Indian Fertility Society

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ARText

Endometriosis & ART

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Dr Pankaj Talwar
President

With great pride and honor, I write this message for the Eighth E-bulletin of IFS-ARText. ARText is our initiative to disseminate scientific and ethical (subject-related) knowledge, and to constantly update everyone with new researches and developments across the world. Through this endeavor, we aim to discuss and simplify the various complexities in clinical ART.

I am sure that you would be benefited from this academic initiative of publication wing of IFS. Indian Fertility society feels proud and congratulates the editors for this bulletin.

Dr Shweta Mittal
Secretary General

To start with, I would like to thank all the readers for appreciating and acknowledging the previous bulletins of ARTexT. Your encouragement motivates us to present more such bulletins in the field of the Assisted Reproductive Techniques. We have always believed in spreading awareness about the common issues in ART and tried to gather and present the evidence that will undoubtedly help both the clinicians and the patient.

I am sure that you would appreciate and learn from this academic initiative of IFS and will be able to apply the take home message in your busy daily clinical practice.

Editor's Message

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Endometriosis is a condition with myriad presentation and manifold implications for those who suffer from it. It is not merely a physical disease, because its principal symptoms - both pain and subfertility; have profound emotional effects and significantly lower patients' quality of life. in this article, we have tried to present all relevant information about endometriosis particularly in relation to subfertility, in a precise manner. We hope that it will be an effortless read for you all, and clear certain common dilemma faced by clinicians.

We acknowledge the contribution made by Dr.Shubhi Yadav (Senior Resident) and Dr. Srishti Priyadarshini (Post Graduate student) at ESI PGIMSR, Basaidarapur

Dr Anu Meena
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"I am grateful to Dr. Leena Mam for the opportunity to contribute to this article. I have tried my best to cover all aspects of endometriosis related infertility, and made an effort to provide answers to common questions that young clinicians have regarding this topic."

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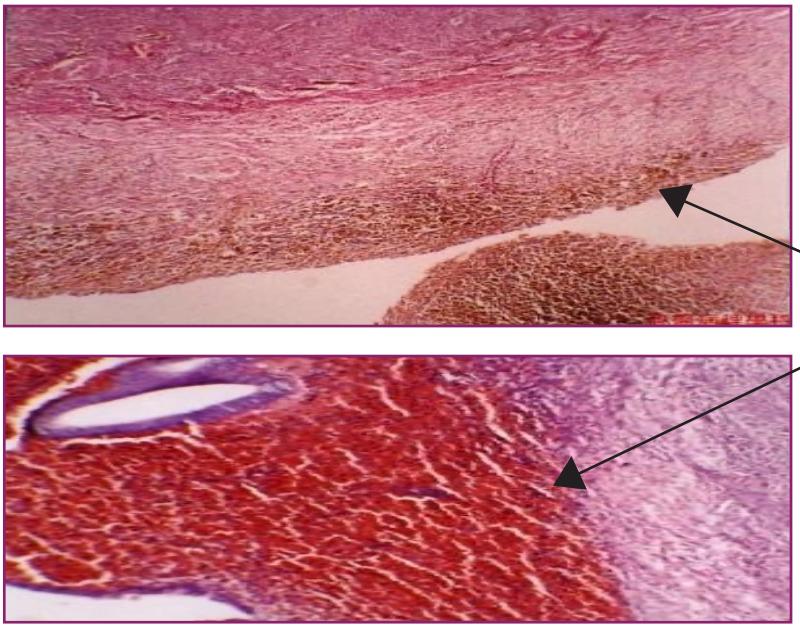
PART - 1
The Clinical Spectrum

I. Definition

Endometriosis is a benign disease and is defined by the presence of endometrial glands and stroma outside the uterus. Microscopically, the endometrial glands and stroma are seen with hemosiderin-laden macrophages.



Histopathological picture of endometriosis showing haemosiderin laden macrophages (Black Arrow)

II. Prevalence of endometriosis

The prevalence of endometriosis varies with age and clinical presentation. The prevalence of asymptomatic endometriosis is 1-7%. The overall prevalence of endometriosis in reproductive aged women is between 3-10%. Among women in reproductive age group, 12-32% women with complaint of pelvic pain have endometriosis and 9-50% women with infertility have endometriosis. (Marc A. Fritz MD, Leon Speroff MD. 2010)

III. Association of endometriosis

Fibroids	26% (Outi Uimari 2011)
Mullerian Anomalies	20% (Tasuku Harada 2016)
Ovarian Malignancy	1.3-1.9% (Tasuku Harada 2016)

IV. Pathogenesis

a. Theories for pathogenesis

There is no accepted theory regarding the origin of endometriosis. There are multiple proposed mechanism and even though no one mechanism explain all cases and each probably contributes to the pathogenesis.

The various mechanisms are:

i. Retrograde menstruation
ii. Coelomic metaplasia
iii. Direct lymphatic/ vascular invasion
iv. Stem cell differentiation
v. Spread of endometrial tissue during pelvic surgeries
vi. Retrograde menstruation: The retrograde menstruation and implantation theory holds that endometrial tissue shed during the menstruation is transported via the fallopian tubes into the peritoneal cavity.
vii. Coelomic metaplasia: According to the coelomic metaplasia theory, spontaneous metaplastic changes coelomic epithelium results in conversion of mesothelial cells into endometrial cells, which spreads in the peritoneal cavity.
viii. Vascular/lymphatic dissemination Endometrial cells disseminate into the peritoneal cavity and other places by vascular and lymphatic channels
ix. Stem cell differentiation The circulating stem cells derived from bone marrow gets differentiated into endometriotic tissue at various locations.
x. Direct transplantation of endometrial tissue This transplantation takes place at the time of caesarean section, pelvic surgeries, and episiotomy repair. These mechanism offers the most plausible explanation for endometriosis found at scar sites.

(i). Genetic Factors

The disease is frequently observed in monozygotic and dizygotic twins pairs. The risk of endometriosis is also seven times higher if a first degree relative has history of endometriosis. These findings suggest a genetic predisposition to the disease. Activation of k-RAS gene contributes to the genetic basis of endometriosis.

(ii). Immunological Factors

Endometriosis is associated with changes in both humoral and cellular immunity. The peritoneal fluid of women with endometriosis contains increased number of immune cells, but their action promotes the progression of the disease.

(a). Macrophages: They secrete growth factors and cytokines that stimulate proliferation of ectopic endometrial and inhibit the scavenger functions.

(b). Natural Killer Cells: Natural killer cells have both killer-activating and killer-inhibiting receptors. In endometriosis, there is over exppression of killer-inhibiting receptors in both peripheral and peritoneal cells. Thus, the ectopic endometrial tissue escape immune mediated destruction.

(c). Cytokines and growth factors: They promote growth and implantation of ectopic endometrium by facilitating the attachment to peritoneal surfaces and stimulating proliferation and angiogenesis. The various cytokines involved are, Interleukin-1, Interleukin-8, Monocyte chemotactic protein-1, RANTES (regulated upon activation, normal T cell expressed and secreted), Tumour necrosis factor-alpha, vascular endothelial growth factor.

(iii). Hormonal Factors

High local production of Prostaglandin E2, stimulates aromatase expression, resulting in increased local production of estradiol, which stimulates COX-2 activity, thus maintaining the stimulus for increased prostaglandin E2 production. Prostaglandins also induce inflammatory response, which increases the production of cytokines and growth factors.

V(a) Risk factors

The various risk factors associated with endometriosis is as follows:

1. Infertility
2. Early age at menarche
3. Shorter menstrual cycle
4. Heavy menstrual bleeding
5. Nulliparity
6. Mullerian anomalies
7. Diethylstilbestrol exposure
8. Dioxin exposure
9. Endometriosis in first degree relative
10. Prior medical or surgical therapy for endometriosis

V(b) Protective factors

1. Multiparity
2. Lactation
3. Increased BMI
4. Increased waist-to-hip ratio
5. Diet high in vegetable and fruit

VI Protective factors

Pelvic

a. Ovaries
b. Posterior cul-de-sac
c. Broad ligament
d. Uterosacral ligament
e. Rectosigmoid colon
f. Bladder
g. Distal ureter

Extra Pelvic

a. Umbilicus
b. Scars
c. Lungs and pleura

VII(a) Symptoms

- Endometriosis can be asymptomatic.
- Pain is the most common presenting feature. Patient can present with dysmenorrhea, dyspareunia and chronic pelvic pain, dyschezia and disturbances in menstrual cycle. Pain in endometriosis can be due to the following mechanisms:
  - Effects of focal bleeding from endometriotic implants
  - Actions of inflammatory cytokines in the peritoneal cavity
  - Irritation and infiltration of nerves in the pelvic floor

- Endometriosis also presents frequently with infertility. Almost 50% women with infertility have endometriosis.
- Extra pelvic Endometriosis-Colon and rectum is the most common site of extra pelvic disease.
  - Extra pelvic endometriosis presents as abdominal and back pain, abdominal distension, cyclic rectal bleeding, constipation and obstruction.
  - Ureteral involvement can lead to obstruction and cyclic pain, dysuria and hematuria.

- Pulmonary endometriosis manifests as pneumothorax, hemothorax or hemoptysis during menses.
- In umbilical endometriosis, umbilical mass is palpated with cyclic pain in umbilical region.

VII(b) Signs

The examination findings of endometriosis are varied. Physical examination has low sensitivity, specificity and predictive value. The following clinical signs on pelvic examination are present in endometriosis:

1. External genitalia: normal or episiotomy scar endometriosis
2. On per speculum examination: Blue coloured implants or red proliferative lesions
3. Pelvic tenderness
4. Focal thickening, nodularity and induration of uterosacral ligaments
5. Adnexal mass
6. Retro verted fixed uterus

VIII Differential diagnosis of endometriosis

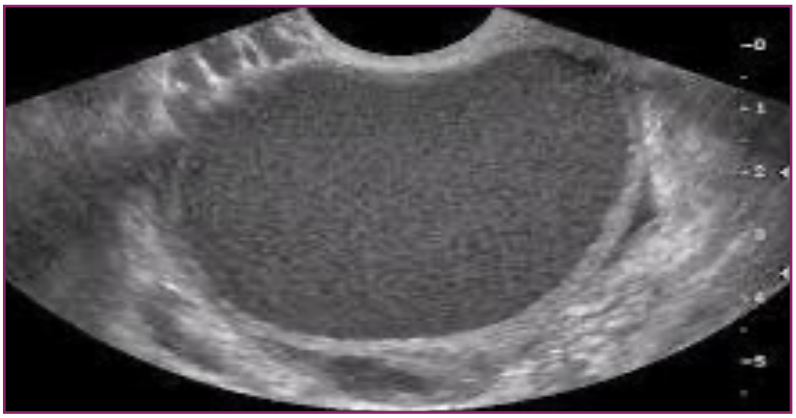
- PID/TO mass
- Endometriosis
- Ectopic pregnancy
- Ovarian cysts
- Ovarian malignancy

Diagnosis of Endometriosis

IX Ultrasonography

Peritoneal endometriosis cannot be diagnosed on imaging modalities. However, ultrasonography can be used to diagnose or rule out an ovarian endometrioma.

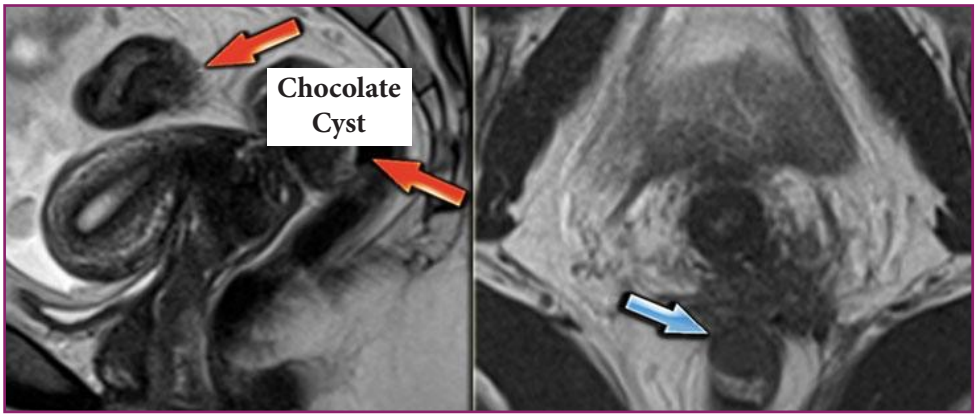
The typical ultrasonography feature of endometrioma is a cystic lesion with diffuse low-level internal echoes, described as "ground glass appearance. Multilocularity and echogenic foci in the wall are also seen in endometrioma. Sonographic imaging of endometrioma and hemorrhagic cyst overlap, hence, a follow up ultrasound can be done after 6-12 weeks.



Ultrasound image of endometrioma showing diffuse low level internal echoes- Ground glass appearance

X MRI

MRI can be helpful for detection and differentiation of ovarian endometrioma form other cystic ovarian masses. MRI detects only 30-40% peritoneal lesions observed at surgery. MRI helps to differentiate between acute hemorrhage and blood clots. The blood clots in endometrioma are homogenous and have high signal intensity on T1-weighted images and hypo intense on T2 weighted images. Acute hemorrhage has low intensity on both T1 and T2 weighted images. MRI is also helpful in assessing endometriomas for enhancing mural nodules and for restricted diffusion in those suspected of undergoing malignant transformation.



MRI showing endometrioma

CA 125

Ca 125 is a surface antigen derived from the coelomic epithelium. It is a marker for monitoring epithelial ovarian cancer. The levels of Ca125 are elevated in advanced endometriosis. But the overall sensitivity and specificity is low and thus, this cannot be used as a marker for screening of endometriosis. Serial CA125 determinations may be useful to predict the recurrence of endometriosis as the levels decrease after treatment of endometriosis.

XI Laparoscopy

Laparoscopy is no longer the diagnostic gold standard for diagnosis of endometriosis. In patients with negative imaging results or where empirical treatment was unsuccessful or inappropriate, the GDG recommends that clinicians consider offering laparoscopy for the diagnosis and treatment of suspected endometriosis.

Laparoscopic examination should include a complete inspection in a clockwise or counterclockwise direction with a blunt probe, with palpation of lesions to check for nodularity as a sign of deeply infiltrative endometriosis of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, or broad ligament.

Laparoscopic Appearance

a. Superficial Peritoneal Lesions

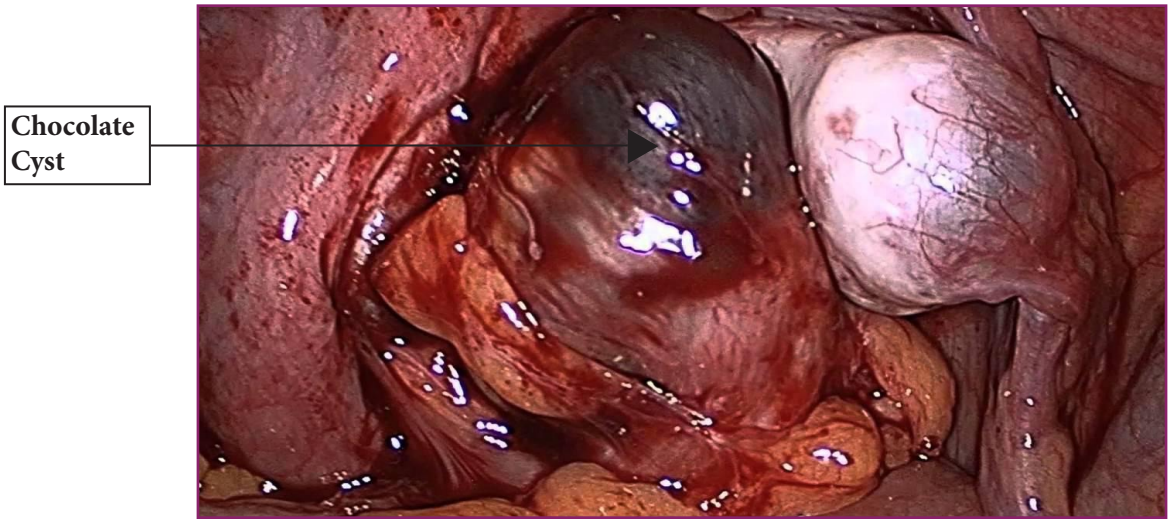
These are located on the pelvic organs or pelvic peritoneum. Classically seen as bluish or blue-brown lesions and are associated with hemosiderin deposits.

Laparoscopic appearances

- Typical powder burn or gunshot
- Dark brown puckered lesions
- Red implants
- Small cysts with old hemorrhage
- Serous or clear vesicles
- Scarring or white plaques
- Characteristic findings include typical powder-burn or gunshot lesions on the serosal surfaces of the peritoneum

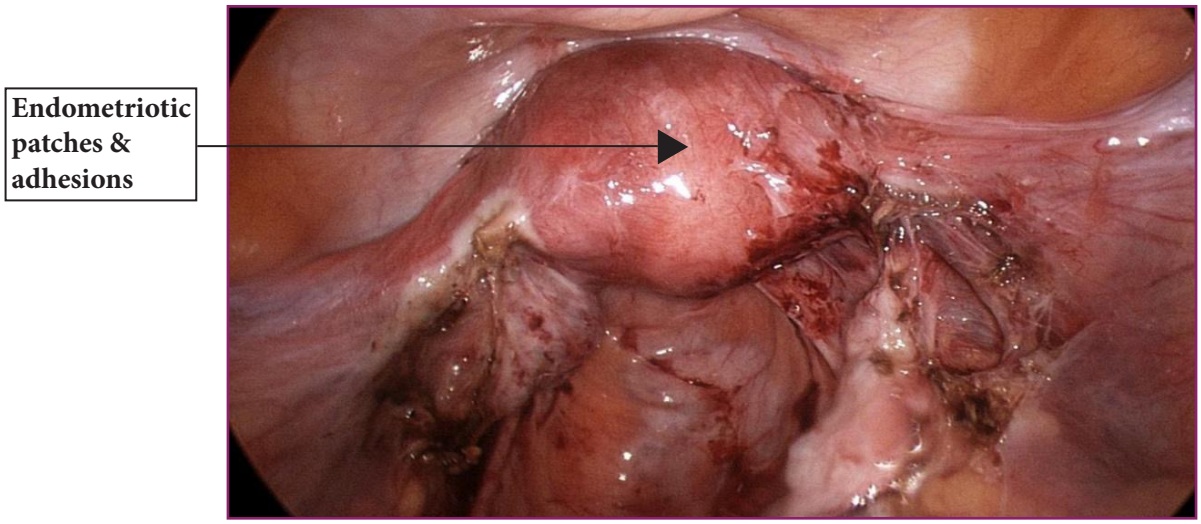
b. Endometrioma (Endometriosis cyst)

These are formed by the invagination of ovarian cortex and are characterized by fibrosis and retraction of cortex. There is presence of glandular endometrial tissue and blood clots. These are also called as "chocolate cyst".



Deep Endometriosis

Deep endometriosis is defined as endometriosis infiltrating deeper than 5mm. This may give the appearance of minimal disease, thus resulting in underestimation of severity.



XII Classification of endometriosis

a. Revised American society for reproductive medicine classification

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) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
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 CUL-DE-SAC OBLITERATION	Partial	Complete
		4	40

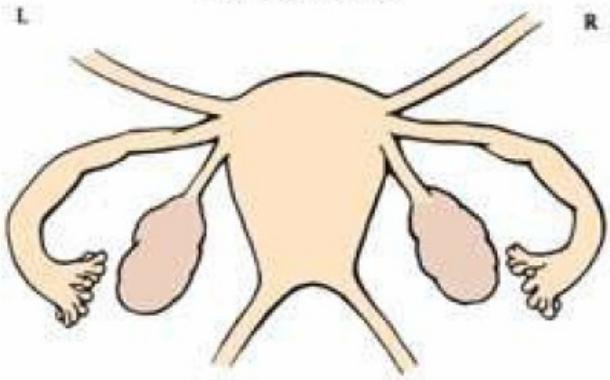
	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

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

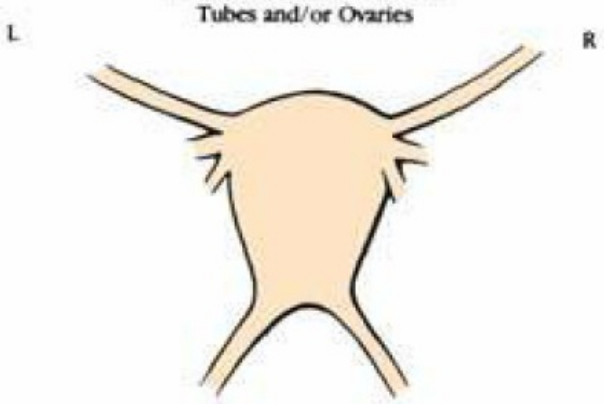
Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

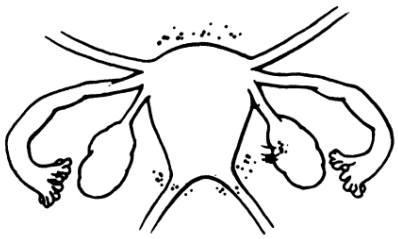


To Be Used with Abnormal Tubes and/or Ovaries



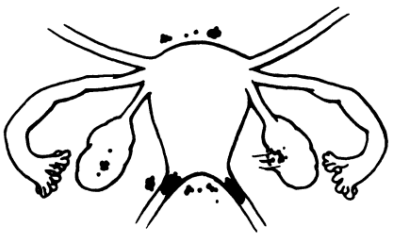
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



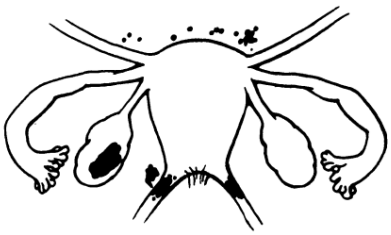
PERITONEUM		
Superficial Endo	1-3cm	- 2
R. OVARY		
Superficial Endo	< 1cm	- 1
Filmy Adhesions	< 1/3	- 1
TOTAL POINTS		4

STAGE II (MILD)



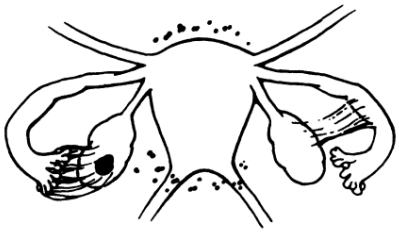
PERITONEUM		
Deep Endo	> 3cm	- 6
R. OVARY		
Superficial Endo	< 1cm	- 1
Filmy Adhesions	< 1/3	- 1
L. OVARY		
Superficial Endo	< 1cm	- 1
TOTAL POINTS		9

STAGE III (MODERATE)



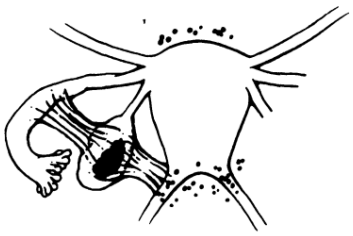
PERITONEUM		
Deep Endo	> 3cm	- 6
CULDESAC		
Partial Obliteration		- 4
L. OVARY		
Deep Endo	1-3cm	- 16
TOTAL POINTS		26

STAGE III (MODERATE)



PERITONEUM		
Superficial Endo	> 3cm	-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

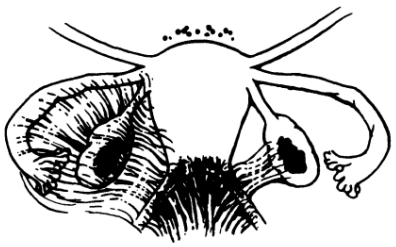
STAGE IV (SEVERE)



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

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)



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

XIII Endometriosis fertility index

The endometriosis fertility index (EFI) is used to predict fecundity after endometriosis surgery. In addition to providing a detailed score to the appendix (fallopian tubes, fimbriae of fallopian tubes, ovaries) by calculating the least-function scores, the EFI also combines conception-related factors such as age, duration of infertility, and gravidity history. The EFI score ranges from 0-10 (0-poorest prognosis, 10- best prognosis)

Descriptions of least function terms.

Structure	Dysfunction	Description
Tube	Mild	Slight injury to serosa of the fallopian tube
	Moderate	Moderate injury to serosa or muscularis of the fallopian tube; moderate limitation in mobility
	Severe	Fallopian tube fibrosis or mild/moderate salpingitis isthmica nodosa; severe limitation in mobility
	Nonfunctional	Complete tubal obstruction, extensive fibrosis or salpingitis isthmica nodosa
Fimbria	Mild	Slight injury to fimbria with minimal scarring
	Moderate	Moderate injury to fimbria, with moderate scarring, moderate loss of fimbrial architecture and minimal intrafimbrial fibrosis
	Severe	Severe injury to fimbria, with severe scarring, severe loss of fimbrial architecture and moderate intrafimbrial fibrosis
	Nonfunctional	Severe injury to fimbria, with extensive scarring, complete loss of fimbrial architecture, complete tubal occlusion or hydrosalpinx
Ovary	Mild	Normal or almost normal ovarian size; minimal or mild injury to ovarian serosa
	Moderate	Ovarian size reduced by one-third or more; moderate injury to ovarian surface
	Severe	Ovarian size reduced by two-thirds or more; severe injury to ovarian surface
	Nonfunctional	Ovary absent or completely encased in adhesions

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right
4	=	Normal	Fallopian Tube		
3	=	Mild Dysfunction			
2	=	Moderate Dysfunction	Fimbria		
1	=	Severe Dysfunction			
0	=	Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score	Left	+	Right	=	LF Score

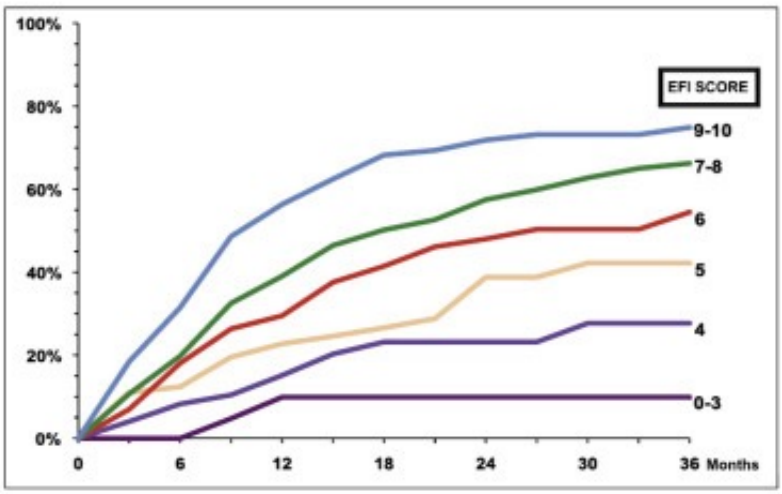
ENDOMETRIOSIS FERTILITY INDEX (EFI)

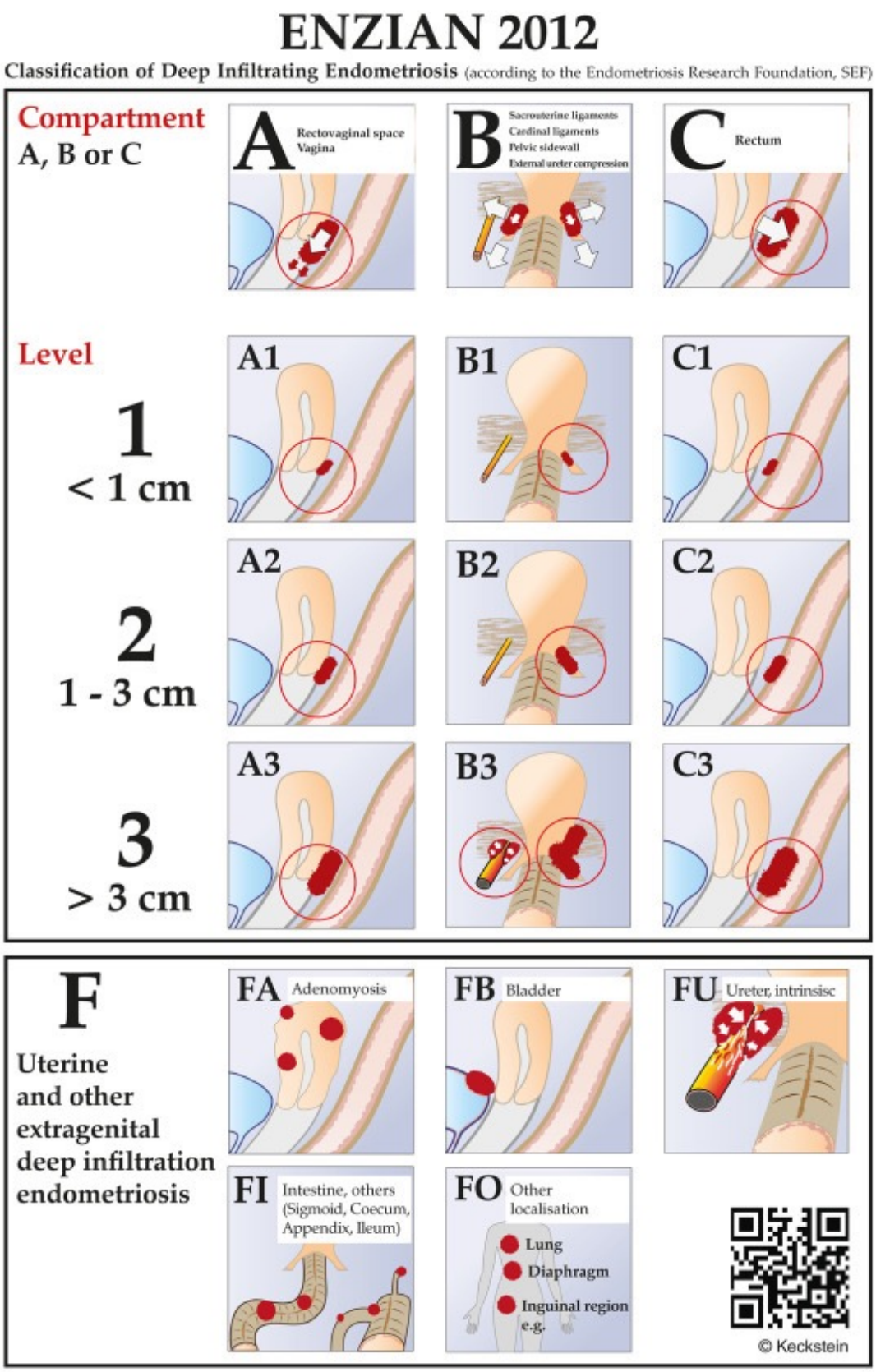
Historical Factors			Surgical Factors		
Factor	**Description**	**Points**	**Factor**	**Description**	**Points**
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			**Total Surgical Factors**		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:

Historical	+	Surgical	=	EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE





The ENZIAN staging system for women with deep endometriosis. This system was developed as a supplement to the revised American Society for Reproductive Medicine score, in order to provide detailed descriptions of the retroperitoneal structure. Adapted from 7th Conference of the Stiftung Endometriose Forschung[16] (https://www.endometriose-sef.de/aktivitaeten/klassifikation-enzian/).

Lee SY, Koo YJ, Lee DH. Classification of endometriosis. Yeungnam Univ J Med. 2021 Jan;38(1):10-18. doi: 10.12701/yujm.2020.00444. Epub 2020 Aug 7. PMID: 32764213; PMCID: PMC7787892.

XIV Endometriosis and infertility

The mechanisms of infertility associated with endometriosis remain controversial and include abnormal folliculogenesis, elevated oxidative stress, altered immune function, and hormonal milieu in the follicular and peritoneal environments, and reduced endometrial receptivity. These factors lead to poor oocyte quality, impaired fertilization, and implantation. (ASRM. Fertil Steril 2012; 98:591-8.)

a. Distorted pelvic anatomy
Disruptions impair oocyte release or pick-up, alter sperm motility, cause disordered myometrial contractions, as well as impair fertilization and embryo transport

b. Altered peritoneal function, due to
- Increased production of cytokines and eicosanoids
- Activated macrophages
- Prostaglandins
- Interleukin -1
- Ovum capture inhibitor (responsible for prevention of ovum capture by fimbrial end)
Affects sperm motility, penetration, acrosome activity, embryo implantation and tubal function.

c. Altered hormonal & cell-mediated function
- Increased macrophage number and activity
- Increased cytokine production
- Increased humoral response
- Increased B cell and immunoglobulins and complements
- Decreased cell mediated immunity
- Decreased NK cell and T cell response to ectopic endometrium

d. Endocrine and ovulatory abnormalities Endometriosis is associated with the following hormonal changes:
- Abnormal follicular growth and anovulation
- Reduced circulating estradiol levels in preovulatory phase
- Altered LH surge patterns
- Premenstrual spotting
- Luteinizing unruptured follicle syndrome
- Galactorrhoea
- Hyperprolactinemia

e. Impaired implantation: Progesterone receptors dysregulation and progesterone resistance also appear to play a role in implantation failure. progesterone induces endometrial decidualization during the luteal phase, its presence is crucial for a normal pregnancy. . Down-regulation of receptors is seen prior to implantation in normal endometrium, but is delayed in the endometrium of endometriosis.

f. Oocyte and embryo quality: Altered ovulation and oocyte production is seen in endometriosis and is associated with the increased inflammatory cells in the peritoneal fluid and endometriomas. Inflammatory effects resulting from the presence of endometriomas have been shown to affect both oocyte production and ovulation in the affected ovary (33). There is also a luteal phase disruption in endometriosis.

g. Abnormal uterotubal transport: Inflammation impairs tubal function and decreases tubal motility. Disordered myometrial contractions associated with endometriosis can also impair gamete transport and embryo implantation

h. Endometrial receptivity: Inadequate expression of various endometrial receptivity molecules occur in the endometrium of women with endometriosis Decreased expression of biomarkers of implantation, such as glycodelin A, osteopontin, lysophosphatidic acid receptor 3, and HOXA10 and integrins(cell adhesion molecule) indicate impaired endometrial receptivity in patients with endometriosis.

Progesterone resistance and dysregulation of progesterone receptors results in aberrant progesterone signaling in the endometrium and plays a significant role in impaired decidualization and establishment of ectopic endometrial implants.

It has been shown that abnormal levels of aromatase are present in both endometriotic implants as well as eutopic endometrium where it is normally absent, resulting in increased estradiol production.; increased estrogen production in the endometrium may also affect endometrial development and receptivity.

XV Adenomyosis and infertility

Adenomyosis is a benign uterine disorder characterized by the presence of heterotopic endometrial glands and stroma in the myometrium and reactive fibrosis of the surrounding smooth muscles cells of the myometrium.

Mechanism of infertility in Adenomyosis

- Intrauterine Abnormalities- Anatomical distortion of the uterine cavity may be one important factor leading to infertility. Adenomyoma that distorts the uterine cavity may obstruct the tubal ostia and interfere with sperm migration and embryo transport.
- Disturbed Uterine Peristalsis and Sperm Transport- Directed sperm transport toward the peritoneal opening of the tubes on the side of dominant follicle by uterine peristalsis is fundamental to the early reproductive process, and it depends on the architecture of the myometrial wall. Adenomyosis gives rise to the development of hyperplastic muscular tissue that causes dysfunctional uterine hyperperistalsis, thus leads to impaired fertility.
- Impaired Implantation- In adenomyosis, there is decreased levels of cell adhesion molecules (integrin, selectin, and cadherin) which are essential for the embryo and endometrium interaction. Thus, this leads to impaired implantation which causes reduced fertility.

XVI Recurrent endometriosis

Risk factors are

- Younger age at the time of surgery (<25 years)
- Bilaterality
- Size of endometriotic lesion
- Revised AFS score > 24
- Pre-operative cyst rupture
- Type and extent of surgery [Laparoscopy less risk Vs Laparotomy (Sawa Ta et al (Laparoscopy versus laparotomy management)

XVII Endometriosis and cancer

- Some cancers (ovarian cancer,specially endometroid and clear cell CA and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.
- lower risk of cervical cancer
- Endometriosis is not associated with an altered risk of uterine cancer (Munksgaard and Blaakaer, 2011)
- The relationship between endometriosis and breast cancer is uncertain

PART - 2
Frequently Asked Questions: Art

XVIII Effect of endometriosis on IVF

Women with endometriosis often require in vitro fertilization. The outcome of IVF varies with the stages of endometriosis.

Meta-analysis done by **Harb et al 2013,** included 27 observational studies,8984 women, comparing the IVF outcomes in women with and without endometriosis undergoing IVF. ART results were dependent on the severity of the disease. The presence of severe endometriosis was associated with reduced implantation and clinical pregnancy rates, although the reduction in live birth rate was not statistically significant. Women with mild endometriosis showed comparable results in terms of implantation, clinical pregnancy and live birth rates.

Ashrafi et al observed a significantly poorer ovarian response to stimulation and lower number of metaphase-II oocytes retrieved among women with endometriomas as compared with a control group. Nevertheless, the quality of the embryos obtained and clinical pregnancy rates were comparable.Reproductive outcomes among women undergoing IVF and diagnosed with endometriosis-associated infertility do not differ significantly from women without the disease. Although women with endometriosis generate fewer oocytes, fertilization rate is not impaired and the likelihood of achieving a live birth is also not affected.

(Mireia González-Comadran 2017,Ashrafi M et al 2014,Harb HM, 2013)
Endometrioma surgery has a deleterious effect on short, medium, and long-term post-operative AMH levels. Bilateral endometriomas and endometriomas greater than 7 cm have been associated with greater decreases in AMH. (Moreno 2022)

Review by (Edgardo Somigliana 2023) suggests that endometriosis does not affect IVF outcomes. Deciding different regimens of treatment or different laboratory protocols solely based on the diagnosis of endometriosis is not justified. On the other hand, it must be reminded and emphasized that the present review investigated possible sources of impairment beyond the damage to the ovarian reserve. In fact, the main relevant challenge in infertile women with endometriosis undergoing IVF is the prevention of surgically induced ovarian damage.

XIX Effect of IVF on endometriosis?

Four studies evaluated the recurrence rate of disease in women with endometriosis submitted to MAR treatments. Although using different criteria of recurrence and different follow-up periods, all reached the conclusion that gonadotrophin ovarian stimulation for IVF/ICSI was not associated with increased risk of recurrence of the disease(Benaglia, et al., 2011, Benaglia, et al., 2010, Coccia, et al., 2010, D'Hooghe, et al., 2006).

XX Should cystectomy be done prior to IVF to improve the reproductive outcome?

- In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates.
- Clinicians to consider cystectomy prior to IVF only to improve endometriosis-associated pain or the accessibility of follicles.
- Clinicians should counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary.

Previous ovarian surgery results in longer stimulation, higher FSH requirement, decreased oocyte number but no difference in fertilization, pregnancy outcome in subsequent ART cycles. (ESHRE 2022)

4. Management of Endometriosis

XXI. Medical
XXII. surgical
XXIII. ART(IUI/IVF/ICSI)

a. Approach to a patient

A detailed infertility workup should be done in a patient with endometriosis and any other cause related to infertility other than endometriosis should be ascertained, as despite enormous amount of information there is still uncertainty regarding etiologies and treatment. Management is still challenging in patients of endometriosis with sufertility. Treatment depends on

- Age of the patient
- Extent of the disease
- Stage of endometriosis
- Duration of infertility
- Previous therapy
- Priority of the patient and cost of treatment should also be taken under consideration.

Treatment modalities and preferences vary in patients based on classification, patients with mild endometriosis on one end can be treated like those with unexplained infertility and those with severe disease require IVF.

XXI Medical management

Are hormonal therapies effective for infertility associated with endometriosis?

Medical management improves the quality of life for patients with endometriosis. Therapies for endometriosis cause hormonal suppression and most of them have contraceptive effects. **According to Cochrane review subfertile women should not prescribed hormonal ovarian suppression to improve fertility as first line treatment in patients of endometriosis** who wish to conceive **(Hughes, et al., 2007).**

i. Pre operative medical management- Not recommended
- Changes appearance of endometriosis
- Delay of diagnosis
- Cost and side effects
- Delay attempting pregnancy
- No difference for pain relief or infertility

ii. Post –op medical management? -No evidence of benefit
- Leads to ovulation suppression:
- It works well for pain but does not appear to improve fertility
- As ovulation and periods are stopped, fertility may be reduced

(Cochrane database of systematic reviews) 2008, Eshre 2013 Grade A

Current place of Dienogest in treatment of endometriosis

Dienogest is a fourth-generation progestin of 19-nortestosterone derivative. It is well tolerated with no androgenic, glucocorticoid or mineralocorticoid activity. binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule.

Dienogest is associated with relatively moderate inhibition of gonadotropin secretion, leading to a reduction in the endogenous production of estradiol. When given continuously, dienogest induces a hypoestrogenic, local endocrine environment, causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions.It also inhibits aromatase and COX-2 expression as well as prostaglandin E2 production in endometriotic stromal cells. It also normalizes the activity of natural killer cells and decreases the release of interleukin-1b by macrophages.dienogest increases progesterone receptor expression and decreases proinflammatory cytokines. Patel BG et al (2017)

Dienogest at 2 mg once daily is used as the optimal dose in the treatment of endometriosis for a duration of 12-24 week.
Pretreatment with DNG for women with endometriosis who underwent IVF could not improve the number of mature oocytes, the rate of clinical pregnancies, or the rate of live births.(Xueying Li et al. 2023)

Study by Barra F (2020) suggest that in patients with endometriosis, IVF outcomes can be improved by pretreatment with DNG. In particular, the use of DNG allows for better oocyte retrieval and blastocysts in patients with large endometriomas.

Study by Maiorana A(2024)Long-term therapy with Dienogest (2mg once daily for 108 months) has proven effective in controlling the symptoms of the disease and reducing the size of endometriomas, with an increase in the positive effects related to the duration of the intake and in the absence of serious adverse events.

XXII Is surgery effective for infertility associated with endometriosis?

- Surgical management is warranted for women with symptoms of dysmenorrhea, dyschezia and chronic pelvic pain or to improve accessibility of follicles. GPP
- Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit andsurgery is likely to have a negative impact on ovarian reserve. Strong recommendation. (ESHRE 2022)
- 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.CO2 laser vaporization of endometriosis can be considered, instead of monopolar electrocoagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates .Now a days bipolar electrocoagulation is considered safe over monopolar energy source, as there are less likelihood of complications with the same. (ESHRE 2022)
- Conservative surgical management could be through laparotomy or laparoscopic approach. With development of fine surgical skills laparoscopy is now considered as gold standard in the surgical management of endometriosis. Laparoscopic approach to management of endometrioma is preferred over laparotomy, as laparoscopy offers benefits of magnification and illumination, shorter hospital stay, faster postoperative recovery, less analgesic requirement, less morbidity. Endoscopic procedures include ablation of endometrial implants, adhesiolysis, ovarian cystectomy and oophorectomy.

a. How to manage an ovarian endometrioma

The most common procedure for treatment of ovarian endometrioma and/or "chocolate cysts" is either excision of the cyst capsule or drainage and electrocoagulation of cyst wall."

Small ovarian endometrioma of (<3cm diameter) can be treated by drainage and electrocoagulation i.e. it is aspirated and irrigated and inspected with ovarian cystoscopy for intracystic lesion and the mucosal lining of the cyst wall is destroyed by vaporization

Large ovarian cysts greater than 3 cm in diameter can be aspirated and excision and removal of cyst wall done. Cystectomy of endometriomas involves the opening of the cyst (using scissors or electrosurgical or laser energy). After identifying the plane of cleavage between the cyst wall and ovarian tissue, the cyst wall is then excised or "stripped away" by applying opposite bimanual traction and counter action with two grasping forceps. The ovarian edges could be sutured or inverted by light application of bipolar coagulation or kept as they are.

Excision of the endometrioma capsule (>3cm), is recommended instead of drainage and electrocoagulation of the endometrioma wall, to increase clinical pregnancy rates **(Hart, et al., 2008) Grade A, ESHRE 2022**

Counsel women with endometrioma regarding the reduction of ovarian reserve following surgery.

Malignancy should be ruled out, as it is associated with endometrioma in 0.8% of cases

b. What intraoperative steps should be taken to prevent complications?

- Preservation of the vascular blood supply to the ovary is important, as proper blood supply is vital for the preservation of ovarian volume and antral follicular counts. So it is postulated that when approaching the hilus, where the ovarian tissue is more functional and the plane of cleavage is less visible, partial cystectomy is performed and the remaining tissue is electro coagulated or CO2 Laser is used for vaporization
- Strict adherence to the principles of microsurgery
- To remove all visible endometriotic disease.

- Plane of dissection should be identified clearly between cyst wall and normal ovarian tissue to avoid inadvertent injury to normal ovarian tissue, for this hydro dissection or dilute vasopressin injection can be used beneath the capsule
- During adhesiolysis and release of ovaries from ovarian fossa ureters should be identified clearly.
- Avoid spillage of endometriotic contents as this may increase the risk of recurrence o the disease and adhesion formation

c. Is there any role of adhesion prevention agents during surgery

Use of oxidized regenerated cellulose during operative laparoscopy for endometriosis, is promoted as it prevents adhesion formation (Ahmad, et al., 2008). Anti-adhesion agents like polytetrafluoroethylene surgical membrane, hyaluronic acid products, have been effective for adhesion prevention in pelvic surgeries, although their specificity is yet to be proven in women with endometriosis. (ESHRE 2014)

XXIII Assisted Reproductive Technology (ART) in Endometriosis

Is MAR (Medically Assisted Reproduction) effective for infertility associated with endometriosis

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 (Eshre 2013 Grade C)

Ovulation Induction and intrauterine insemination (IUI)

IUI with or without controlled ovarian hyper stimulation (COH) is cost effective, first line treatment for many infertility problems mainly for ovulatory infertility others include unexplained, male factor, cervical infertility and endometriosis and is associated with a higher pregnancy rate than expectant management.

In stage I and II endometriosis, treatment with super ovulation and IUI improve fertility compared to expectant management as it increases live birth rate (Tummon et al., 1997). Age, duration of infertility, ovarian reserve and male factor should also be taken under consideration. [Evidence level A] Patients should be advised to begin attempting to conceive soon after laparoscopic surgery. In a RCT, the live birth rate was found to be 5.6 times higher in couples with minimal to mild endometriosis after controlled ovarian stimulation with gonadotrophins and IUI compared with couples after expectant management (Tummon et al., 1997). Clomiphene Citrate(CC) and IUI is an effective treatment option resulting in a higher clinical pregnancy rate compared to Natural Contact and timed intercourse. Treatment with gonadotrophins and IUI results in a higher clinical pregnancy rate compared to CC and IUI.

Endometriosis and infertility have has decreased per cycle conception rate compared with male factor and unexplained infertility. (Huges et al 1997) Also repetitive superovulation with IUI (3-4 cycles) may have a plateau effect over time, so timely decision for IVF to be considered.
(Tummon et al., 1997,Nulsen et al., 1993,Huges et al 1997)

Although the value of IUI in infertile women with rASRM stage III/IV endometriosis with tubal patency is uncertain, the use of IUI with ovarian stimulation could be considered. Weak recommendation ESHRE 2022

Emerging role of Aromatase inhibitors in women with endometriosis-associated with infertility undergoing ART

The orally active third-generation AIs letrozole and anastrozole have gained attention as a cotreatment for endometriosis associated infertility. High levels of aromatase P450 enzyme expression has been shown in eutopic endometrial tissue as well as in ectopic endometrial implants in endometriotic patients. This abnormal aromatase expression results in local estrogen (E2) production by endometriotic implants, produced estrogen leads to inflammation, proliferation and survival of endometriotic implants. AIs suppress the locally produced E2 by endometriotic deposits thus correcting abnormal endocrine and reproductive function of patients with endometriosis.

Third generation aromatase inhibitors produce a thicker endometrium, no downstream effect on cervical mucus, comparable pregnancy rate but fewer follicles in comparison to clomiphene citrate. The co-treatment of letrozole with gonadotropins during the antagonist protocol was associated with a reduction in the total dose of gonadotropins, although it had no effect on the oocyte or embryo yield and pregnancy rates in patients with endometriosis. (Ebrahimi M 2022)

Abu Hashim et al 2016. in a RCT compared pregnancy rates following superovulation between letrozole and CC in stage I-II endometriosis. No significant differences were found between both groups for clinical pregnancy rate per cycle, cumulative pregnancy rate, miscarriage, or live birth rates.

Miller et al 2012 did a retrospective cohort study with endometriosis undergoing IVF and found Letrozole co-treatment might improve the IVF success rates by improving endometrial receptivity.

In women with endometriosis-associated pain refractory to other medical or surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain. Aromatase inhibitors may be prescribed in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonists. (ESHRE 2022)

When do you move these patients to IVF?

- Primarily IVF would be suggested if during laparoscopy severe endometriosis is found compromising tubal function
- Secondly after cystectomy if no conception even after superovulation and IUI for 3-4 cycles
- Early referral for IVF in case of reduced ovarian reserve, Tubal factor and Male factor

What stimulation protocol will you choose for IVF?
Ultra-Long Protocol:

As per ESHRE 2022 guidelines the extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis is not recommended, as the benefit is uncertain. (Strong Recommendation)

With the use of GnRH agonist and transvaginal oocyte retrieval there is increased success in use of IVF for endometriosis associated infertility. COS using GnRh agonists or antagonists is effective in IVF patients with mild to moderate endometriosis and in those with endometrioma who did not undergo surgery [Evidence level A].

GnRH agonist protocol: Women with all stages of endometriosis who underwent luteal phase GnRH agonist down-regulation followed by IVF/ICSI treatment had a similar pregnancy and live birth rate and lower miscarriage rate compared with women with tubal factor infertility. GnRH-agonist prevent deleterious effects of premature endogenous LH surge but also suppress a number of inflammatory cytokines (modulate NK cells of the uterus and also reduce uterine aromatase production. the long down-regulation pretreatment with GnRHa suppression with hormonal therapy add back 3 months (and up to 6 months) before IVF or ICSI will increase the clinical pregnancy rates **(Cochrane review 2014)**

GnRH antagonist protocol: They are good choice for poor responders, patients with poor ovarian reserve due to ovarian endometrioma or after its surgical excision in IVF cycles as they cause immediate suppression of LH surge.

A randomized prospective trial compared GnRH agonist with antagonist protocol in women with minimal to mild endometriosis and the results of antagonist were not inferior to GnRH agonist protocol who did not undergo previous surgery **(Pabuccu et al., 2007).** Similar implantation and clinical pregnancy rates were seen in both the groups but higher number of embryos were available for cryopreservation in those patients treated with GnRH agonist .

OCP'S: The use of OC before IVF-ET given for a period of 6–8 weeks in patients with endometriosis compared to the control group **De Ziegler et al..**

Need for Oocyte Donor
There is adverse effect of both superficial endometriosis and ovarian endometriomas on ovulation rates, markers of ovarian reserve, and response to ovarian stimulation. Surgical treatment of endometriomas may further worsen ovarian responsiveness by inadvertently removing healthy ovarian tissue or compromising vascular supply to the ovary. If ovarian reserves are poor, the couple has to be counseled regarding need for with oocyte donor.

IVF OR ICSI, which is better?
IVF/ICSI can be considered as an effective approach for managing endometriosis associated infertility although there is no exact consensus concerning the impact of endometriosis on the IVF/ICSI outcomes. Higher fertilization rate and mean number of embryos and lower rates of total fertilization failure and triploid fertilization are seen in patients treated with ICSI in comparison to conventional IVF in cases with endometriosis.

Assisted Hatching
Assisted Hatching is a technique performed after in vitro fertilization and involves the artificial thinning or opening of the zona pellucida by the embryologist prior to ET to improve the embryo implantation rate.

Nadir Ciray et al (2005), conducted a prospective randomized control study in women with endometriosis who had Laser Assisted Hatching(LAH)performed for their embryos to women with endometriosis who did not have LAH. They did not find any significant difference between the two groups regarding pregnancy rate and implantation rate. **K Kavoussi et al 2014**

Role of Frozen Embryo Transfer (FET)
Frozen-thawed embryo transfer (FET) not only achieves higher pregnancy rates but, most importantly, also generates lower maternal and infant morbidity and mortality than fresh embryo transfer does **[Evans J, Hannan NJ, Edgell TA, et al. Fresh versus frozen embryo transfer. 2014; 20:808–21. [PubMed]**

In retrospective study Mohamed AM et al found that women with endometriosis undergoing IVF, the preparation of the endometrium for frozen ET with GnRH agonists compared to fresh cycles is associated with higher LBR (16.9% versus 11.9%) and a significantly higher CPR (18.2% versus 12.7%, P=0.048). These results suggest that, in cases of endometriosis, the combined effect of GnRHa on the endometrium and the low level of ovarian steroids may simultaneously offer a better endometrial environment for implantation which may lead to better outcomes. (Mohamed AM et al 2011)

Precautions during ovum pickup with endometrioma
In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval to reduce the risk of ovarian abscess. [Evidence level C].

Vaginal preparation with better bactericidal substances as well as stronger antibiotic prophylaxis might be useful in the prevention of PID. The use of povidone-iodine followed by saline solution is more effective procedure than saline douching alone to prevent OPU-pelvic infection, without spoiling the oocyte quality. (Funabiki M, Taguchi S, Hayashi T, Tada Y, Kitaya K, Iwaki Y, Karita M, Nakamura Y.s.)

Other preventive measures during ovum pickup are the use of strict asepsis in the surgical field, avoiding successive punctures of the vaginal wall and ovarian capsule and avoiding puncture and aspiration of the endometrioma. A retrospective study of Benaglia et al (2014) found reduced pregnancy rates outcome in women with accidental contamination of follicular fluid with endometrioma content.

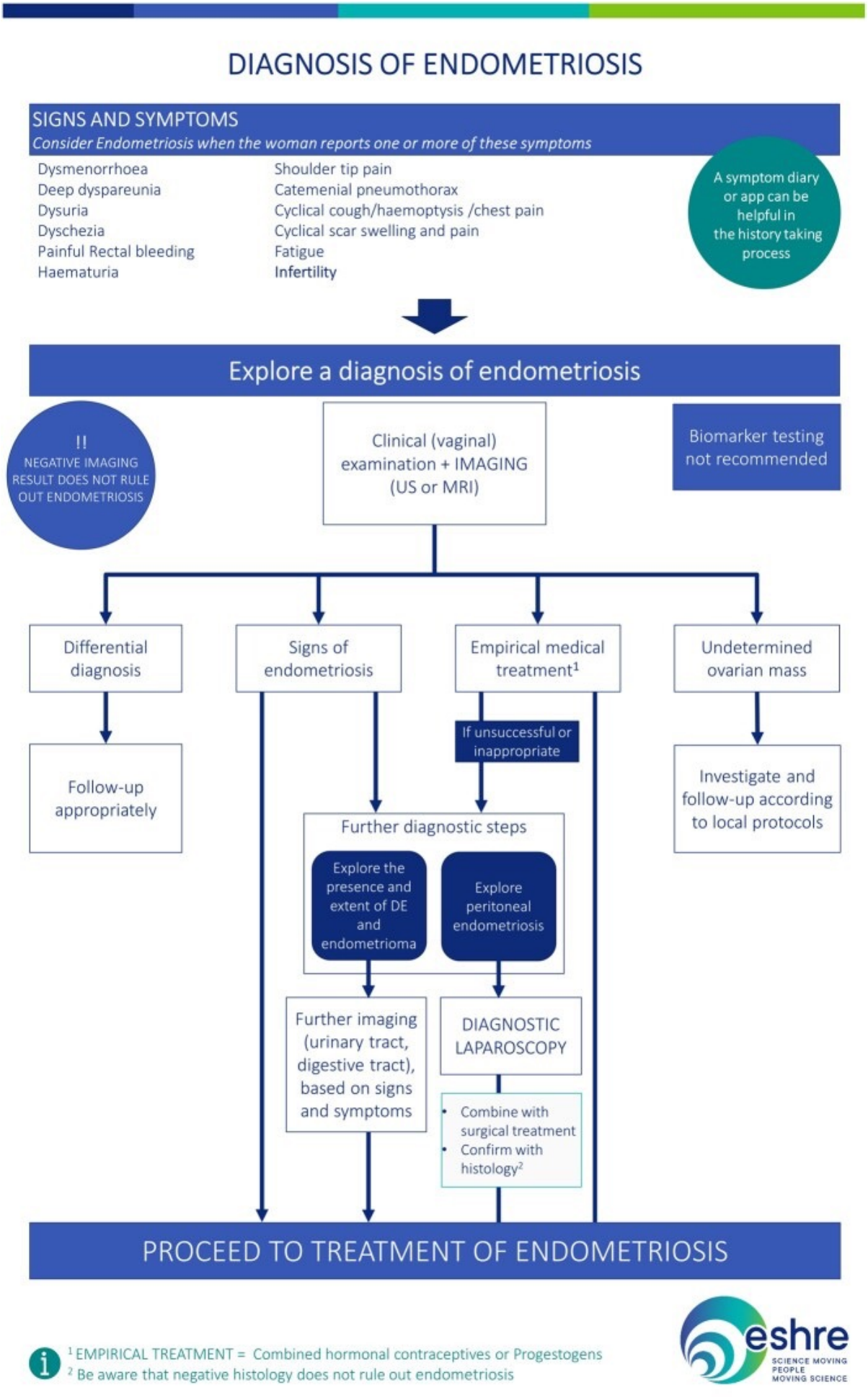
What is the role of USG guided aspiration ?
No Role
Side effects:
Leakage-pelvic adhesions
Ovarian abscess
Oopherectomy

Treatment of adenomyosis in infertility
Treatment of adenomyosis with hypoestrogenic agents or surgical removal of the adenoma lesions may restore normal immunity in patients. Currently, the accepted treatment of adenomyosis in infertile patients is with Gn-RH agonists followed by IVF. This is due to the transient suppression of the hypothalamic-pituitary-ovarian axis by Gn-RH agonists with resultant shrinkage of the lesions in the uterus thereby reducing its size and relief of symptoms. It promotes uterine and endometrial receptivity. A combined hormonal and surgical approach can also be used to improve fertility in women with adenomyosis with subfertility. Surrogacy may be required in those cases where pelvic anatomy is completely distorted.

Adenomyosis negatively impacts reproductive outcomes in patients undergoing ART. This association appears to be less significant after patients follow a long GnRH-a protocol, which improves implantation rates. GnRH-a pre-treatment can also prove beneficial prior to engaging in natural conception attempts.

The role of conservative surgeries in infertile women with adenomyosis is controversial at present, as only small serial studies have shown improved reproductive outcomes.

For patients with adenomyosis undergoing in vitro fertilization, gonadotropin-releasing hormone agonist downregulation for a period of 2 to 4 months may be considered before transferring fresh or frozen embryos (SOGC 2023)


DIAGNOSIS OF ENDOMETRIOSIS
SIGNS AND SYMPTOMS
Consider Endometriosis when the woman reports one or more of these symptoms
Dysmenorrhoea
Deep dyspareunia
Dysuria
Dyschezia
Painful Rectal bleeding
Haematuria
Shoulder tip pain
Catemenial pneumothorax
Cyclical cough/haemoptysis /chest pain
Cyclical scar swelling and pain
Fatigue
Infertility
A symptom diary or app can be helpful in the history taking process
Explore a diagnosis of endometriosis
!! NEGATIVE IMAGING RESULT DOES NOT RULE OUT ENDOMETRIOSIS
Clinical (vaginal) examination + IMAGING (US or MRI)
Biomarker testing not recommended
Differential diagnosis
Signs of endometriosis
Empirical medical treatment1
Undetermined ovarian mass
Follow-up appropriately
If unsuccessful or inappropriate
Investigate and follow-up according to local protocols
Further diagnostic steps
Explore the presence and extent of DE and endometrioma
Explore peritoneal endometriosis
Further imaging (urinary tract, digestive tract), based on signs and symptoms
DIAGNOSTIC LAPAROSCOPY
Combine with surgical treatment
Confirm with histology2
PROCEED TO TREATMENT OF ENDOMETRIOSIS
1 EMPIRICAL TREATMENT = Combined hormonal contraceptives or Progestogens
2 Be aware that negative histology does not rule out endometriosis
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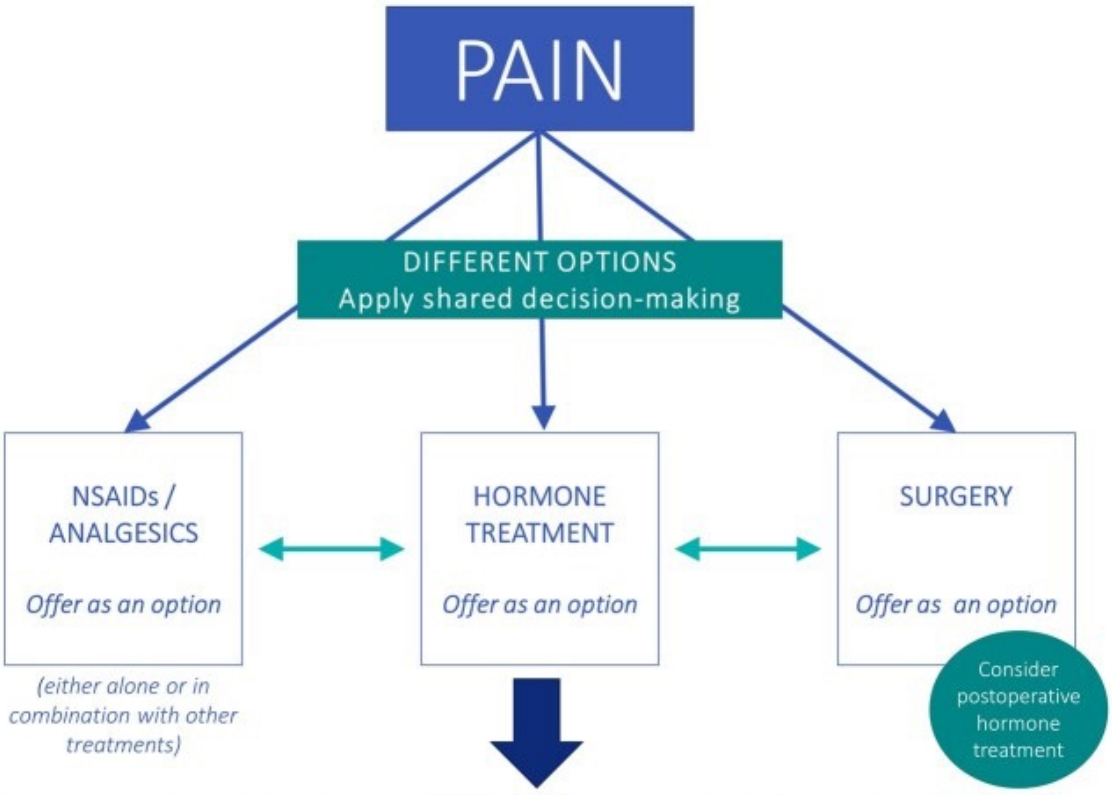
TREATMENTS FOR ENDOMETRIOSIS



Options hormone treatment	Considerations
Combined hormonal contraceptives	• Oral, vaginal ring, or transdermal • Continuous use can be considered
Progestogens	• Oral medication (e.g., progesterone-only pill), levonorgestrel-releasing intrauterine system or etonogestrel-releasing subdermal implant • Side effect profiles need to be considered
GnRH agonists	• As second-line treatment, based on side-effect profile • Consider combined hormone add-back therapy to prevent bone loss and hypoestrogenic symptoms
GnRH antagonists	• As second-line treatment • Evidence is limited regarding dosage or duration of treatment, and the need for add-back therapy • Considerable side effects, including potential impact on bone density
Aromatase inhibitors	• As second/third line treatment • For pain, refractory to other medical or surgical treatment • Must be combined with any of the above in reproductive-age women

NON-PHARMACOLOGICAL TREATMENTS FOR PAIN?

Discuss non-medical strategies to address quality of life and well-being.
No recommendation can be made for a specific intervention

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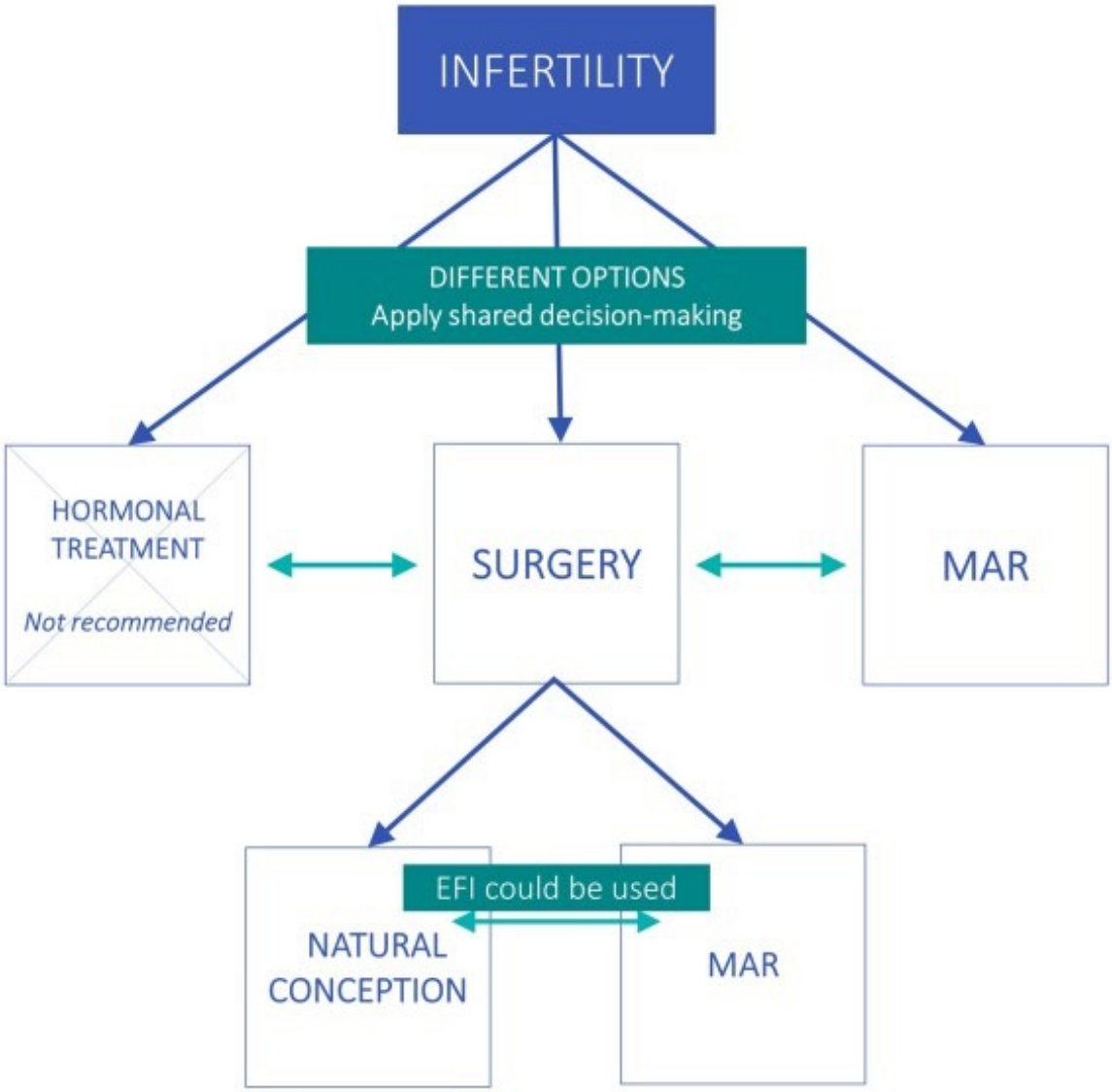
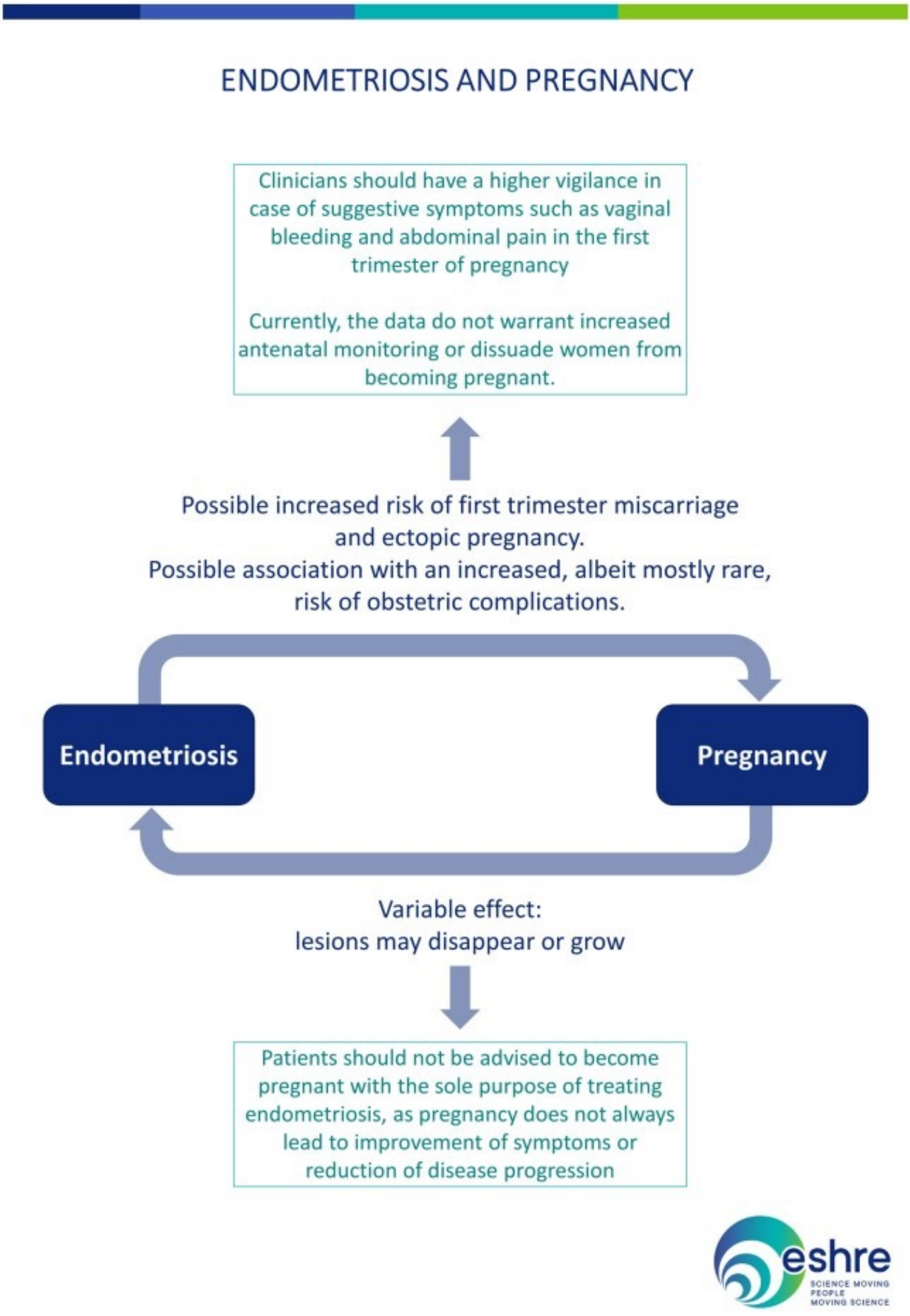

TREATMENTS FOR ENDOMETRIOSIS
INFERTILITY
DIFFERENT OPTIONS
Apply shared decision-making
HORMONAL TREATMENT
Not recommended
SURGERY
MAR
EFI could be used
NATURAL CONCEPTION
MAR


ENDOMETRIOSIS AND PREGNANCY
Clinicians should have a higher vigilance in case of suggestive symptoms such as vaginal bleeding and abdominal pain in the first trimester of pregnancy
Currently, the data do not warrant increased antenatal monitoring or dissuade women from becoming pregnant.
Possible increased risk of first trimester miscarriage and ectopic pregnancy.
Possible association with an increased, albeit mostly rare, risk of obstetric complications.
Endometriosis
Pregnancy
Variable effect:
lesions may disappear or grow
Patients should not be advised to become pregnant with the sole purpose of treating endometriosis, as pregnancy does not always lead to improvement of symptoms or reduction of disease progression
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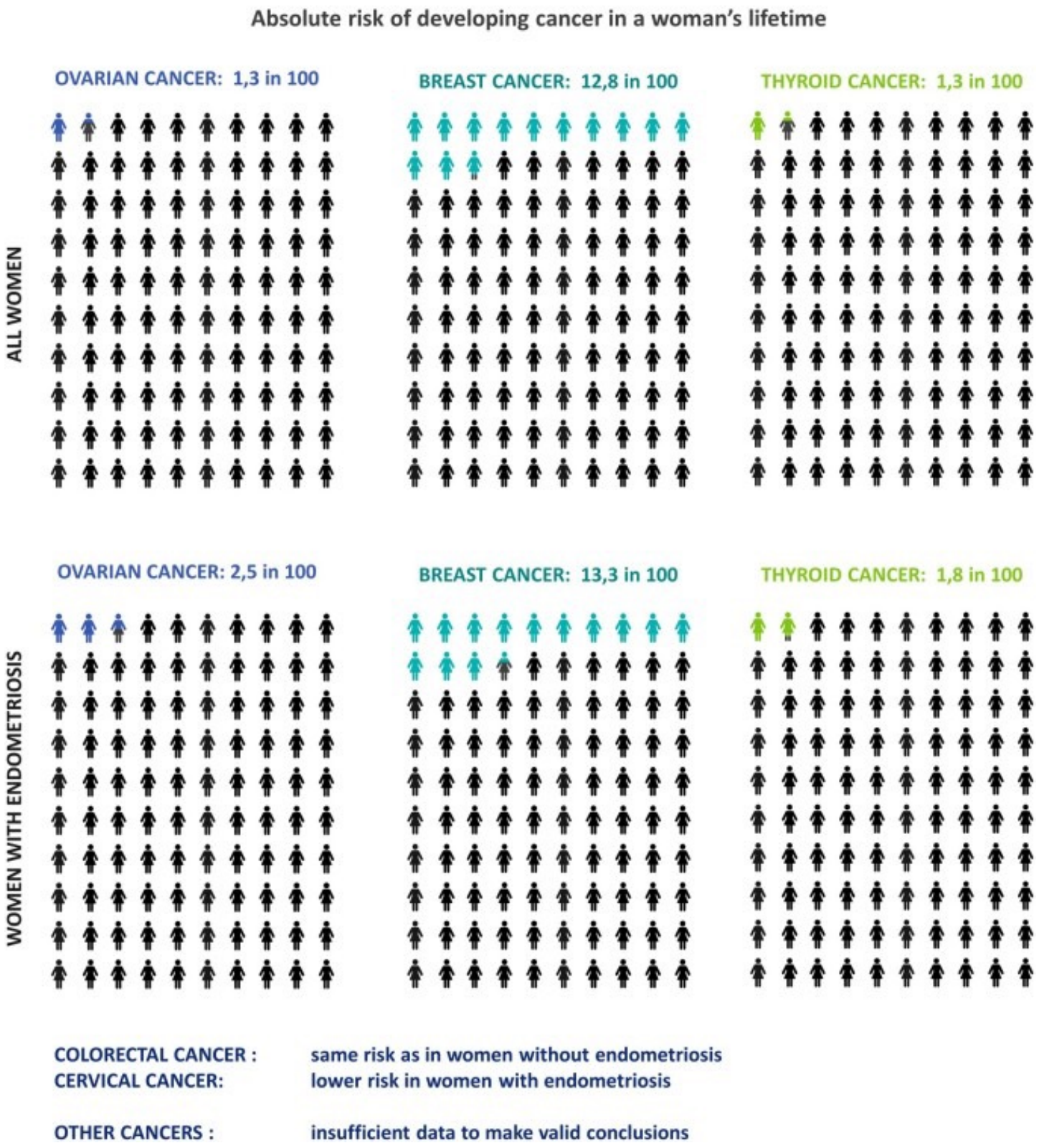
ENDOMETRIOSIS AND CANCER



Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group. ESHRE guideline: endometriosis. Hum Reprod Open. 2022 Feb 26;2022(2):hoac009. doi: 10.1093/hropen/hoac009. PMID: 35350465; PMCID: PMC8951218.

5. Conclusion

- Laparoscopy is no longer the diagnostic gold standard, and it is now only recommended in patients with negative imaging results and/or where empirical treatment was unsuccessful or inappropriate.
- The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis (ultralong protocol) is no longer recommended due to unclear benefits. (ESHRE 2022)
- The Endometriosis Fertility Index (EFI) was added as a step in the treatment as it can support decision-making for the most appropriate option to achieve pregnancy after surgery.
- Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.
- Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit and surgery is likely to have a negative impact on ovarian reserve. Strong recommendation. (ESHRE 2022)
- 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 (ESHRE 2013 Grade C). Although the value of IUI in infertile women with rASRM stage III/IV endometriosis with tubal patency is uncertain, the use of IUI with ovarian stimulation could be considered. Weak recommendation (ESHRE 2022)
- Moderate –severe endometriosis with prior one or more infertility operations, IVF-ET is better therapeutic option than another infertility operation

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