

ARText: 2



Second Issue

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“Endometriosis” and infertility



Editor :
Prof (Dr) Pankaj Talwar

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ARText

“Endometriosis” & infertility



President-IFS
Dr Sohani Verma

It gives me immense pleasure to write few words for E-bulletin of IFS-ARTexT to highlight the importance of “Endometriosis” and infertility. Endometriosis is a chronic inflammatory disease, characterized by implantation and growth of endometrial tissue outside the endometrial cavity.

Endometriosis is a common challenge in ART and with the mention of the very word endometriosis a series of questions are conjured up into our minds. With this new edition of the bulletin , we have tried to answer questions about the etiology, pathophysiology and various modalities for early investigations of the disease. Emphasis would be on managing young women with the disease and infertility. An intensive review of literature at the end would throw light on the current consensus.

I am sure you would enjoy reading the bulletin.

I wish the editor Dr. Pankaj Talwar and his team all the best in his endeavour

Secretary General-IFS

Dr. K.D. Nayar

It is always been a matter of great privilege and pride to write this message for the E-bulletin of IFS named ARTexT.

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 clinician and the patient . We intend to cover common day-to-day challenges in the field of clinical ART and thus bring out this E- bulletin named ARTexT at regular intervals. The aim would be to simplify the complex issues in clinical ART and present before you in a concise manner.I am sure that you would appreciate and learn from this academic initiative of Publication wing of IFS and will be able to apply the take home messages in your busy daily clinical practice. In this issue we would be covering endometriosis which is still an enigma . This manual may help you find the required answers for the queries related to this distressful condition of women called as Endometriosis.





Chief Editor

Prof (Dr) Pankaj Talwar

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At the very onset, the editorial team would like to thank all of you for reading this E-bulletin ARText. It was my dream to create a bulletin on the lines of NEXUS, which would cover burning issues in clinical ART. We intend to cover common topics in great detail touching on basic sciences, advanced management and the controversies. The bulletin has been named ARText - which mean amalgamating different clinical conditions in ART and Reviewing the Text. All appreciated our first bulletin on Hydrosalphinx and we are grateful unprecedented positive appraisal.

The present issue pertains to one of the most debatable topics in ART - Endometriosis. Endometriosis is a common disease entity confronting gynecologists, and is defined as the presence of endometrial glands and stroma tissue outside the uterus.

The bulletin is penned in three parts. **Part 1** deal with the basics of endometriosis. **Part 2** deals with frequently asked questions debatable issues concerning ART and the disease and **Part 3** covers exhaustively the guidelines pertaining to endometriosis in regards to Infertility.

I am sure this bulletin will immensely benefit you all. Team 'ARText' sincerely hopes to bring out such teaching material for you regularly. It would not only help to disseminate scientific & ethical content but also constantly update everyone with new researches and developments across the world.

Our motto is "knowledge empowers" and we sincerely hope that you would enjoy reading this Write-up. Feel free to communicate with us at any point of time and contribute critically. Your comments would be published in the next bulletin, which is titled " Poor ovarian responders and ART".

We would also like to place on record our truthful thanks to Cadila health care limited for supporting us in this academic venture and off course I promise that there is no conflict of interest at any level.

Wish you happy reading and yes don't forget to file this issue.

I would formally like to thank my friend Dr. Leena Wadhwa from ESI Hospital, Basaidarapur , New Delhi. Dr Leena and Dr Shubhi have worked un-relentlessly towards bringing out this issue from conception to end.

Jai hind



Guest Editor
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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, Delhi.

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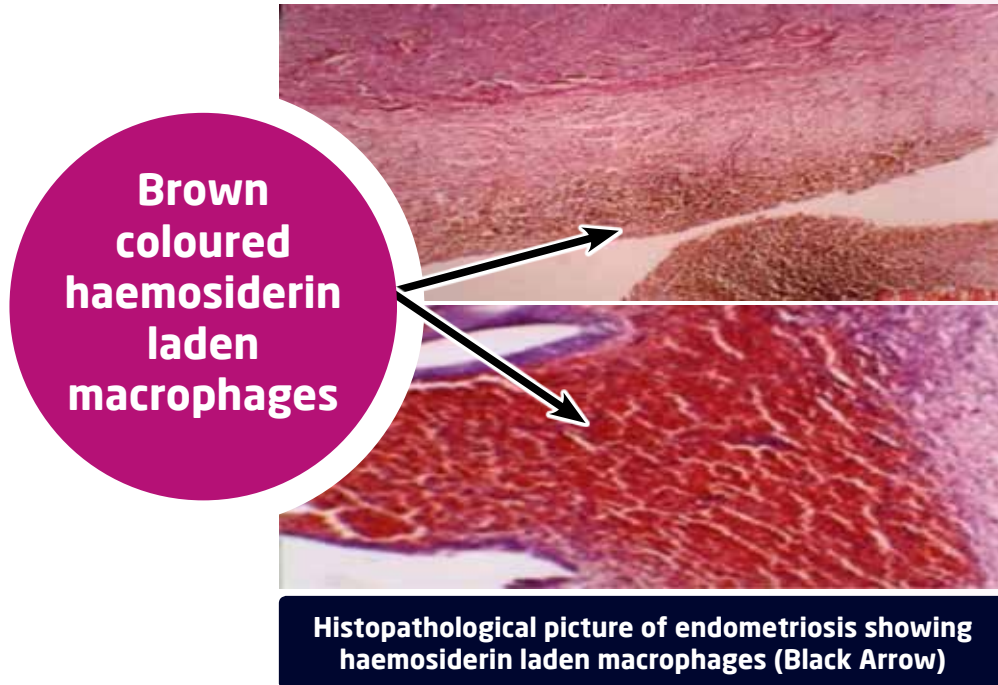
"I am grateful for the opportunity to contribute to this article. I have tried my best to cover all aspects of endometriosis related infertility, and made an effort to provide answers to common questions that young clinicians have regarding this topic."



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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.



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 age 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

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

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.

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.

Vascular / lymphatic dissemination

Endometrial cells disseminate into the peritoneal cavity and other places by vascular and lymphatic channels

Stem cell differentiation

The circulating stem cells derived from bone marrow gets differentiated into endometriotic tissue at various locations.

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.

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.

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 expression 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.

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.

Risk factors

The various risk factors associated with endometriosis 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

Protective factors

- 1) Multiparity
- 2) Lactation
- 3) Increased BMI
- 4) Increased waist-to-hip ratio
- 5) Diet high in vegetable and fruit (**Jonathan S. Berek. 2012**)

VI. Sites of endometriosis

Pelvic

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

Extra pelvic

- h. Umbilicus
- i. Scars
- j. Lungs and pleura

VII. 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.

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

- Pelvic Inflammatory Disease / Tubo Ovarian mass
- Endometriosis
- Ectopic pregnancy
- Ovarian cysts
- Ovarian malignancy

IX. Diagnosis of endometriosis

a) Ultrasonography

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

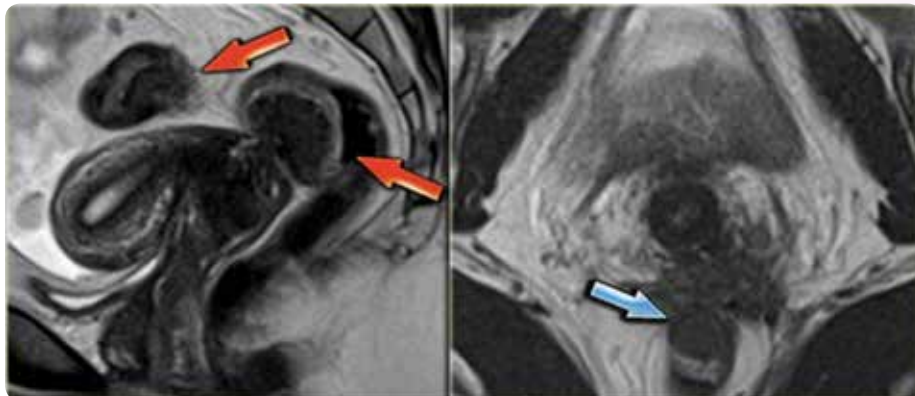
The typical ultrasonography feature of endometrioma is a cystic lesion with diffuse low-level internal echoes, described as "ground glass appearance. Multilocularity and echogenic foci in the wall are also seen in endometrioma. Sonographic imaging of endometrioma and hemorrhagic cyst overlap, hence,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



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

b) MRI

MRI can be helpful for detection and differentiation of ovarian endometrioma from other cystic ovarian masses. MRI detects only 30-40% peritoneal lesions observed at surgery. It 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

c) 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.

d) Laparoscopy

Laparoscopy is the standard technique for inspection of pelvis and to establish a definitive diagnosis of 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.

X. Laparoscopic Appearance

a. Superficial Peritoneal Lesions

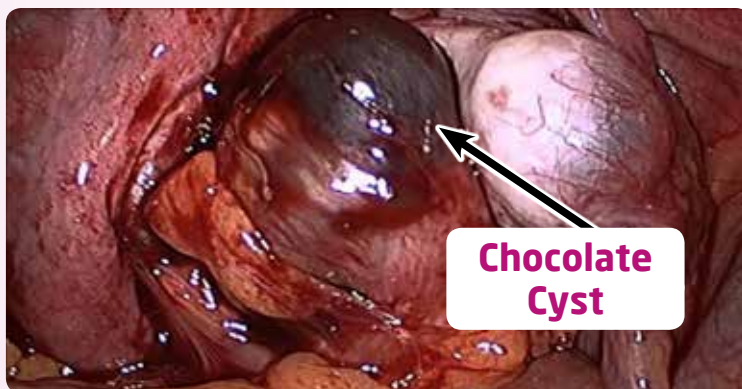
These are located on the pelvic organs or pelvic peritoneum. Classically seen as bluish or blue-brown lesions and are associated with hemosiderin deposits.

- 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**".

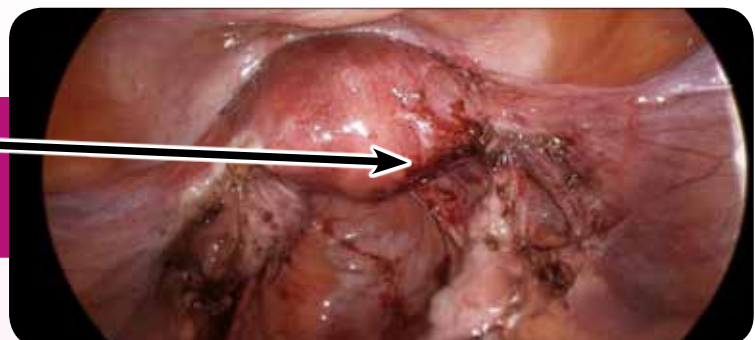


Chocolate Cyst

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.

Endometriotic patches & adhesions



XI. Classification of endometriosis

a. Revised American society for reproductive medicine classification (Am Soc Reprod Med 1997; 5:817-21)

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 _____

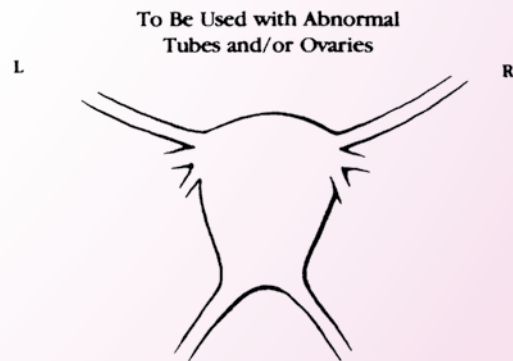
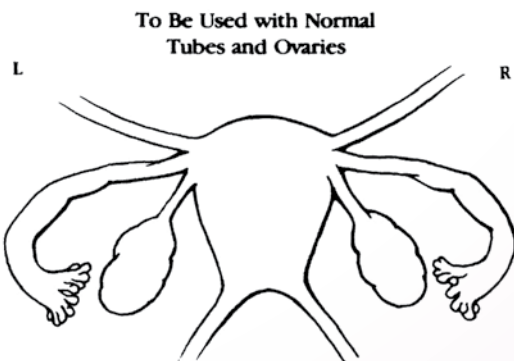
PERITONEUM	ENDOMETRIOSIS	< 1cm	1-3cm	> 3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CULDESAC OBLITERATION		Partial	Complete	
		4	40	
OVARY	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
	TUBE	R Filmy	1	2
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 [(R), 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%.

Additional Endometriosis: _____

Associated Pathology: _____



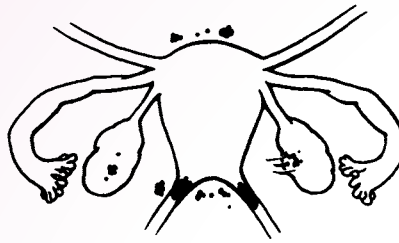
EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



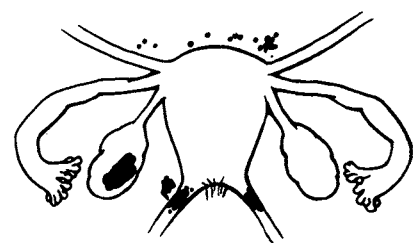
PERITONEUM		
Superficial Endo	- 1-3cm	- 2
R. OVARY		
Superficial Endo	- < 1cm	- 1
Filmy Adhesions	- < 1/3	- 1
TOTAL POINTS		<u>4</u>

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		<u>9</u>

STAGE III (MODERATE)



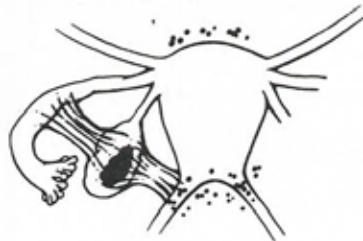
PERITONEUM		
Deep Endo	- >3cm	- 6
CULDESAC		
Partial Obliteration		- 4
L. OVARY		
Deep Endo	- 1-3cm	- 16
TOTAL POINTS		<u>26</u>

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		<u>30</u>

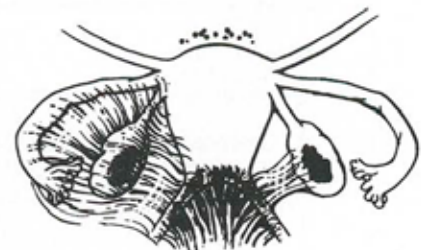
STAGE IV (SEVERE)



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		<u>52</u>

*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		<u>114</u>

XII. 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 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

Adamson G D, Pasta DJ. Fertil Steril 2010;94;1609-15

XIII. 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 -

- 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. 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 glycodefin 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.

XIV. 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 muscle 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.

XV. Recurrent endometriosis

Risk factors are

1. Younger age at the time of surgery (<25 years)
2. Bilaterality
3. Size of endometriotic lesion
4. Revised AFS score > 24
5. Pre-operative cyst rupture
6. Type and extent of surgery

XVI. Endometriosis and cancer

- Some cancers (ovarian cancer, specially endometrioid 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



FREQUENTLY ASKED QUESTIONS: ART

XVII. Effect of endometriosis on IVF - 19

XVIII. Effect of IVF on endometriosis - 19

XIX. Should cystectomy be done prior to IVF? - 19

XX. What is the current management of endometriosis - 20

XVII. Effect of endometriosis on IVF outcome

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.

A meta-analysis by Barnhart et al. on the effects of endometriosis on outcome of ART concluded that the chance of achieving pregnancy was lower for endometriosis patients compared to those with tubal factor infertility. The inferior IVF/ICSI outcomes of endometriosis women may be the result from decreased number of oocytes, poor quality of oocytes, development negative effect on embryogenesis and implantation and impaired uterine receptivity although IVF-ET remove critical steps in reproduction such as fertilization and early embryo development.

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.

(Harb HM et al 2013, Barnhart K 2002, Ashrafi M et al 2014)

XVIII. Effect of IVF on endometriosis?

Four studies evaluated the recurrence rate of disease in women with endometriosis submitted to Medical Assisted Reproduction (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. There is a crucial role of ovulation in the development of endometriomas. The main difference between IUI and IVF is represented by the aspiration of the follicles prior to spontaneous dehiscence, and this may explain why COH is associated with increased risk of endometrioma formation if superovulation precedes IUI, but not if it precedes IVF. Based on reproductive success and both disease progression and recurrence, IVF should be considered the first-line approach in the management of infertility associated with advanced endometriosis when ART is considered.

(Benaglia et al 2011, Benaglia et al 2010, Coccia et al 2010, D'Hooghe et al 2006)

XIX. 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.

(Dunselman GA et al. ESHRE guideline: 2014)

XX. MANAGEMENT OF ENDOMETRIOSIS

Medical

surgical

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 subfertility. 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.

b. 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 be prescribed hormonal ovarian suppression to improve fertility as first line treatment in patients of endometriosis who wish to conceive

(Hughes E 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

Women with endometriosis, should not be prescribed adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates

Hart RJ et al 2008, Dunselman GA et al. ESHRE guideline: 2014

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.

Dienogest at 2 mg once daily is used as the optimal dose in the treatment of endometriosis for a duration of 12-24 week.

Several trials are going on to assess the role of Dienogest pretreatment for endometriosis in comparison to gonadotropin releasing hormone agonist in patients of endometriosis undergoing IVF, with hypothetical results no significant difference was noted in no. of oocyte retrieved, pregnancy and miscarriage rate. Further studies and trials for validation of these results is still needed

(Patel BG et al 2017, Adolf E Schindler 2011)

C(I). Is surgery effective for infertility associated with endometriosis?

- Surgical management is warranted for women with symptoms of dysmenorrhea, dyschezia and chronic pelvic pain.
- Two randomized trial studied the effect of laparoscopic procedure in patients with mild to moderate endometriosis. In multi center Canadian trial a total of 341 infertile women with minimal to moderate endometriosis were randomized to diagnostic laparoscopy and ablation of endometrial lesion with adhesiolysis. They found that resection and ablation group had higher likelihood of pregnancy. Cochrane review agrees that operative laparoscopic surgery improves ongoing pregnancy rate in stage I and II endometriosis when compared to diagnostic laparoscopy alone **(Nowroozi et al 1987, Marcoux S 1997, Duffy 2014)**
- 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.
- In several, randomized control trials, comparing laparotomy and laparoscopy, results were similar in terms of pregnancy rate, fecundity and cyst recurrence. **(Busaca et al 1998)**

C(II). 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 electro-surgical 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

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 (Hart RJ et al 2008, Dunselman GA et al. ESHRE guideline: 2014)

C(III). 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 of the disease and adhesion formation

C(IV). 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. 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. (Ahmad, et al., 2008)

d. 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

Dunselman GA et al. ESHRE guideline: 2014

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. Age, duration of infertility, ovarian reserve and male factor should also be taken under consideration. Patients should be advised to begin attempting to conceive soon after laparoscopic surgery. 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. A longitudinal study showed a 5.1 times higher pregnancy rate (95% CI 1.1-22.5) in couples receiving Intrauterine insemination (IUI) after controlled ovarian stimulation with gonadotrophins compared with IUI alone. 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. 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 al1993, Huges et al 1997)

Emerging role of Aromatase inhibitors (AIs) 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.

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,

Lu et al. compared E₂ production and P450 aromatase mRNA expression of cultured luteinized granulosa cells and the effect of letrozole on these parameters between women with and without endometriosis and found comparatively lower parameters with letrozole. They included women with advanced stage of endometriosis in their study

(Abu Hashim et al 2016, Miller et al 2012, Lu et al. 2012)

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 : Down regulation for 3-6 months with GnRHa in women with endometriosis increases the odds of clinical pregnancy by more than 4-fold. **Dunselman GA et al. ESHRE guideline: 2014**

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

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

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. 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. **(Pabuccu et al 2007, Brown J, Farquhar C 2014).**

Oral contraceptive (OC) pill : The use of OC before IVF-ET given for a period of 6-8 weeks in patients with endometriosis improves outcome. **(Vanessa Gayet et al 2010)**

Oocyte donation

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.

Role of Fertility Preservation(FP):

Patients with endometriosis should be counselled about not delaying first pregnancy and when this is not a realistic option fertility preservation should be considered. Current ovarian reserve, disease extent, progression rate, need for ovarian surgeries, and high recurrence rate should be taken into

consideration. FP should be offered in patients suffering from mild endometriosis with reduced ovarian reserve and at older reproductive age. It should also be considered before an extensive or bilateral pelvic surgery for endometriosis and in those cases if a woman is not planning immediate conception after surgery.

The technique for fertility preservation in women suffering from endometriosis is freezing embryos or unfertilized oocytes. Several COH cycles may be needed to freeze adequate number of oocytes or embryos

The benefits of storing ovarian tissue harvested during surgery for endometriosis has not yet been tested and the concentration and quality of oocytes surrounding endometrioma wall needs further studies.

(Carrillo L 2016)

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.

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.

In retrospective study women with endometriosis undergoing IVF, the preparation of the endometrium for frozen ET with GnRH agonists compared to fresh cycles was 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 GnRH α 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.

(Evans J 2014, 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.

Vaginal preparation with better bactericidal substances as well as stronger antibiotic prophylaxis might be useful in the prevention of PID. vaginal douching prior to ovum pick up **(OPU)** with povidone-iodine decreases the risk 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. **(Tsai et al 2005).**

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

Oophorectomy

Treatment of adenomyosis in infertility

Treatment of adenomyosis with hypoestrogenic agents or surgical removal of the adenoma lesions may restore normal fertility. Currently, the accepted treatment of adenomyosis in infertile patients is with GnRH agonists followed by IVF. This is due to the transient suppression of the hypothalamic-pituitary-ovarian axis by GnRH 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.

CONCLUSION

- Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.
- 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
- Moderate -severe endometriosis with prior one or more infertility operations, IVF-ET is better therapeutic option than another infertility operation

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PART III

Burning issues and guidelines

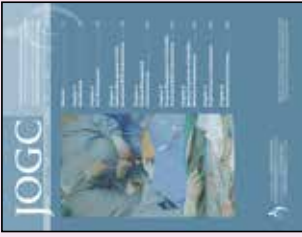

1: Endometrioma : Role of surgery - 32




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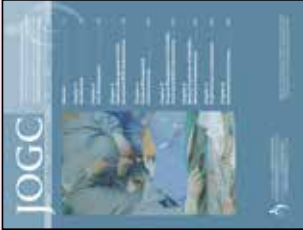

4 : Laparoscopy for all before ART to diagnose endometriosis - 38


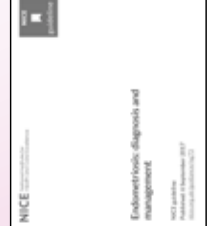

Burning issue I : Endometrioma : Role of surgery

Burning issue	Endometrioma	Recommendation level	Reference
	<p>Laparoscopic excision of ovarian endometriomas more than 3 cm in diameter may improve fertility.</p>	<p>II</p>	<p>Somigliana E, Vercellini P, Viganó P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? Hum Reprod 2006;21:57-64.</p>
	<p>For women who are found to have an asymptomatic endometrioma and who are planning to undergo IVF/ICSI, there is insufficient evidence to suggest that removal of the endometrioma will improve IVF success rates</p> <p>Surgical management of an endometrioma should include resection or ablation, rather than drainage, with resection preferred.</p> <p>Laparoscopic cystectomy for ovarian endometriomas greater than 4 cm improved fertility compared to cyst drainage and coagulation, which is associated with a high risk of cyst recurrence</p> <p>Benefits of surgical treatment prior to IVF, especially for large endometriomas, include prevention of possible ruptured endometrioma, facilitation of oocyte retrieval, detection of occult malignancy (particularly in view of a large study confirming an association between endometriosis and certain ovarian cancers, avoidance of contamination of follicular fluid with endometrioma content, and prevention of progression of endometriosis</p> <p>Disadvantages of surgery include surgical trauma, surgical complications, economic costs, potential decreased ovarian response, and lack of evidence for improved IVF pregnancy rates</p>	<p>Evidence level I</p>	<p>Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. Hum Reprod Update 2002;8:591-7</p> <p>Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-Roux F. Large ovarian endometriomas. Hum Reprod 1996;11:641-6.</p> <p>Somigliana E, Vercellini P, Viganò P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? Hum Reprod Update 2006;12: 57-64.</p> <p>Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down- regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006:CD004635.</p>

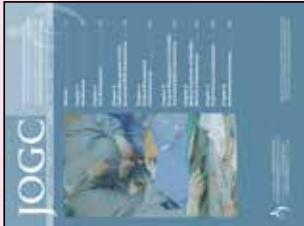


Burning issue	Endometrioma	Recommendation level	Reference
	<p>Laparoscopic excision of ovarian endometriomas more than 3 cm in diameter may improve fertility.</p>	<p>II</p>	<p>Somigliana E, Vercellini P, Viganó P, Ragni G, Crosignani PG. Should endometriomas be treated before IVF-ICSI cycles? Hum Reprod 2006;21:57-64.</p>
	<p>Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. [2004] Laparoscopic cystectomy increased cumulative pregnancy rates at 24 months when compared with drainage and coagulation in the treatment of large ovarian endometrioma</p>	<p>Ib</p>	<p>Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 1998;70:1176-80.</p>
	<p>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. In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles. The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. In women with endometrioma, clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of ovarian abscess following follicle aspiration is low</p>	<p>A GPP GPP D</p>	<p>Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008 Benschop L, Farquhar C, van der Poel N and Heineman MJ. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database Syst Rev 2010;CD008571. Donnez J, Wyns C and Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin? Fertil Steril 2001; 76:662-665. Hart RJ, Hickey M, Maouris P and Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev 2008;CD004992. [Edited (no change to conclusions), published in Issue 5, 2011.] Benaglia L, Somigliana E, Iemello R, Colpi E, Nicolosi AE and Ragni G. Endometrioma and oocyte retrieval- induced pelvic abscess: a clinical concern or an exceptional complication? Fertil Steril 2008; 89:1263-1266.</p>



Burning issue II : GnRH Pretreatment before ART




Burning issue	GnRH Pretreatment before ART	Recommendations	Reference
	<p>If a patient with known endometriosis is to undergo IVF, GnRH agonist suppression with HT add back for 3 to 6 months before IVF is associated with an improved pregnancy rate.</p> <p>Three months of suppression with a GnRH agonist and HT addback before IVF in women who have pelvic pain and infertility associated with endometriosis will greatly improve quality of life and reduce discomfort during ovarian stimulation and oocyte retrieval.</p> <p>Medical management of infertility related to endometriosis in the form of hormonal suppression is ineffective and should not be offered.</p>	<p>(I) (I-E) v</p>	<p>Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril 2002;77:1148-55.</p> <p>Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006;Jan 25;(1):CD004635.</p>
	<p>Whereas medical therapy is effective for relieving pain associated with endometriosis, there is no evidence that medical treatment of endometriosis improves fertility. In actuality, fertility is essentially eliminated during treatment because all medical treatments for endometriosis inhibit ovulation.</p> <p>A summary of three randomized controlled trials that included a total of 165 women concluded that administration of GnRH agonists for a period of 3-6 months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy (OR 4.28, 95% CI, 2.00 to 9.15).</p>	<p>Evidence level I</p>	<p>Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down- regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006;CD004635.</p>

Burning issue	GnRH Pretreatment before ART	Recommendations	Reference
	<p>Treatment with ovulation suppression agents (medroxyprogesterone, gestrinone, combined oral contraceptives and gonadotrophin-releasing hormone agonist [GnRHa]) did not improve clinical pregnancy rates in women with endometriosis-associated infertility compared with no treatment (pooled odds ratio [OR] 0.74; 95% confidence interval [CI] 0.48 to 1.15) or danazol (pooled OR 1.3; 95% CI 0.97 to 1.76).666</p>	<p>Evidence level 1a</p>	<p>Hughes E, Fedorkow D, Collins J, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2000;(2) :CD 000155. Update in: Cochrane Database Syst Rev 2003;(3):CD 000155.</p>
	<p>Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.</p>		<p>Endometriosis: diagnosis and management (NG73) NICE 2017</p>
	<p>Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis.</p>	<p>B</p>	<p>Sallam HN, Garcia-Velasco JA, Dias S and Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006:CD004635. [Edited (no change to conclusions), published in Issue 1, 2010.]</p>

Burning issue III : GnRH Post surgery before ART

Burning issue	GnRH post surgery before ART	Recommendations	Reference
	<p>Hormonal suppression before or after surgical treatment of endometriosis is contraindicated since there is no evidence of increased effectiveness over that of surgery alone, and the treatment prolongs or delays the opportunity for conception to occur.</p>	<p>Chapter 6, medical treatment of infertility related to endometriosis</p>	<p>Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2007 Jul 18 ;(3):CD 000155.</p>
	<p>Postoperative medical therapy has been advocated as a means of eradicating residual endometriotic implants in patients with extensive disease in whom resection of all implants is impossible or inadvisable. Postoperative hormonal therapy also may treat "microscopic disease"; however, none of these treatments has been proven to enhance fertility</p>		<p>Somigliana, E, Vercellini, P, Vigano, P, Ragni, G, and Crosignani, P.G. Should endometriomas be treated before IVF-ICSI cycles?. Hum Reprod Update. 2006; 12 American Society for Reproductive Medicine, Birmingham, Alabama</p>
	<p>Postoperative GnRH with expectant management found no significant difference in pregnancy rates between the two regimens (11.6% with goserelin versus 18.4% with expectant management and 33% with leuprolide depot versus 40% with expectant management, respectively).</p>	<p>Evidence level 1b</p>	<p>Vercellini P, Crosignani PG, Fadini R, Radici E, Belloni C, Sismondi P. Agonadotrophin releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis. Br J Obstet Gynaecol 1999;106:672-7. Busacca M, Somigliana E, Bianchi S, De Marinis S, Callia C, Candiani M, et al. Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial. Hum Reprod 2001;16:2399-402.</p>

Burning issue	GnRH post surgery before ART	Recommendations	Reference
	<p>Hormonal treatment to women with endometriosis who are trying to conceive is not recommended, because it does not improve spontaneous pregnancy rates.</p>		<p>Endometriosis: diagnosis and management (NG73) NICE 2017</p>
	<p>In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates.</p>	<p>A</p>	<p>Furness S, Yap C, Farquhar C and Cheong YC. Pre and post-operative medical therapy for endometriosis surgery. Cochrane Database Syst Rev 2004:CD003678. [New search for studies, and content updated (no change to conclusions), published in Issue 1, 2011.]</p>

Burning issue	Should laparoscopy be performed for all to diagnose endometriosis	Recommendations	Reference
	<p>Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy.</p> <p>With moderate and severe endometriosis operative treatment with laparoscopy or laparotomy suggest that pregnancy rates may be the same or increased in those treated by laparoscopy</p>	<p>Evidence level 1a</p> <p>Evidence level 2b</p>	<p>Jacobson TZ, Barlow DH, Koninckx PR, Olive D, Farquhar C. Laparoscopic surgery for subfertility associate with endometriosis. Cochrane Database Syst Rev 2002;(4):CD 001398</p> <p>Adamson GD, Hurd SJ, Pasta DJ, Rodriguez BD. Laparoscopic endometriosis treatment: is it better? Fertil Steril 1993;59:35-44.</p>
	<p>Offer excision or ablation of endometriosis plus adhesiolysis for endometriosis not involving the bowel, bladder or ureter, because this improves the chance of spontaneous pregnancy.</p>		<p>Endometriosis: diagnosis and management (NG73) NICE 2017</p>
	<p>In women with minimal to mild endometriosis (rASRM classification), operative laparoscopy including adhesiolysis is effective in increasing the pregnancy/live birth rate, compared to diagnostic laparoscopy. Although treatment of minimal to mild lesions is associated with a (marginally) significant effect, no more than 50% of these women had this type of endometriosis. This translates into a number needed to treat of 25.</p> <p>In 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</p>	<p>A</p>	<p>Jacobson TZ, Duffy JM, Barlow D, Farquhar C, Koninckx PR and Olive D. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst Rev 2010:CD001398.</p>



Letisha

Letrozole 2.5 mg Tablets

ZyStim

Filgrastim 300 µg/ml single dose pre-filled syringe

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