regulation of cytokines, growth factors in decidualized stromal cells.[5]

In endometriosis, reduced expression of progesterone receptors in the endometrium may cause progesterone resistance. There is also a luteal phase disruption that may result from progesterone receptor dysregulation, as well as from an effect on progesterone target genes, which in turn leads to decreased endometrial receptivity or impaired oocyte release. Studies have shown abnormal expression of glutathione peroxidase and catalase in the endometrium of patients with endometriosis.

Lower pregnancy rates (PR) in endometriosis are due to functional alteration within the oocyte impairing embryo's capability to implant rather than defective endometrium. This is based on the finding that patients who received oocytes from donors without endometriosis had same chances of conception as donor.[16]

Immunological Explanation for Infertility

Chronic intraperitoneal inflammation seen during endometriosis is hypothesized to induce an acute inflammatory reaction, which is associated with recruitment and activation of T helper and regulatory T (Treg) cell subsets that suppresses effector T cells and promote proliferation and invasion of endometrial stromal cells. Altered humoral & cell mediated immunological function could affect endometrial receptivity. Autoantibodies against endometrial antigen and generalized polyclonal B-Cell can result in autoimmune activation. Higher concentrations of anti-laminin-1 IgG found in women with endometriosis prevent trophoblast proliferation & differentiation. Moreover, altered concentration and function of immune related cells (increased concentrations of cytokines, growth factors & activated macrophages) in peritoneal fluid of women with endometriosis have adverse effect on sperm function and embryo survival, higher apoptotic incidence, more alterations of cell cycle and higher incidence of oxidative stress. Women who test positive for 3 or more autoantibodies had a significantly lower chance of conception (22.9% than those testing negative 45.7 %).

Potential Explanation of Endometriosis Related Adverse Pregnancy Outcomes

Endometriosis ca affect endometrial receptivity, decidualization ad invasion of blastocyst resulting in implantation failure thus causing infertility. Progesterone resistance can result in deferred implantation and defective placentation with placenta previa/accreta, IUGR, pre-eclampsia and increased risk of miscarriage and recurrent pregnancy loss. Premature decidual senescence ca result in pre-term birth and even fetal death. Shallow evasion may result in pre-eclampsia. Increased ROS can result in shallow invasion with increased incidence of pre-eclampsia and pre-term birth.[17]

Summary

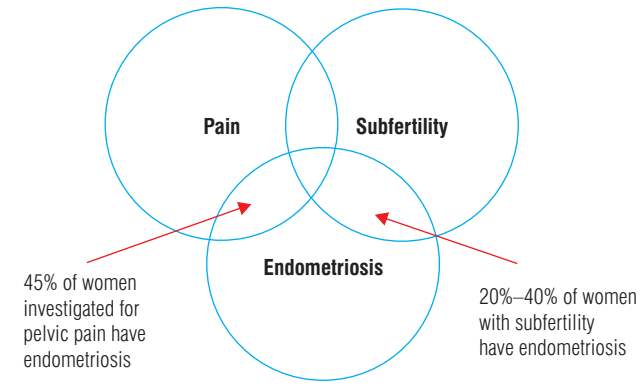
- Changes associated with endometriosis may affect
  - Ovulation and corpus luteum function
  - Oocyte quality
  - Oocyte capture
  - Sperm transport and function
  - Fertilization
  - Embryo development
  - Implantation
- Lower pregnancy rates seen in women with endometriosis as compared with healthy women or those with tubal factor Evidence B Level 2b
- Poorer success (IR & PR) increases with severity of endometriosis
- Follicular microenvironment and altered endometrial receptivity are the main causes of decreased pregnancy rate
- Increased concentrations of interleukin-1b (IL-1b), IL-8, IL-10, and tumor necrosis factor-alpha in follicles adjacent to endometriomas are associated with a reduced ovarian response.

Diagnosis and Staging of Endometriosis

Symptoms

The symptoms of endometriosis remain extremely variable. Some patients remain asymptomatic; however, the common umbrella of symptoms includes dysmenorrhea; chronic pelvic pain; infertility; deep dyspareunia; cyclic intestinal; and urinary symptoms, such as pain or bleeding on defecation/urination during the menstrual period (Figure 2).[18] Interestingly, dyschezia and deep dyspareunia have been identified as reasonably strong predictors of endometriosis.[19]

Figure 2: Symptoms of endometriosis.



A study was conducted to describe the clinical and epidemiological aspects of patients with pelvic endometriosis and suggested that 62.2% of women had dysmenorrhea, followed by chronic pelvic pain and deep dyspareunia, reported by 56.8% and 54.7% of patients, respectively.[18]

ESHRE Recommendations on Symptoms and Clinical Examination for Diagnosis of Endometriosis

The European Society of Human Reproduction and Embryology (ESHRE) guidelines remain the bible for the diagnosis, management, and clinical care of endometriosis. The recommendations for symptoms and clinical diagnosis of endometriosis are summarized in Table 4.[20]

Table 4: ESHRE recommendations on symptoms and clinical examination for diagnosis of endometriosis[20]

Recommendation	Grade of recommendation
Clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, and fatigue in the presence of any of the above.	GPP
Clinicians should consider the diagnosis of endometriosis in women of reproductive age with nongynecological cyclical symptoms (dyschezia, dysuria, hematuria, and rectal bleeding, shoulder pain).	GPP
Clinicians should perform a clinical examination in all women suspected of endometriosis, although a vaginal examination may be inappropriate for adolescents and/or women without previous sexual intercourse. In such cases, a rectal examination can be helpful for the diagnosis of endometriosis.	GPP
Clinicians may consider the diagnosis of deep endometriosis in women with (painful) induration and/or nodules of the rectovaginal wall found during clinical examination or visible vaginal nodules in the posterior vaginal fornix.	C
Clinicians may consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during a clinical examination.	C
Clinicians may consider the diagnosis of endometriosis in women suspected of the disease even if the clinical examination is normal.	C

GPP: Good practice point. GPP is based on expert opinion. C: Single randomized trial, large nonrandomized trial(s), or case-control/cohort studies (of moderate quality).

Imaging Techniques Used in Diagnosis of Endometriosis

Laparoscopy

Laparoscopy is the gold standard method for the diagnosis of endometriosis. However, existing data provide limited evidence with regard to the effectiveness of laparoscopy for confirming a diagnosis of endometriosis. Nonetheless, individual, small studies do confirm its application.[20,21] Definitive diagnosis of endometrium is possible when laparoscopy is coupled with biopsy.

A systematic review suggested that a negative diagnostic laparoscopy seems to be highly accurate for excluding endometriosis and, thereby, useful for the clinician in decision-making. However, this is based on the assumption that the diagnostic laparoscopy is performed well and preceded by appropriate preoperative assessment. A positive laparoscopy is less informative and is of limited value when used without obtaining biopsies to arrive at a histological confirmation of the diagnosis. The ESHRE guidelines for the application of laparoscopy in the diagnosis of endometriosis are summarized in Table 5.[20,21]

Table 5: ESHRE recommendations for the application of laparoscopy in the diagnosis of endometriosis[20]

Recommendation	Grade of recommendation
Clinicians perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy without histology proves the presence of disease.	GPP
Clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis (even though negative histology does not exclude it).	GPP
Clinicians obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or deep infiltrating disease, to exclude rare instances of malignancy.	GPP

GPP: Good practice point. GPP is based on expert opinion.

Transvaginal Sonography

Transvaginal sonography (TVS) has proved to be a sensitive tool for the detection of ovarian endometriomas when compared to traditional clinical assessment alone. In addition, recent studies also suggest that TVS could be an accurate method for the detection of endometriosis in extra-ovarian locations as well. Transvaginal sonography is a readily available, cost and time-effective diagnostic tool when compared to other radiological procedures.[22] Transvaginal ultrasound appears to be a good test for the differentiation of endometrioma from other adnexal masses.[23]

A meta-analysis included 10 studies (1106 patients) with suspected endometriosis and suggested that TVS with or without the use of prior bowel preparation is an accurate test for non-invasive, presurgical detection of deep infiltrating endometriosis of the rectosigmoid and improved the quality of non-invasive assessment in patients with suspected pelvic pathologies. The ESHRE guidelines for the application of transvaginal sonography in the diagnosis of endometriosis are summarized in Table 6.[22]

Table 6: ESHRE recommendations for the application of transvaginal sonography in the diagnosis of endometriosis[20]

Recommendation	Grade of recommendation
In women with symptoms and signs of rectal endometriosis, transvaginal sonography (TVS) is useful for identifying or ruling out rectal endometriosis.	A
Clinicians are advised to perform TVS to diagnose or exclude an ovarian endometrioma.	A
Clinicians base the diagnosis of ovarian endometrioma in premenopausal women on the following ultrasound characteristics: ground glass echogenicity and one to four compartments, and no papillary structures with detectable blood flow.	GPP
Clinicians should be aware that the usefulness of 3D ultrasound to diagnose rectovaginal endometriosis is not well established.	D

GPP: Good practice point. GPP is based on expert opinion. A: Meta-analysis or multiple randomized trials (of high quality), D: Non-analytic studies or case reports/case series (of high or moderate quality).

3D Sonography

Considering the few shortcomings of TVS in deep endometriosis in certain locations, 3D introital ultrasonography can be considered the next choice of diagnostic procedure, especially when rectovaginal endometriosis is suspected. Its advantages include its high reproducibility and ability to reconstruct the image after a single sweep of the ultrasound beam across the target. In addition, it may also allow unobstructed access to various planes; which can be reviewed multiple times. It provides precision with respect to the location of the lesion and the surrounding organs. However, further studies are required to prove its efficacy.[24]

Magnetic Resonance Imaging

The technique of fat suppression used in MRI is known to help detect endometriomas and peritoneal lesions; thus, MRI may aid in understanding the size and position of disease. However, the evidence regarding its application and effectiveness remains variable. One study has suggested that MRI was very sensitive, detecting all 27 endometriosis implants of 4 mm in diameter in women with severe disease.[25]

However, on the contrary, in another study that included women with all stages of the disease, MRI failed to identify endometriosis in 7 of 27 women. Further, a prospective trial including 48 women suggested that although MRI doesn't efficiently identify areas of endometriosis than seen at surgery, endometriosis was detected in 75% of those with mild disease. Thus, MRIs have been fairly insensitive in defining the extent of disease or in identifying peritoneal lesions, even deep or large superficial ones. The ESHRE guidelines for the application of MRI for the diagnosis of endometriosis are summarized in Table 7.[25]

Table 7: ESHRE recommendation for the application of MRI in the diagnosis of endometriosis[20]

Recommendation	Grade of recommendation
Clinicians should be aware that the usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established.	D

D: Non-analytic studies or case reports/case series (of high or moderate quality).

Biomarkers in the Diagnosis of Endometriosis

Considering the symptoms of endometriosis are vague and no other diagnostic method is 100% reliable, finding a reliable solution for the diagnosis of endometriosis is the need of the hour. Data suggest that women can suffer for up to 8–12 years before being diagnosed with endometriosis. Biomarkers seem to be a less invasive method to diagnose and monitor treatment efficacy. However, it cannot be denied that more studies are required to confirm their absolute application. The most commonly evaluated biomarkers include cytokines, antibodies, cell populations, glycoproteins, growth factors, proteomics, hormones, etc. A few biomarkers are discussed in the Table 8.[26]

Classification and Staging of Endometriosis

Most commonly used classification and staging system is the revised American Fertility Society (AFS) system that ranges from Stage I (minimal) to Stage IV (severe). The staging system involves location, depth of disease and extent of adhesions (Figure 3).[27]

Table 8: Biomarkers in the diagnosis of endometriosis[11]

Biomarker	Description
Interleukin 6	• Six studies have indicated a link between raised serum levels of IL-6 and endometriosis. • One study found elevated levels of serum IL-6, but only in women with stages I–II disease, yielding a sensitivity of 75% and specificity of 83.3% for disease of this severity.
Tumor necrosis factor-alpha	• Seven studies demonstrated an increase in TNF-alpha levels in women with endometriosis, but four studies showed no such difference. • Infertility could be a confounding factor when assessing TNF-alpha levels.
Interferon-gamma	Most studies have failed to find a correlation between peripheral blood levels and endometriosis.
Anti-endometrial antibodies	• When compared with CA125, the diagnostic accuracy of endometrial antibody testing appeared favorable with a sensitivity of 83% and specificity of 79% versus 27 and 83%, respectively, for CA125. • Autoantibodies may also be affected by treatment: levels of nine types of autoantibody were reduced by 6 months' treatment.
Natural killer cells	Several studies have failed to identify different levels of NK cells in peripheral blood of endometriosis patients.
B cells	Several studies have failed to identify a difference in B cell levels when comparing healthy women to those with endometriosis.
Cancer antigen 125 endometriosis	• The most consistently studied glycoprotein in infertile women without endometriosis tend to have a slight elevation in serum CA125 levels during menstruation; however, the magnitude of this increase is much greater in women with endometriosis. • A sensitivity of 93% and specificity of 92% for the diagnosis of endometriosis has been achieved, using a threshold of an 83% increase in CA125 during menses.

CA: Cancer antigen, NK: Natural killer, TNF: Tumor necrosis factor, IL: Interleukin.

Summary

- The symptoms of endometriosis remain extremely variable.
- Laparoscopy is the gold standard method for diagnosing endometriosis; however, its use is not supported by high-quality data. But ddefinitive diagnosis of endometrium is possible when laparoscopy is coupled with biopsy.
- Transvaginal sonography (TVS) has proved to be a sensitive and cost-effective tool for the detection of ovarian endometriomas when compared to traditional clinical assessment alone.
- 3D introital ultrasonography can be used for the diagnosis of rectovaginal endometriosis. Its advantages include its high reproducibility and ability to reconstruct the image after a single sweep of the ultrasound beam across the target, and unobstructed entrance to various planes.
- The technique of fat suppression used in MRI is known to help detect endometriomas and peritoneal lesions; thus, MRI may support in understanding the size and position of disease. However, evidence on its application and effectiveness remains variable.
- CA-125, History, Pelvic examination – Inconclusive
- Cystoscopy and proctosigmoidoscopy - to assess ureter, bladder and bowel involvement
- IL-8 and CEA - Role still to be established
- Biomarkers seem to be a less invasive method to diagnose and monitor treatment efficacy; however, further studies are required to confirm their absolute application for diagnosing endometriosis.

Figure 3: Revised American Fertility Society (AFS) system classification of endometriosis.[27]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1–5
Stage II (Mild) - 6–15
Stage III (Moderate) - 16–40
Stage IV (Severe)
Total _____

Laparoscopy_____ Laparotomy_____ Photography _____
Recommended Treatment_____

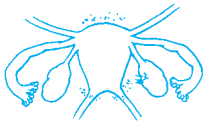
Prognosis _____

	ENDOMETRIOSIS	<1 cm	1–3 cm	>3 cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
OVARY	ADHESIOINS	<1/3 Enclosure	<1/3–2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBED	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

•If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

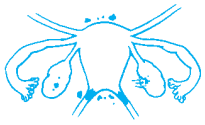
Denote appearance of superficial implant types as red [®, red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R____%, W____% and B____%. Total should equal 100%.

STAGE I (MINIMAL)



PERITONEUM
Superficial Endo – 1–3 cm –2
R. OVARY
Superficial Endo – <1 cm –1
Filmy Adhesions – <1/3 –1
TOTAL POINTS 4

STAGE II (MILD)



PERITONEUM
Deep Endo – >3 cm –6
R. OVARY
Superficial Endo – <1 cm –1
Filmy Adhesions – <1/3 –1
L. OVARY
Superficial Endo – <1 cm –1
TOTAL POINTS 9

STAGE III (MODERATE)

PERITONEUM
Deep Endo – >3 cm –6
CULDESAC
Partial Obliteration – <1 cm –4
L. OVARY
Superficial Endo – 1–3 cm –16
TOTAL POINTS 26

STAGE III (MODERATE)

PERITONEUM
Superficial Endo – >3 cm –4
R. TUBE
Filmy Adhesions – <1/3 –1
R. OVARY
Filmy Adhesions – <1/3 –1
L. TUBE
Dense Adhesions – <1/3 –16*
L. OVARY
Deep Endo – <1 cm –4
Dense Adhesions – <1/3 –4
TOTAL POINTS 30

STAGE IV (SEVERE)

PERITONEUM
Superficial Endo – >3 cm –4
L. OVARY
Deep Endo – <1–3 cm –32**
Dense Adhesions – <1/3 –8**
L. TUBE
Dense Adhesions – <1 cm –8**
TOTAL POINTS 52

*Point assignment change to 16
**Point assignment doubled

STAGE IV (SEVERE)

PERITONEUM
Deep Endo – >3 cm –6
CULDESAC
Complete Obliteration –40
R. OVARY
Deep Endo – 1–3 cm –16
Dense Adhesions – <1/3 –4
L. TUBE
Dense Adhesions – >2/3 –16
L. OVARY
Deep Endo – 1–3 cm –16
Dense Adhesions – >2/3 –16
TOTAL POINTS 114

Management of Endometriosis

Factors Determining Choice of Treatment

Factors that govern the choice of treatment in endometriosis include: woman's age, fertility plans, previous treatment, the nature and severity of the symptoms, and the location and severity of the disease.[28]

The following must be considered prior to deciding the treatment plan of a patient with endometriosis: [20,28]

- Women's age
- Presence and severity of pain
- Grade of endometriosis
- Desire for fertility

Treatment Options

- Expectant/Symptomatic
- Medical treatment – Result in ovarian suppression so no role if fertility is desired. Can be usedfor pain
- Surgery – One can allow 12 months for spontaneous pregnancy but this depends on the stage of disease and pelvic affection.
- Combinations of suppression and surgery
- COS – Endometriosis may or may not alter the effect COH + IUI. May be effective if performed shortly after laparoscopy
- ART- Outcome may be affected by
  - Surgery before ART may decrease ovarian reserve, but may be done in exceptional cases
  - Medical Rx before ART – Improves outcome

Medical Management of Endometriosis

1. Combined estrogen-progestin therapy
2. Progestins
3. Gonadotropin-releasing hormone agonists
4. Gonadotropin-releasing hormone antagonist
5. Danazol
6. Aromatase inhibitors

Medical management is effective for relieving pain associated with endometriosis but there is no evidence that it improves fertility.[29] Fertility is essentially eliminated during treatment because all medical treatments for endometriosis inhibit ovulation.

Medical management is mostly used in adolescents with pelvic pain and dysmenorrhea. However, the response to hormonal treatment does not always predict the presence or absence of endometriosis. Dysmenorrhea is associated with the possible development of deep endometriosis later in life; however, this association remains uncertain. The ESHRE recommends that clinician counsel women with symptoms presumed to be due to endometriosis thoroughly. It also recommends treating such women empirically with adequate analgesics, combined hormonal contraceptives, or progestagens. [20]

Oral Contraceptives

Oral contraceptives remain the first choice of therapeutic treatment for endometriosis-associated chronic pelvic pain. Thus, they restrain ovarian activity and decrease the estrogen-induced production of prostaglandins, decreasing menstrual flow and inflammation. A study has suggested that low-dose oral contraceptive pill is more efficient than placebo in controlling dysmenorrhea and diminishing the ovarian endometrioma size. They can also be used together with the GnRH analogs in 'add-back therapy,' to balance hypoestrogenism and protect bone density. Unfortunately, no high-quality clinical evidence is available regarding the efficacy of low-dose oral contraceptives.[20,32] The ESHRE guidelines for the use of oral contraceptives for the management of endometriosis are summarized in Table 9.

Table 9: ESHRE recommendations for the application of oral contraceptives in endometriosis[20]

Recommendation	Grade of recommendation
Clinicians are recommended to suggest hormonal treatment (hormonal contraceptives [Level B], progestogens [Level A], anti-progestogens [Level A], or GnRH agonists [Level A]) as one of the options, as it reduces endometriosis-associated pain.	A-B
Clinicians take patient preferences, side effects, efficacy, costs, and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.	GPP
Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain.	B
Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhea.	C
Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia, and chronic pelvic pain.	C

GPP: Good practice point. GPP is based on expert opinion, A: Meta-analysis or multiple randomized trials (of high quality); B: Meta-analysis or multiple randomized trials (of moderate quality), or single randomized trial, large nonrandomized trial(s), or case-control/cohort studies (of high quality); C: Single randomized trial, large non-randomized trial(s), or case-control/cohort studies (of moderate quality).

Progestins

Progestins have been used for more than 3 decades for the treatment of endometriosis and are generally safe, effective, and well tolerated in symptomatic patients who do not want to have children. They are primarily used in the management of symptomatic endometriosis, both as primary therapy and as an adjunct to surgical management. They function by inducing pseudo-pregnancy and inhibiting estrogenic stimulation of the ectopic endometrium.[30–33]

Traditional progestins such as cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) have demonstrated several side effects such as menstrual irregularities, mood changes, amenorrhea, weight gain, and breast tenderness. Recent advances, such as levonorgestrel-releasing intrauterine device (IUD-LNG), have been successful in reducing dysmenorrhea, pelvic pain, and deep dyspareunia. They have also been successful in reducing the size of endometriotic implants, in avoiding repeated administrations, in providing effective contraception, in increasing compliance and minimum side effects. Dienogest is another recent and promising progestin being used for the treatment of endometriosis-associated pain. It demonstrates high selectivity to progesterone receptors, powerful progestinic effect on the endometrium, and beneficial antiandrogenic properties. However, dienogest has been associated with a lower incidence of vasomotor symptoms and a lower impact on bone metabolism, with a minimum change in bone density.[30,33] The ESHRE guidelines on the use of progestins for the management of endometriosis are summarized in Table 10.

Table 10: ESHRE recommendations on the application of progestins in endometriosis[20]

Recommendation	Grade of recommendation
Clinicians are recommended to use progestogens (medroxyprogesterone acetate [oral or depot], dienogest, cyproterone acetate, norethisterone acetate, or danazol]) or anti-progestogens (gestrinone) as one of the options to reduce endometriosis-associated pain.	A
Clinicians take the different side-effects profiles of progestogens and anti-progestogens into account when prescribing these drugs, especially irreversible side effects (e.g. thrombosis and androgenic side effects).	GPP
Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system (LNG-IUS) as one of the options to reduce endometriosis-associated pain.	B

GPP: Good practice point. GPP is based on expert opinion. A: Meta-analysis or multiple randomized trials (of high quality), B: Meta-analysis or multiple randomized trials (of moderate quality).

GnRH Analogs

GnRH analogs (GnRH-a) act by creating an acyclic, hypo-estrogenic environment by blocking ovarian estrogen secretion by inducing a pseudo-pregnancy state. This effect is readily reversible after withdrawal of treatment. They are considered as second-line treatment in case of failure of therapy with oral contraceptives or progestins; or when they are not tolerated or contraindicated. GnRH-a reduce symptoms in about 50% of cases and their administration after surgical treatment extends the possibility of pain-free intermission. Treatment for 3 months with a GnRH-a may reduce painful symptoms for about 6 months. However, the following effect also exists: high rate of recurrence of pelvic pain and side effects, such us worsening in the lipid profile, depression, flushes, urogenital atrophy, loss of libido, and decrease in bone mass.[30,34–36] A Cochrane review suggested that treatment with a GnRH-a improved symptom relief no better than any other therapeutic option.[34] The ESHRE guidelines on the use of GnRH agonist for the management of endometriosis are summarized in Table 11.

GnRH Antagonist

A recent addition to the treatment of endometriosis-associated pain has been the use of GnRH antagonists (GnRH-anta). They decrease estrogen levels without triggering the side effects consequent to estrogen withdrawal. A recent study has shown that GnRH-anta have a suitable efficacy and safety profile. More studies are required to integrate its use in clinical practice.[30]

Table 11: ESHRE recommendations on the application of GnRH agonist in endometriosis[20]

Recommendation	Grade of recommendation
Clinicians are recommended to use GnRH agonists as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding the dosage or duration of treatment.	A
Clinicians are recommended to prescribe hormonal add-back therapy to coincide with the start of GnRH agonist therapy, to prevent bone loss and hypoestrogenic symptoms during treatment. This is not known to reduce the effect of treatment on pain relief.	A
Clinicians should give careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density.	GPP

GPP: Good practice point. GPP is based on expert opinion, A: Meta-analysis or multiple randomized trials (of high quality).

Non-steroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently used treatment for endometriosis. However, evidence on its application remains controversial. To date, there are insufficient clinical data to establish the effectiveness of NSAIDs in the treatment of endometriosis-associated pain. They are also associated with peptic ulcer and anovulation if taken at midcycle. The ESHRE guidelines suggest that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.[20,30]

Aromatase Inhibitors

In endometriosis, there is an evident overexpression of the aromatase enzyme, which causes exaggerated estrogen synthesis. This growth and invasion of the endometrial lesion, resulting in prostaglandin-mediated inflammation and pain. The use of aromatase inhibitors has lead to a reduction in extraovarian estrogen synthesis. Thus plasma levels of estrogen in women taking 1–5 mg of letrozole or anastrozole daily are reduced by 97–99%.[30]

However, common side effects of aromatase inhibitors include headache, stiffness or joint pains, nausea, diarrhoea, and flushing. The long-term use of these drugs leads to the onset of bone fractures, osteopenia, and osteoporosis. However, in premenopausal women, bone loss can be reversed by add-back therapy. The combination of conventional therapy and aromatase inhibitors blocks the production of estrogen, reducing painful symptoms. Thus, aromatase inhibitors are commonly prescribed when all other options for medical or surgical treatments have failed. The ESHRE guidelines on the use of aromatase inhibitors for the management of endometriosis are summarized in Table 12.[20]

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators cooperate with estrogen receptors as agonists or antagonists. Although animal studies have shown a positive outcome human data remains unavailable.[30]

Table 12: ESHRE recommendations on the application of aromatase inhibitors for the management of endometriosis[20]

Recommendation	Grade of recommendation
In women with pain due to rectovaginal endometriosis refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills, progestogens, or GnRH analogs, as they reduce endometriosis-associated pain.	B

B: Meta-analysis or multiple randomized trials (of moderate quality).

Immunomodulators

Endometriosis is associated with a significant increase in cytokines and growth factors in the peritoneal fluid, some alterations of the activity of B lymphocytes, increased antibody response, and increased concentration and activity of peritoneal macrophages. Thus, agents stimulating cell-mediated immune response and agents reducing inflammatory response can be useful in the treatment of endometriosis-associated pain.[30]

Role medical treatment in management of infertility by the Practice Committee of the America Society of Reproductive Medicine

In minimal to mild endometriosis: The one-and two-year cumulative pregnancy rates were similar in the groups receiving GnRH-agonist treatment (6 months) or expectant management and so it is not recommended to offer medical therapy but to proceed with active management of fertility.[37] It was also observed that pregnancy rates were similar at one year in both women treated with progestins or expectant management.[38]

Summary

- Counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens (GPP)
- Prescribe hormonal treatment (hormonal contraceptives, progestagens, anti-progestagens, or GnRH agonists as one of the options, as it reduces endometriosis-associated pain) (Grade A-B)
- Take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain (GPP)
- Prescribing a combined hormonal contraceptive may be benificial as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Grade B)
- The continuous use of a combined oral contraceptive pill may be useful in women suffering from endometriosis-associated dysmenorrhea (Grade C)

- Suppression of ovarian function ineffective to improve fertility (Grade A)
- GnRH-agonist treatment may be effective in improving fertility because it increase in natural killer-cell activity and antibody levels, resulting in higher peritoneal fluid levels of IL-1 and decreased levels of TNF-alpha. It also has an effect on cell apoptosis and obliterates the embryotoxic effects of peritoneal fluid. GnRH agonist must be used immediately before IVF–ET and is associated with higher PRs and increased IRs. Patients with stage III or IV endometriosis who were subjected to GnRHa therapy 4–6 months before their IVF–ET cycle showed a 30% increase in PRs per cycle compared with patients who had undergone a standard COS.[39]
- In women with pain from rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills, progestagens or GnRH analogues, as they reduce endometriosis-associated pain.
- Clinicians should consider non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics to reduce endometriosis-associated pain if not controlled by hormonal treatment.

Surgical Management of Endometriosis

The benefit of laparoscopic treatment of minimal or mild endometriosis is insufficient to recommend laparoscopy solely to increase the likelihood of pregnancy. When laparoscopy is performed for other indications, one may consider safely ablating or excising visible lesions of endometriosis. In stage I/II endometriosis, laparoscopic ablation of endometrial implants has been associated with a small but significant improvement in live birth rates with the difference being 8.6% in favor of therapy.[40]

In women with stage III/IV endometriosis-associated infertility, conservative surgical therapy with laparoscopy or possible laparotomy may be beneficial. Surgical management of an endometrioma should include resection or ablation, rather than drainage, with resection being preferred treatment. Avoid cauterization as far as possible to control haemorrhage as it results in destruction of cortex and this decreases the ovarian reserve.[41,42]

For women with stage III/IV endometriosis who fail to conceive following conservative surgery or because of advancing reproductive age, IVF-ET is an effective alternative.

Common indications for surgery include:

- Severe, debilitating pain and functional impairment
- Advanced disease with significant anatomic impairment
- Failure of medical management
- Noncompliance or intolerance to medical treatment
- Rupture or torsion of endometrioma, obstructive uropathy, or bowel obstruction[41,42]

However, risk of pleiotropic disorder, increased recurrence rate and reduction in ovarian reserve are the prime concerns while opting for surgical interventions in the treatment of endometriosis.[41,42]

Surgery for Treatment of Endometriosis-Associated Pain: Laparotomy vs. Laparoscopy?

Laparoscopy is indicated when a woman presents with severe dyspareunia, dysmenorrhea, chronic pelvic pain, deep infiltrating endometriosis or presence of palpable nodule. A Cochrane review showed that laparoscopy is useful in treating pelvic pain associated with endometriosis.[43,44]

But the evidence suggests that the difference in pain relief achieved is not statistically significant between laparoscopy and laparotomy. Advantages of laparoscopy over laparotomy are as follows:

- Laparoscopy can be used as both diagnostic and therapeutic at the same time
- Easier removal and ablation of endometrial implants
- Its associated with reduced patient morbidity
- Post-operative recovery time is much lesser with laparoscopy
- Reduced recurrence

Laparotomy is suggested only in cases of severe endometriosis with widespread adhesions alongside with deeply infiltrating endometriosis or when there is a danger of injury to other organs at laparoscopy due to dese adhesions.[45]

The ESHRE guidelines on the use of laparoscopy for the management of endometriosis-associated pain are summarized in Table 13.[20]

Table 13: ESHRE recommendations on the application of laparoscopy for the management of endometriosis-associated pain[20]

Recommendation	Grade of recommendation
When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain, i.e. 'see and treat.'	A

A: Meta-analysis or multiple randomized trials (of high quality).

Is Surgery Effective for Painful Symptoms Associated with Endometriosis?

A Cochrane review suggests that laparoscopic surgery results in improved pain outcome when compared to diagnostic laparoscopy alone. It was not possible to draw conclusions from the meta-analysis as to which specific laparoscopic surgical intervention is most effective.[46]

Laparoscopic treatment of endometriosis does lead to improvement in disease and pain and thus supports the recommendation to treat endometriotic lesions at the time of diagnostic laparoscopy. Surgical

options for the treatment of endometriosis include the use of unipolar or bipolar cautery, laser ablation using potassium-titanyl-phosphate, carbon-dioxide, or neodymium: yttrium, aluminum, garnet lasers, and excision techniques. Each has advantages and disadvantages with respect to lesion removal, tissue trauma, and bleeding.[47,48] The only adequately powered, randomized study comparing excision versus ablation found no significant difference in pain scores up to 1 year after surgery. In addition, the results were not influenced by the stage of disease or whether the lesions were superficial or deep.[49]

Ablation vs. Excision of Endometriosis

Laparoscopic treatment of endometriosis is of two types ablation and excision. Although the decision is made based on the clinical experience, and expertise there is an ongoing debate regarding the choice. Excision was associated with improved symptom relief and lower recurrence rates compared to ablation and eversion, which had a high recurrence rate. However, excision is associated with higher incidence adhesion formation, reduced ovarian volume and reserve.[50]

Surgical Interruptions of Pelvic Nerve Pathways

This method disrupts the cervical sensory nerve fibers, thus reducing pain in patients with endometriosis. It includes uterine nerve ablation (UNA), in which there is transection of the uterosacral ligaments at the level of cervix; and pre-sacral neurectomy (PSN), which is interruption of the superior hypogastric plexus at the interiliac triangle. Generally, PSN involves elimination of a large number of nerve fibers, and is comparatively an intricate and precarious procedure. Due to the complexity of the procedure PSN, patients for whom this operation is recommended should be carefully selected. Zullo *et al*. demonstrated the effectiveness of pre-sacral neurectomy for women with severe dysmenorrhea due to endometriosis who had been treated with conservative laparoscopic surgical intervention.[51] Significant reduction in the frequency and severity of dysmenorrhea, dyspareunia, and chronic pelvic pain observed at the end of 24 months after surgery. Pelvic pain not related to menses decreased by 67% and dysmenorrhoea decreased at 3 months by 78%.[52]

The ESHRE guidelines on the use of surgical interruptions of pelvic nerve pathways for the management of endometriosis-associated pain are summarized in Table 14.[20]

Table 14: ESHRE recommendations on the application of surgical interruptions of pelvic nerve pathways for the management of endometriosis-associated pain[16]

Recommendation	Grade of recommendation
Clinicians should not perform laparoscopic uterosacral nerve ablation (LUNA) as an additional procedure to conservative surgery as a method to reduce endometriosis-associated pain.	A
Clinicians should be aware that PSN is effective as an additional procedure to conservative surgery to reduce endometriosis-associated midline pain, but it requires a high degree of skill and is a potentially hazardous procedure.	A

A: Meta-analysis or multiple randomized trials (of high quality).

Surgical Treatment of Ovarian Endometrioma

Surgical treatment can be justified for

- women with concomitant pelvic pain not responding to medical treatment
- when the cyst is larger than 4 cm
- when malignancy cannot be reliably excluded

All patient that opts for surgical treatment should be appropriately counselled about the potential risk of premature ovarian failure and the remote possibility of oophorectomy.

Cystectomy vs. Laser Vaporization

When cystectomy was compared with laser vaporization it was found that laser vaporization was associated with early recurrences and more recurrences during long-term follow-up although the differences were not statistically significant at 60 months of follow-up.[53]

The ESHRE guidelines on the use of laparoscopic cystectomy and laser vaporization for the management of endometriosis-associated pain are summarized in Table 15.[20]

Table 15: ESHRE recommendations on the application of laparoscopic cystectomy and laser vaporization for the management of endometriosis-associated pain[20]

Recommendation	Grade of recommendation
When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain.	A
Clinicians can consider performing cystectomy rather than CO_2 laser vaporization in women with ovarian endometrioma, because of the lower recurrence rate of the endometrioma with the former.	B

A: Meta-analysis or multiple randomized trials (of high quality); B: Meta-analysis or multiple randomized trials (of moderate quality).

Ovarian Cystectomy vs. Fenestration and Coagulation

Cystectomy provides better outcomes than fenestration/coagulation or laser ablation regarding recurrence of symptoms and endometrioma as well as pregnancy rate. The risk of recurrence of signs/symptoms, risk of recurrence compared after surgery was significantly lower for laparoscopic cystectomy compared with fenestration/coagulation. The risk of pregnancy was significantly higher for cystectomy compared with fenestration/coagulation.[54] The study showed that the recurrence of symptoms, such as pelvic pain and dysmenorrhea, was 15.8% with cystectomy and 56.7% with fenestration and coagulation after 2 years, thus concluding that laparoscopic cystectomy is superior to fenestration and coagulation, for the management of endometriosis-associated pain.[55] When endometriosis is associated with infertility it is preferable not to cauterize ovarian endometrioma if IVF or ICSI is indicated as it may cause destruction of ovarian tissues.

Laparoscopic excision of ovarian endometrioma prior to IVF does not offer any additional benefit over expectant management in terms of ovarian response to gonadotropin stimulation or pregnancy outcome, therefore management of women with endometrioma prior to IVF should be individualized to maximize the chances of success and minimize the risks. Any decision for surgery should be carefully considered and balanced against the risks, especially in women who have had ovarian surgery or those with suboptimal ovarian reserve.

Although the evidence is insufficient, drainage and sclero-therapy of endometrioma, possibly followed by post-operative ovarian suppression for 3 months, may be valid for women with a history of previous multiple surgery or those with frozen pelvis who wish to preserve their ovaries.

Surgical Approach for Deep Endometriosis

Optimal surgical approach for the pain associated with deep endometriosis has yet to be defined. Combination treatment with drugs and surgery may offer an advantage in treating pain, but the extent of the advantage is unclear.

Rectovaginal endometriosis is like an iceberg and is frequently misdiagnosed. It can preset as a nodular lesion with, fibrosis and smooth muscle metaplasia, and endometriotic tissue. In patients who are trying to conceive resection of recto-vaginal endometriosis resulted not only in a relief of pain, but also showed a positive effect on the possibilities to conceive spontaneously (67%) within an acceptable delay following surgery.

Nodule excision is less morbid surgical procedure suitable for a majority of women. Colorectal resection should be reserved for patients presenting with major digestive stenosis or with nodules whose features render excision technically impossible. In all cases, associated medical treatment should be administered to improve pain relief and to reduce the risk of recurrences.[56]

Colorectal segmental resection is associated with several unpleasant functional symptoms when compared with nodule excision. Information about functional outcomes should be provided to patients managed for rectal endometriosis and should be considered when deciding on the most appropriate treatment of this disease.[57] The quality of life was better with laparoscopically assisted colorectal resection when compared to open colorectal resection.[58]

Bowel Resection

Deep endometriosis is commonly found in the bowel and is generally treated by segmental bowel resection. A systemic review reported excellent pain outcomes in the first year after surgery; however, a large subsection of patients did report recurrence of painful symptoms.[59]

Hysterectomy for Endometriosis-Associated Pain

Hysterectomy for chronic non-specified pelvic pain associated with endometriosis is a successful approach in many women; however, as the procedure is fairly invasive, it requires further research.[60] The ESHRE guidelines suggest that, clinicians should consider hysterectomy with removal of the ovaries and all visible endometriotic lesions in women who have completed their family and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.[20]

Pre- and Postoperative Hormonal Therapies for Endometriosis Surgery

Although hormonal suppression is used to reduce the size of endometrial implants, there is no concrete evidence that supports the use of hormonal therapy either before or after surgery for the management of endometriosis-associated pain.[61] The ESHRE guidelines suggest that clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis.[20]

Postoperative Hormonal Therapies for Secondary Prevention of Endometriosis

Endometriosis commonly reoccurs even after surgical interventions. To prevent its recurrence, various hormonal therapies have been included as a part of supportive postoperative care. Combined oral contraceptives have a vital role in long-term use, safety, tolerability; and have beneficial outcomes. A systemic review confirmed that postoperative use of oral contraceptives helps reduce the frequency and intensity of dysmenorrhea recurrence and in reducing the anatomical relapse rate.[62] The ESHRE guidelines on the use of postoperative hormonal therapies for the management of endometriosis associated-pain are summarized in Table 16.

Table 16: ESHRE recommendations on the application of postoperative hormonal therapies for the management of endometriosis-associated pain[20]

Recommendation	Grade of recommendation
Clinicians clearly distinguish adjunctive short-term (<6 months) hormonal treatment after surgery from long-term (<6 months) hormonal treatment; the latter is aimed at secondary prevention.	GPP
Clinicians should not prescribe adjunctive hormonal treatment in women with endometriosis for endometriosis-associated pain after surgery, as it does not improve the outcome of surgery for pain.	A

GPP: Good practice point. GPP is based on expert opinion. A: Meta-analysis or multiple randomized trials (of high quality).

Summary

- All therapeutic options including conservative, medical or surgical treatment as well as the advantages and disadvantages should be fully discussed with the patient
- Can consider both ablation and excision of peritoneal endometriosis to reduce endometriosis-associated pain (Grade C)
- Should not perform LUNA as an additional procedure to conservative surgery to reduce endometriosis-associated pain (Grade A)
- PSN is effective as an additional procedure to conservative surgery to reduce endometriosis-associated midline pain, but it requires a high degree of skill and is a potentially hazardous procedure (Grade A)

- In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Grade A)
- Infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Grade A)
- When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation or CO_2 laser vaporization as it reduces endometriosis-associated pain (Grade A)
- Clinicians consider hysterectomy with removal of the ovaries and all visible endometriotic lesions, in women who have completed their family and failed to respond to more conservative treatments
- Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease (GPP)
- Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis (Grade A)
- Clinicians clearly distinguish adjunctive short-term (<6 months) hormonal treatment after surgery from long-term (>6 months) hormonal treatment; the latter is aimed at secondary prevention (GPP)

Treatment of Endometriosis-Associated Infertility

Hormonal Therapies

Studies demonstrated no beneficial evidence for the use of hormonal therapy for ovulation suppression in women with endometriosis and infertility.[63] The ESHRE guidelines suggest that in infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function, to improve fertility.[20]

Optimal Surgical Approach in Following Patient Profiles

The optimal surgical approach for various patient profiles is shown in Table 17.

Hormonal Therapies Adjunct to Surgery for Treatment of Endometriosis-Associated Infertility

The ESHRE guidelines for the use of hormonal therapies adjunct to surgery for treatment of endometriosis-associated infertility are summarized in Table 18.

Medically Assisted Reproduction in Women with Endometriosis

Selection of patient for ART is done based on the following aspects:

Women's age, medical history, health & patency of fallopian tubes, accessibility of ovaries, likelihood of conceiving in natural/stimulated cycle, cost-effectiveness of different Rx options, psychological and physical impact of procedure on couple.

Table 17: Optimal surgical approach various patient profiles[20]

Patient profile	ESHRE Guidelines	Grade of recommendation
Infertile women with AFS/ASRM stage I/II endometriosis	Clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates.	A
Infertile women with AFS/ASRM stage I/II endometriosis	Clinicians may consider CO_2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates.	C
Infertile women with AFS/ASRM stage III/IV endometriosis	Clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates.	B
Infertile women with ovarian endometrioma undergoing surgery	Clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates.	A

A: Meta-analysis or multiple randomized trials (of high quality); B: Meta-analysis or multiple randomized trials (of moderate quality), or single randomized trial, large non-randomized trial(s), or case-control/cohort studies (of high quality); C: Single randomized trial, large non-randomized trial(s), or case-control/cohort studies (of moderate quality).

Table 18: ESHRE guidelines for the use of hormonal therapies adjunct to surgery for treatment of endometriosis-associated infertility[20]

ESHRE Guidelines	Grade of recommendation
In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.	GPP
In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates.	A

A: Meta-analysis or multiple randomized trials (of high quality); GPP: Good practice point. GPP is based on expert opinion.

Studies suggest that the live birth rate is 5.6 times higher in minimal-to-mild endometriosis after controlled ovarian stimulation in comparison to expectant management. Moreover, intrauterine insemination (IUI) after controlled ovarian stimulation with gonadotropins has shown higher success outcomes when compared with IUI alone. Moreover, assisted reproductive technology (ART) is suggested to have no effect on endometriosis.[20] The ESHRE guidelines for the use of intrauterine insemination and assisted reproductive technology for the management of endometriosis-associated infertility are summarized in Table 19.

IVF-ET Outcome in Endometriosis

A retrospective analysis of IVF and oocyte donation programmes was carried out in order to gain clinical knowledge of the factors involved in the etiology of the endometriosis-associated infertility. Comparison between

Table 19: ESHRE guidelines for the use of intrauterine insemination for the management of endometriosis-associated infertility[20]

Recommendation	Grade of recommendation
In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform IUI with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates instead of IUI alone and increases pregnancy rates.	C
In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider performing IUI with controlled ovarian stimulation within 6 months after surgical treatment, since pregnancy rates are similar to those achieved in unexplained infertility.	C
ART is used in infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed.	GPP
In infertile women with endometriosis, clinicians may offer treatment with ART after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI.	C
In infertile women with endometrioma larger than 3 cm, there is no evidence that cystectomy prior to treatment with ART improves the pregnancy rate.	A
In women with endometrioma larger than 3 cm, clinicians only should consider cystectomy prior to ART to improve endometriosis-associated pain or the accessibility to follicles.	GPP

GPP: Good practice point. GPP is based on expert opinion. C: Single randomized trial, large nonrandomized trial(s), or case-control/cohort studies (of moderate quality).

the IVF outcomes from 96 cycles in 78 patients with tubal infertility and from 96 cycles in 59 women with endometriosis indicated that endometriosis patients have a poor IVF outcome in terms of reduced pregnancy rate per cycle ($p<0.0004$), reduced pregnancy rate per transfer ($p<0.002$), and reduced implantation rate ($p<0.003$).[64]

The analysis of patients undergoing oocyte donation showed that patients with this disease have the same chances of implantation and pregnancy as other recipients when the oocytes came from donors without known endometriosis. However, when the results of oocyte donation were classified according to the origin of the oocytes donated, patients who received embryos derived from endometriotic ovaries showed a significantly ($p<0.05$) reduced implantation rate as compared to the remaining groups. Taken together, all these observations suggest that infertility in endometriosis patients may be related to alterations within the oocyte, which in turn result in embryos with decreased ability to implant.[64]

Stage of Endometriosis and IVF Outcome

Factors affecting outcome of IVF – ET in endometriosis:

1. Response to COH in endometriosis:

   Ovarian endometriosis may affect follicular recruitment and patients with severe endometriosis who had undergone multiple surgical procedures involving endometrioma resection may have had damage to the normal ovarian tissue, thus resulting in diminished ovarian reserve.

   Al-Azemi *et al*. have shown that endometriotic patients are low responders, hence requiring higher gonadotropin dose and also have observed that these patients have lower peak estradiol levels.[65]

   Use of GnRH agonist is preferable to antagonist for pituitary suppression as it is more effective in overcoming steroid dependent problems associated with endometriosis, improves follicular phase periovulatory defects & follicular luteinization, prevent premature LH surge, increase number of oocytes retrieved, improve fertilization with better pregnancy outcome. In case of stage III and IV endometriosis extended pituitary downregulation with depot preparations for 3 months is beneficial.

2. Factors affecting oocyte quality and number:
   - Technical difficulties during oocyte retrieval due to ovarian adhesions, affects the no. of oocytes harvested
   - Endometriotic fluid inadvertently incorporated into oocyte-cumulus complex at OR may have a negative effect on fertilization & implantation
   - Patients who received oocytes from donors without endometriosis had same chances of conception as donor
   - Reduced pregnancy rates in endometriosis is due to functional alteration within the oocyte impairing embryo's capability to implant
3. Factors affecting Implantation
   - Poor embryo quality
   - Disorders of endometrial function
   - Reduced endometrial expression of avb3 integrin during the time of implantation
   - Very low levels of an enzyme involved in the synthesis of the endometrial ligand for L-selectin
   - HoxA-10 and HoxA-11 not up regulated during implantation window
   - Persistent expression of Matrix metalloproteinase 7 and 11 during secretory phase affects implantation.

A meta-analysis was conducted to investigate the IVF outcome for patients with endometriosis. Twenty-two published studies were included in the overall analysis. The chance of achieving pregnancy was significantly lower for endometriosis patients (odds ratio, 0.56; 95% confidence interval, 0.44–0.70) when compared with tubal factor controls. The study suggested that patients with endometriosis-associated infertility undergoing IVF respond with significantly decreased levels of all markers of reproductive process, resulting in a pregnancy rate that is almost one half that of women with other indications for IVF. These data suggest that the effect of endometriosis is not exclusively on the receptivity of the endometrium, but also on the development of the oocyte and embryo.[66]

Role of Lifestyle in Infertile Patients With Endometriosis

Endometriosis is an estrogen-dependent disease, so any lifestyles that production of E2 may reduce the risk of endometriosis. The correlation between BMI and the risk of developing endometriosis is still controversial

in literature. Moreover, regular exercise lowers estrogen levels and may benefit women with endometriosis. In addition, caffeine and alcohol both increase estrogen levels, and thus the risk of endometriosis.[8,67–69] Further, there seems to be an inverse relationship between smoking and endometriosis. Incidence of endometriosis was lower in women who started smoking at a younger age (<17 years) and smoked more than one pack a day than those who began later in life and smoked less frequently. This is because smoking has been found to lower estrogen levels.[68,69] Diet also plays a vital role in endometriosis. There is a noted positive relationship between consumption of red meat, palmate acid and endometriosis. Also, there is a negative association between endometriosis and consumption of fruits and vegetables.[8,70]

Summary

- In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may perform intrauterine insemination with controlled ovarian stimulation, instead of expectant management, as it increases live birth rates (Grade C)
- Recommended to use of ART for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed (GPP)
- IVF is appropriate treatment if tubal function is compromised, in presence of male factor infertility, and/or other treatments have failed. (Evidence B Level 2b)
- COH for IVF/ICSI is equally effective with both GnRH-a and GnRH antagonist in terms of implantation and CPR, but COH with GnRHa may be preferred because of availability of more MII oocytes and embryos (Evidence B Level 1b)
- Infertile patients with endometriosis should undergo surgical treatment as the primary option
- Those who do not become pregnant after surgery must be treated with IVF and their possibilities of pregnancy will be identical to those of patients who come to IVF for other indications
- The combination of surgery and IVF offers the best chance of pregnancy for these patients
- IVF/ICSI in patients with severe endometriosis is a safe procedure
- In patients treated with long-term pituitary down-regulation, ongoing pregnancy rates are diminished after fresh embryo transfer however, including cryopreserved embryo transfers, long-term pituitary down-regulation is beneficial in achieving an ongoing pregnancy
- There is insufficient evidence to indicate that resection of endometriomas prior to IVF improves outcomes
- IVF success rates in women with endometriosis appear to be diminished compared to women with tubal factor infertility; however, IVF likely to maximizes cycle fecundity for those with endometriosis
- Women with endometriosis have higher incidences of preterm delivery, pre-eclampsia, antepartum bleeding/placental complications, and cesarean section when compared to women without endometriosis
- In younger women (under age 35 years) with stage I/II endometriosis-associated infertility, expectant management or SO/IUI can be considered as first-line therapy
- For women 35 years of age or older, more aggressive treatment, such as SO/IUI or IVF may be considered

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Notes

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