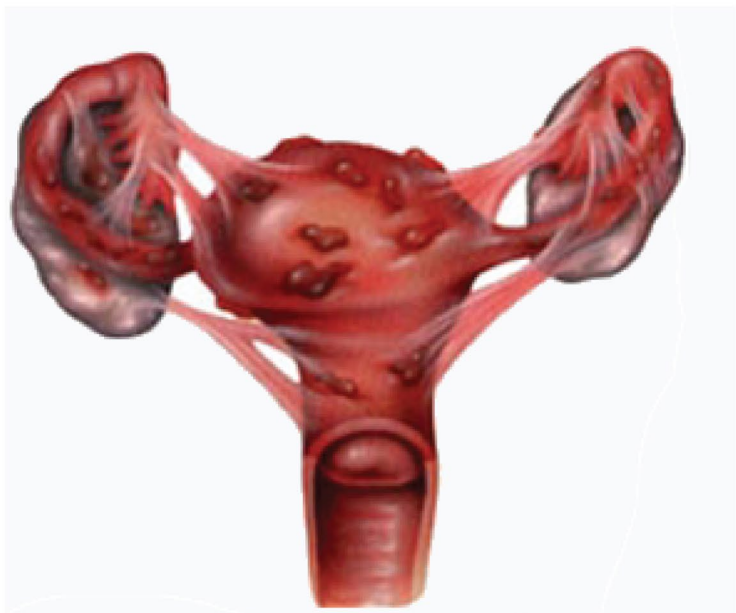
IFS CONVERSATIONS

Volume 5 : February, 2018

INDIAN FERTILITY SOCIETY

ENDOMETRIOSIS



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IFS SECRETARIAT

Akanksha IVF Centre

A-3/7, Janak Puri, New Delhi-110058

T: +91 9899308083, 45682024

E: indianfertilitysocietydelhi@gmail.com

W: www.indianfertilitysociety.org

MESSEGE FROM THE **PRESIDENT DESK**

Dear Friends,

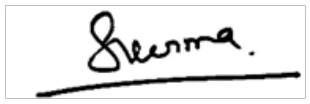
The "Endometriosis and Adenomyosis", with a reported prevalence rate of 10 to 50% among infertile population, continue to present a significant diagnostic and clinical challenge.The pathogenesis is complex and multi factorial, and recurrence is common. These disorders can have significant physical, sexual, psychological and social impact, and there are several specific challenges while dealing with these conditions and ART. I congratulate Dr Surveen Ghumman for taking up this very important topic and applaud all contributors for their scholarly evidence based articles. I am sure, readers will find these informative and helpful in clearing doubts on this enigmatic disorder.

I take this opportunity to congratulate and thank each member of the IFS Family for making our recent "Fertivision 2017-National Annual Conference" a great success and memorable event! My special sincere thanks are to each and every member of organizing team for their exemplary hard work, and each faculty for enriching this conference with the most updated practice guidelines and innovations in infertility and ART! It was highly gratifying that the conference was rewarded with excellent feedbacks including appreciation by all international faculty.

As the two year tenure of our current office bearers is about to end next month, I wish to convey my heartfelt sincere gratitude to each one of the 18 IFS Chapter Secretaries and more than 1800 distinguished members across the country and in Nepal, for your invaluable support, relentless hard work and outstanding performance during the current term. It is with immense pride that I acknowledge the extra ordinary achievements of the present team. Apart from organizing "22nd IFFS World Congress" in collaboration with ISAR, two Annual National Conferences- Fertivision 2016 and 2017, and regular CMEs across the country, the initiation of 15 different Special Interest Groups (SIG), launch of two new e-bulletins – "NEXUS" and "ARTEXT", the two redesigned IFS Courses- "Diploma in Clinical ART" and "Diploma in Clinical Embryology" in collaboration with prestigious Amity University, the first time conducted IFFS workshop in India and approval for ESHRE e-Exam (for Certification in Clinical Embryology)to be held at New Delhi on 30th June 2018, are some of the proud initiatives made during the current term. I am sure, that the new team,under very able and dynamic leadership of Dr Gouri Devi will certainly take IFS to further heights and I wish them the very best.

I once again congratulate and sincerely thank our distinguished editors- Dr Bharati Dhorepatil and Dr Surveen Ghumman for their dedication and hard work in creating high quality news bulletins - "IFS Conversations" throughout this term.

With warm regards and best wishes



Dr Sohani Verma
President - Indian Fertility Society
drsohaniverma@gmail.com / 9810116623

MESSEGE FROM THE **SECRETARY DESK**

It gives me immense pleasure to bring to all IFS members the next edition of "IFS Conversation". IFS has been doing excellent work by focusing on academic activities all over the country, helping young faculty to learn from experienced senior members.
I would like to congratulate the Editorial board, the authors and contributors for their continuous efforts in providing opinions on the controversies in ART.

In this issue we would be covering Endometriosis and Adenomyosis which is still an enigma, full of mystery. The prevalence of endometriosis in reproductive age women is around 3-10%. This manual may help you find the required answers for the queries related to this distressful condition of women called as Endometriosis. Hope all experienced as well as young members will enjoy this opportunity to enhance their knowledge.

As my term as Secretary General in office comes to an end, I would like to thank all the members of IFS most sincerely for their help and cooperation in these past two years and all the support in making FERTIVISION 2017 a great success. Many International and National Stalwarts have contributed in so many ways and with excellent academic discussions making FERTIVISION 2017 a new benchmark.

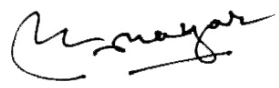
I am delighted that we have achieved so much. The year 2017 has been a landmark for IFS. IFS have entered into collaboration with Amity University for IFS fellowship courses which have now been renamed as Diploma in Clinical ART & Diploma in Clinical Embryology, both of 1 year duration. A new beginning has also been made about IFS initiative of collaborating with ESHRE and from 2018, ESHRE Certification Examination for Embryologists will be conducted simultaneously in New Delhi as the only centre outside of Europe.

"Fertility Science & Research" a peer reviewed indexed biannual Journal is also being published by IFS. It has regular updates of the latest research in the field and opinions on the controversies in ethical and legal issues, contributed by experts across the globe.

In the end, I would like to thank the Editorial board for working diligently to bring out e Bulletins- Nexus ,and ARText also in providing in depth information and keeping us all updated with recent advances in the field contributed by experts across the country.

I wish all the best to the IFS family for making IFS the biggest academic platform for scientific interactions.

With warm Regards



Dr.K.D.Nayar
Secretary General - Indian Fertility Society
kdnayar@usa.net / 9810398765

THE EXECUTIVE **MEMBERS**

MESSEGE FROM THE **EDITOR DESK**

Dear Friends,

We welcome the New Year with the discussion on the controversial topic of 'Endometriosis' in this issue of IFS Conversations. We have attempted to solve some dilemmas pertaining to this topic. Both surgical and medical management of endometriosis and adenomyosis are discussed in detail. The topic is extensively reviewed with special reference to role of ART and endometriosis fertility index in infertile women. The most commonly detected pathology of this disease – Endometrioma and its debatable issues are discussed. We hope it will be useful to our members

We had a successful annual conference - Fertivision 2017 and have tried to cover the event through pictures in this issue. Renowned national and international faculty has contributed to the scientific deliberations and the conference was well attended.

Besides, the Annual Conference regular CMEs conducted all over India has facilitated IFS to create academic awareness in every corner of our country. We are continuing with strong training programs through conducting Fellowships in Clinical Embryology and ART.

We invite all IFS members to contribute their articles to the IFS Journal – The Fertility Science and Research. The journal is available to all IFS members to highlight and publish their research.

As this term comes to an end, we would like to thank the President, Dr Sohani Verma, Secretary, Dr K.D. Nayar and all executive members for the support extended to the editorial board during this term. It has been a gratifying academic exercise taking out the IFS conversations during this term and we hope you have enjoyed reading the content.

Happy New Year!

With Best Wishes

Dr. Bharati Dhorepatil
Editor-IFS

Dr. Surveen Ghumman
Joint Editor-IFS

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INVITED
ARTICLES

Endometriosis and ART - A Review

DR K.D. NAYAR
MD, DGO, Dip. Obst.(Ireland), FICOG
Chief Consultant, Akanksha IVF Centre
Mata Chanan Devi Hospital, New Delhi

DR NUPUR AGARWAL
DGO, DNB, FNB
Consultant, Akanksha IVF Centre
Mata Chanan Devi Hospital, New Delhi

"There is much that is still not understood and the condition continues to arise interest and controversies". (Robert W. Shaw).

Endometriosis remains an enigma, full of mystery even today. It is an inflammatory condition characterized by lesions of endometrial-like tissue outside of uterus and is associated with pelvic pain and infertility. It is a benign, estrogen dependent and progressive gynaecological disease in women of reproductive age. Endometriosis affects an estimated 1 in 10 women during their reproductive years (i.e. usually between the ages of 15 to 49), which is approximately176 million women in the world. 25 to 50% of infertile women have endometriosis and 30-50% of women with endometriosis are infertile. Endometriosis is found in 45% - 82% of women with chronic pelvic pain and in 2.1%-78% of infertile women.[1]

Mechanism of infertility:

Mild endometriosis - Peritoneal fluid abnormalities, altered hormonal and cell mediated function, eutopic endometrium abnormalities, ovulatory dysfunction, Oocyte and embryo quality, follicular and oocyte abnormalities, embryonic implantation failure.

Advanced endometriosis - extensive adhesions, large endometriomas, distortion of the tubovarian relationship. [2]

In Endometriosis,endometrial receptivity is defective due to altered αvβ3 integrin expression (a cell adhesion molecule) during the time of implantation, low levels of an enzyme involved in the synthesis of the endometrial ligand for L-selectin (a protein that coats the trophoblast on the surface of the blastocyst). Eutopic endometriosis has high aromatase which leads to the increased estradiol causing negative impact on implantation. Anti endometrial antibodies,that is increased IgG, IgA and lymphocytes in the endometrium of women with endometriosis also alter endometrial receptivity and embryo implantation. Absence of mid luteal rise of HOXA 10 increases oxidative stress whichaffects endometrium/embryo.

Types of endometriotic lesions

1. **Superficial endometriosis (free endometriosis)**
   - peritoneal implants and ovarian implants
   - responds to menstrual cycle.

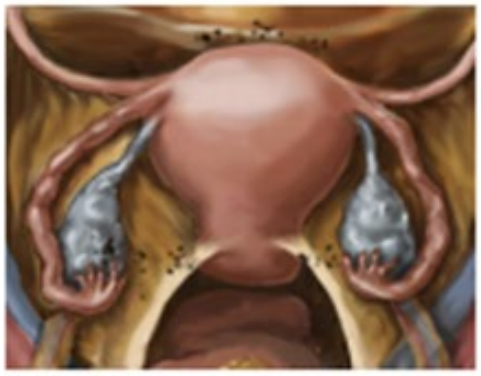
2. **Deep infiltrating (adenomatous) endometriosis**
   - Proliferative fibromuscular tissue with sparse endometrial glandular and stromal tissue.
   - Does not show significant changes during the menstrual cycle.
   - Typically seen in the rectovaginal space and can involve the uterosacral ligament, the posterior vaginal wall, and the anterior rectal wall.

3. **Ovarian endometriotic cysts (endometriomas)**
   These are found in ovaries and may be 0.5 cm to large cysts of 10cm

Classification and Staging Systems

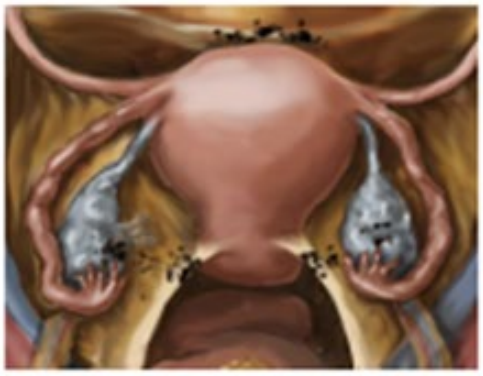
1. Revised American Fertility Scoring, 1995[3]

STAGE I (MINIMAL)



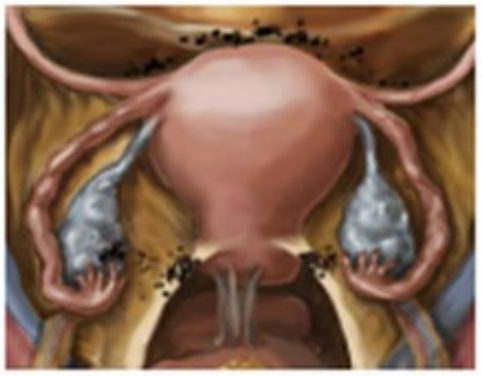
PERITONEUM		
Superficial Endo	— 1–3cm	-2
L. OVARY		
Superficial Endo	— <1cm	-1
Filmy Adhesions	— <1/3	-1
TOTAL POINTS		4

STAGE II (MILD)



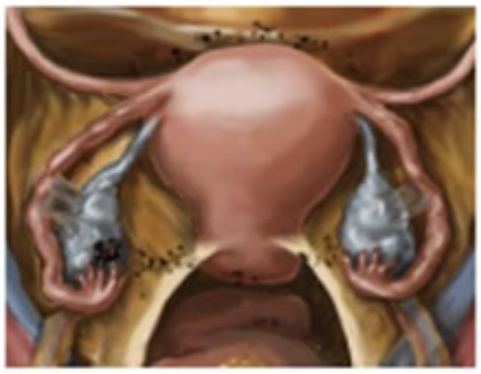
PERITONEUM		
Deep Endo	— >3cm	-6
L. OVARY		
Superficial Endo	— <1cm	-1
Filmy Adhesions	— <1/3	-1
R. OVARY		
Superficial Endo	— <1cm	-1
TOTAL POINTS		9

STAGE III (MODERATE)



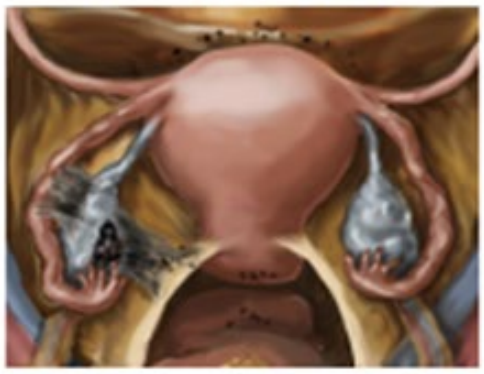
PERITONEUM		
Deep Endo	— >3cm	-6
CULDESAC		
Partial Obliteration		-4
L. OVARY		
Deep Endo	— 1–3cm	-16
TOTAL POINTS		26

STAGE III (MODERATE)



PERITONEUM		
Superficial Endo	— >3cm	-3
L. TUBE		
Dense Adhesions	— <1/3	-16*
L. OVARY		
Deep Endo	— <1cm	-4
Dense Adhesions	— <1/3	-4
R. TUBE		
Filmy Adhesions	— <1/3	-1
R. OVARY		
Filmy Adhesions	— <1/3	-1
TOTAL POINTS		29

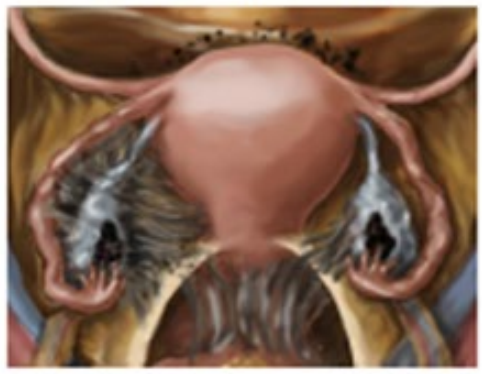
STAGE IV (SEVERE)



PERITONEUM		
Superficial Endo	— >3cm	-3
L. OVARY		
Deep Endo	— 1–3cm	-32**
Dense Adhesions	— <1/3	-8**
L. TUBE		
Dense Adhesions	— <1/3	-8**
TOTAL POINTS		51

*Point assignment changed to 16
**Point assignment doubled

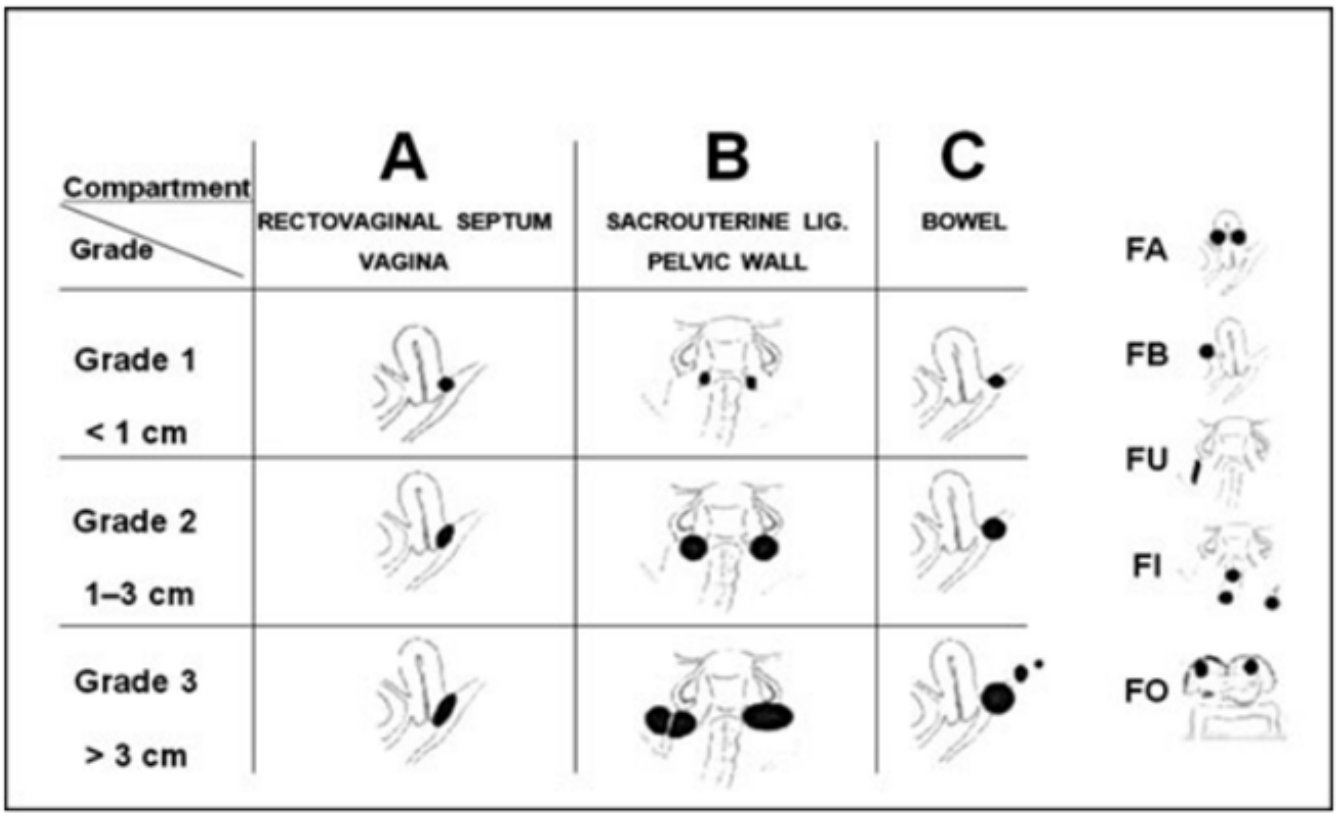
STAGE IV (SEVERE)



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

Stage I - Minimal	Few or superficial implants are evident in the early stages of endometriosis
Stage II - Mild	More implants, deeper involvement
Stage III - Moderate	More implants; ovaries affected, adhesions present
Stage IV - Severe	Similar to Stage III, but multiple and more dense adhesions present

2. Enzian Classification 2005[4]:



The ENZIAN score was introduced to provide a means of registering deeply infiltrating endometriosis.The revised version combines morphological structures into compartments in order to simplify the system. Retroperitoneal structures are divided into the following three compartments:

- Compartment A, rectovaginal septum and vagina.
- Compartment B, sacrouterine ligament to pelvic wall.
- Compartment C, rectum and sigmoid colon.

Severity was rated in the same way for all compartments, as follows:

- Grade 1, invasion <1 cm
- Grade 2, invasion 1–3 cm
- Grade 3, invasion >3 cm

Deep invasion of endometriosis beyond the lesser pelvis and invasion of organs can also be registered separately in the Enzian classification. The prefix "F" stands for "far" or "foreign," because it refers to retroperitoneal distant locations (FA = adenomyosis, FB = involvement of the bladder, FU = intrinsic involvement of the ureter, FI = bowel disease cranial to the rectosigmoid junction and FO ("other") = other locations, such as abdominal wall endometriosis).

3. Endometriosis fertility index (EFI) [5]:

The endometriosis fertility index (EFI), proposed by Adamson and Pasta in 2010, 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 contains all of the components of the r-AFS stage score, but the r-AFS score includes only 20% of the EFI score.

Clinical features

Asymptomatic in about one-fifth of patients. Main presenting symptoms are dysmenorrhoea, noncyclical pelvic pain and/or dyspareunia. Pain severity does not correlate with disease severity. Dysmennorrhoeaaffects 85% of patients.

Diagnosis

ASRM committee opinion 2012 on diagnosis

- Surgical procedure likelaparoscopy needed fordefinitive diagnosis.
- Histological evaluation needed if diagnosis not apparent on visual examination at surgery.
- History and clinical examination suggestive of endometriosis (cyclic pain/chr.pelvic pain/dysmenorrhoea/dyspareunia/fixed retroverted uterus/adnexal mass/uterosacral lig nodularity ,thickening and tenderness) and USG evidence of endometrioma provide presumptive diagnosis.
- ***Asymptomatic endometriosis:*** Always limited to minimal /mild disease. Therapeutic benefit of laparoscopy to increase fecundity in mild disease is minimal.So,laparoscopy in asymptomatic infertile women for diagnosis is unwarranted.

ESHRE guideline 2013 recommendations on diagnosis[6]:

Symptoms and signs:

- Consider diagnosis of endometriosis if gynecological symptoms are present. i.e. : dysmenorrhoea, noncyclic pelvic pain ,deep dyspareunia,infertility,fatigue in the presence of any of the above.
- Consider diagnosis of endometriosis in women of reproductive age with nongynaecological symptoms like: dyschezia, dysuria, hematuria, rectal bleeding , shoulder pain.

Clinical examination in the diagnosis of endometriosis.

- Clinical examination to be performed in all women suspected of endometriosis.
- Adolescents /unmarried: Rectal examination to be done.
- Consider deep endometriosis if painful induration &/or nodules of recto-vaginal wall or visible vaginal nodules in posterior vaginal fornix on Clinical examination.
- Consider the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination.
- Consider endometriosis in women suspected of the disease even if the clinical examination is normal.

Laparoscopy for diagnosis of endometriosis

- Clinicians should perform a laparoscopy to diagnose endometriosis, although evidence is lacking that a positive laparoscopy without histology proves the presence of disease.
- A positive laparoscopy should be confirmed by histology, since positive histology confirms the diagnosis of endometriosis, even though negative histology does not exclude it.
- Obtain tissue for histology in women undergoing surgery for ovarian endometrioma and/or deep infiltrating disease, to diagnose endometriosis & exclude rare instances of malignancy.

USG for the diagnosis of rectovaginal endometriosis

- If symptoms and signs of rectal endometriosis, transvaginal sonography is useful for identifying or ruling out rectal endometriosis.
- 3D sonography :to diagnose rectovaginal endometriosis is not well established.
- Perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma.
- For the diagnosis of ovarian endometrioma in premenopausal women the following ultrasound characteristics: ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow.

MRI for peritoneal endometriosis

- Usefulness of magnetic resonance imaging (MRI) to diagnose peritoneal endometriosis is not well established.

Biomarkers in the diagnosis of endometriosis[7]

- Not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis.
- Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis.
- Clinicians should assess ureter, bladder, and bowel involvement by additional imaging if there is a suspicion based on history or physical examination of deep endometriosis, in preparation for further management.

Management

- Medical
- Surgical
- ART(IUI/IVF/ICSI)

Factors to consider when planning endometriosis treatment:

- Age
  - Presenting symptom (pain, infertility or both)
  - Severity of pain and its impact on quality of life
  - Type, extent and location of endometriotic lesions.

Role Of Medical Therapy:

Are hormonal therapies effective for infertility associated with endometriosis?

In infertile women with endometriosis, the Guideline Development Group (GDG) do not recommend adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates[6]. Post op adjunctive hormonal treatment is also not recommended to improve spontaneous pregnancy rate. It is important to realize that clinicians should not withhold hormonal treatment for symptomatic women in the waiting period before undergoing surgery or medical assisted reproduction.

Role of Dienogest in treatment of endometriosis

Dienogest is a fourth-generation progestin, a derivative of 19-nortestosterone. It is well tolerated and has no androgenic, glucocorticoid or mineralocorticoid activity. It binds to the progesterone receptor and produces a potent progestogenic effect . It also results in moderateinhibition of gonadotropin secretion, leading to a reduction in the endogenous production of estradiol. With continuous administration, dienogest induces a hypoestrogenic state causing a decidualization of endometrial tissue followed by atrophy of the endometriotic lesions. It also normalizes the activity of natural killer cells and decreases the release of interleukin-1b by macrophages.

Dose is 2 mg once daily for a duration of 12-24 weeks is used in the treatment of endometriosis. 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 are still needed[8].

Role of Surgery

Is there a benefit of surgical treatment of stage I–II of endometriosis and successful pregnancy rate?

In infertile women with AFS/ASRM StageI-II, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) includingadhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoingpregnancy rate.[9] According to ESHRE guidelines, in stage I–II endometriosis, clinicians may consider CO2 laser vaporization of endometriosis, instead of monopolar electro-coagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates[10]. In Infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma

capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates.[11]

Is there a benefit of surgical treatment of stage III–IV of endometriosis and successful pregnancy rate?

In infertile women with AFS/ASRM Stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates.[12]

B	No RCTs or meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. Based upon studiesthere seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study.	Evidence Level 3
A	Laparoscopic cystectomy for ovarian endometriomas >4 cm diameter improves fertility compared to drainage and coagulation. Coagulation or laser vaporization of endometriosis without excision of the pseudo-capsule is associated with a significantly increased risk of cyst recurrence [11,12.]	Evidence Level 1b

The major benefit of surgery is achieved shortly after the first attempt because severe peri-ovarian adhesions will generally recur and will limit tubal pick-up of the ovum. If initial surgery does not result in pregnancy, subsequent surgical procedures are not likely to be effective for increasing fecundability.

A systematic review demonstrated a halving of pregnancy rates after re-operative surgery compared with first line surgery (22% for repetitive surgery versus 40% after primary surgery[13]). The decision for re-operative surgery versus IVF must be made on symptoms, the presence of complex cysts requiring histological diagnosis, age, ovarian reserve, male factor infertility, and availability of skilled surgeons [14].

Assisted Reproductive Technology (ART) In Endometriosis

Intrauterine Insemination

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians mayperform IUI with controlled ovarian stimulation,

-Instead of expectant management, as it increases live birth rates.
-Instead of IUI alone, as it increases pregnancy rates.

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. 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.

A	Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥ 4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles and possibly improve ovarian response. The woman should be counselled	Evidence Level 1b

Cycle fecundity in women with stage I or II endometriosis, according to treatment (reported as percentage).

	Group				
Treatment	Unexplained infertility	Endometriosis-associated infertility			
Reference	Guzick et al. (55)	Deaton et al. (41)	Chaffkin et al. (57)	Fedele et al. (42)	Kemmann et al. (43)
No treatment or intracervical insemination	2	3.3	–	4.5	2.8
IUI	5[a]	–	–	–	–
Clomiphene	–	–	–	–	6.6
Clomiphene/IUI	–	9.5[a]	–	–	–
Gonadotropins	4[a]	–	6.6	–	7.3[a]
Gonadotropins/IUI	9[a]	–	12.9[a]	15[a]	–
IVF	–	–	–	–	22.2[a]

Note: Data presented as percent.
[a] $P < .05$ for treatment vs. no treatment.
Practice Committee. Endometriosis and infertility. Fertil Steril 2012.

IVF

Invitro fertilization is an important option for infertile women with endometriosis

Indications For IVF

1. Primarily IVF is indicated if during laparoscopy severe endometriosis is found compromising tubal function.
2. Secondly after cystectomy there is no conception even after superovulation and IUI for 3-4 cycles.
3. Early referral for IVF in case of reduced ovarian reserve, tubal factor and male factor.

B	In vitro fertilisation (IVF) is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.	Evidence Level 2b
A	IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility.	Evidence Level 1A
A	Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the authors of the Cochrane review stressed that the recommendation is based on only one properly randomised study and called for further research, particularly on the mechanism of action (Sallam et al., 2006)[16].	Evidence Level 1b
B	Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF.	Evidence Level 2a
	regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.	

Should surgery be performed prior to treatment with ART to improve reproductive outcomes?

In infertile women with AFS/ASRM Stage I-II endometriosis undergoing laparoscopy prior to treatment with ART, clinicians may consider the complete surgical removal of endometriosis to improve live birth rate,although the benefit is not well established.15In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rates 16. In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to ART to improve endometriosis associated pain or the accessibility of follicles. The effectiveness of surgical excision of deep nodular lesions before treatment with ART in women with endometriosis is not well established with regard to reproductive outcome[17].

Stimulation protocol 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 6. 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: GnRHagonist is a preferred protocol as it prevents deleterious effects of premature endogenous LH surge but also suppress a numberof 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: This is a good protocol 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. Similar implantation and clinical pregnancy rates were seen in both agonist and antagonist groups but higher number of embryos were available for cryopreservation in those patients treated with GnRH agonist[18,19].

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[20].

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.

Nadir Ciray et al (2005)[21], 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.[21]

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 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.[22,23]

Precautions during ovum pickup with endometrioma

In women with endometrioma, clinicians may consider antibiotic prophylaxis at the time of oocyte retrieval to reduce the risk of ovarian abscess. The use of povidone-iodine followed by saline solution is more effective procedure than saline douching alone to prevent OPU-pelvic infection, without compromising the oocyte quality.[24] Other precautions during ovum pickup are the use of strict asepsis in the surgical field, avoiding repeated punctures of the vaginal wall and ovarian capsule and avoiding punctureand aspiration of the endometrioma. Accidental contamination of follicular fluid with endometrioma content may reduce the pregnancy rate.[25]

What is the role of USG guidedaspiration?

No Roleof aspirating enddometrioma. There are side effects like pelvic adhesions and ovarian abscess

Treatment of Adenomyosis in Infertility

Treatment of adenomyosis with hypoestrogenic agents or surgical removal of the adenoma lesions may improve 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

For women 35 years of age or older, more aggressive treatment, such as superovulation/IUI or IVF may be considered.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[2].In women with Stage III-IV endometriosis associated infertility, conservative surgical therapy with laparoscopy may be beneficial. Moderate tosevere endometriosis with prior one or more infertility operations, IVF-ET is better therapeutic option than another infertility operation.

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Surgical Management of Endometriosis

DR KULDEEP JAIN
Director
KJIVF and Laparoscopy Centre

DR MAANSI JAIN
Senior Resident
Kasturba Hospital

"He who knows Endometriosis, knows Gynecology"
---Sir William Osler

Endometriosis is a common and debilitating condition that can have a significant impact on the quality of life of the sufferer. It is a disease of controversy / complexity , chronic / multi – factorial, progressive / recurrent, not malignant but behaves like one and Difficult to diagnose and treat. Once diagnosed clinically and by various imaging modalities, there is a wide variation of interventions available for treatment ranging from ovarian suppression with hormonal agents to radical excisional surgery. This suggests that the condition is heterogeneous and that there is a lack of consensus over optimal management. Laparoscopy remains gold standard and is the best tool for diagnosis, treatment and follow-up evaluation of endometriosis.

Choice of management depends on the presenting symptoms , age , fertility history and progression and recurrence. If the primary symptom is pain and fertility is not the issue, definitive surgery with as much cytoreduction as possible, is the treatment of choice. However if the fertility is the issue or patient is young, a conservative approach is recommended. Medical treatments that inhibit ovulation have been found to be effective in reducing pain in 80–90% of women.[1]. Medical therapy, however, is not cytoreductive and pain recurrence is frequent after treatment withdrawal.[2] Moreover, side effects and costs discourage long-term use and it does not improve pregnancy rates in women with associated infertility.

For generations it has been taught that abdominal hysterectomy and removal of both ovaries is the definitive surgery for endometriosis. However, our understanding of the disease has evolved. Technological advances in camera optics and electrosurgical devices and improved surgical experience, combined with the limitations of medical treatment, now make operative laparoscopy the preferred management choice for a considerable proportion of women.

In the current article, we aim to look at the evidence for the various different surgical approaches according to the location of the disease and to discuss their benefits and limitations and complications. In view of involvement of different sites and organs , we can divide the surgical management as per the organ involved however if more than one site is involved ,techniques may be combined . The surgical management of endometriosis involves careful consideration of the indications for surgery, preoperative evaluation, surgical techniques, surgeon experience, and ancillary techniques and procedures.

Indications Of Surgical Management

Surgical management of endometriosis is indicated in the following groups.

1. Patients with pelvic pain

- who do not respond to, decline, or have contraindications to medical therapy
- who have an acute adnexal event (adnexal torsion or ovarian cyst rupture).
- who have severe invasive disease involving the bowel, bladder, ureters, or pelvic nerves .

2. Patients who have or are suspected to have an ovarian endometrioma

- Patients for whom the uncertainty of the diagnosis affects management (as with chronic pelvic pain).
- Patients with infertility and associated factors (i.e. pain or a pelvic mass)

Surgical techniques

- Excision of lesions
- Fenestration and Ablation (Fulguration or Vaporization)
- Total Cystectomy
- Cystectomy with Combined Technique - Adehesiolysis and nodule resection / excision

Ovarian disease

Endometriotic deposits within the ovary are commonly referred to as endometriomas. (Fig 1) However the disease usually starts as surface endometriosis .Their pathogenesis is uncertain but they are thought to result from progressive invagination of the lateral ovarian aspect after adhesion to the pelvic peritoneum. According to this theory, an endometrioma is, therefore, a pseudocyst, the wall of which is the inverted gonadal cortex. If the fertility is an issue or in young patients before deciding for surgical approach one should access ovarian reserve by AFC and AMH and a thorough counselling is required before taking decision for surgery .

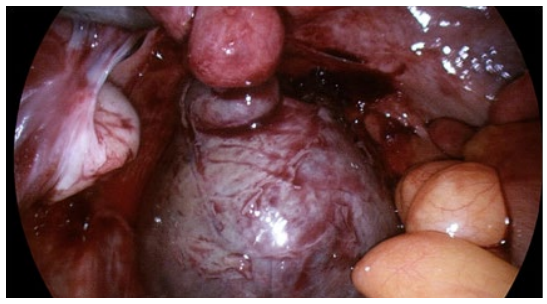


Fig 1: Endometrioma

Controversy exists between two approaches to treatment: excision of the cyst capsule or drainage and electrocoagulation of the cyst wall. One would expect the latter to be adequate if the pseudocyst theory of pathogenesis is correct. However, a Cochrane review,[3] which included two randomised controlled trials, found that laparoscopic excision of the cyst wall was associated with a lower rate of recurrence and a higher pregnancy rate when compared with drainage and ablation. There is a possible explanation for this apparent failure of ablative techniques. It could be that the depth of endometrial glandular invasion into the cortex of the ovary may be greater than the depth that most commonly used ablative modalities can reach. Stripping technique: This technique takes care to minimize damage and inadvertent removal of normal ovarian tissue.[4] Drainageshould be performed through single incision. Identify cleavage plain, gentle stripping to prevent bleeding. Another method to minimize complications and damage to normal tissue is infiltration of diluted vasopressin before stripping. Also, one should avoid excessive use of bipolar cautery.[5]

Another innovative technique to reduce the risk of decreased ovarian reserve is a combined technique of stripping and ablation as suggested by Donnez which involves partial cystectomy followed by ablation in area of hilum. [6]

Analysis of anti-Müllerian hormone (AMH) levels showed that surgery for ovarian endometriosis was associated with a significant decrease in AMH concentrations. AMH levels decreased by 24% after unilateral surgery and by up to 67% after bilateral surgery. Surgeon must weigh the necessity for adequate excision against the potential iatrogenic decrease in ovarian reserve. Despite the fact that excision of the entire cyst wall is more destructive to the ovary than coagulation, the available evidence suggests that it should be regarded as the standard treatment for endometriomas.

Principles of Surgery

- Good surgical techniques
- Meticulous haemostasis
- Operating in right planes
- Gentle tissue handling especially tubes.
- Minimal use of cautery

Tips for optimal surgical outcome

1. Perform all endometriosis surgery in post menstrual phase – reduces risk of recurrence
2. First surgery is always the best opportunity so should be done meticulously by an expert gynae endoscopic surgeon .
3. Always keep in mind about future fertility before taking decision on type of surgical technique .

4. Asses ovarian reserve by AFC and AMH and counsel the patient accordingly.

Peritoneal disease

Endometriotic implants can be found throughout the pelvic peritoneum. They are typically superficial and their appearance varies.(Fig 2)

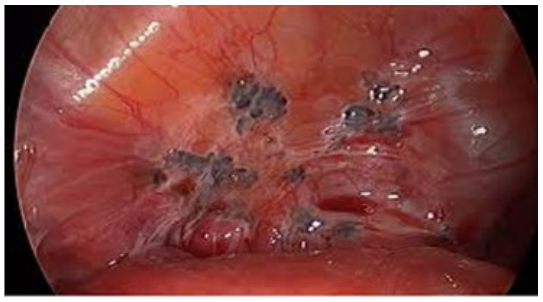


Fig 2: Peritoneal Endometriosis

Laparoscopic ablation using a carbon dioxide (CO_2) laser was first introduced in the early 1980s. Since then other modalities for ablation have been applied, such as bipolar diathermy and techniques for excision of implants using monopolar electrosurgery, bipolar scissors and the harmonic scalpel.

Reports from uncontrolled studies suggest symptomatic relief in 60–70% of women following ablation of peritoneal endometriotic implants.[7] It was not until 1994, however, following the publication of the Guildford laser laparoscopy trial,[8] that evidence from a randomised controlled trial was published. This study randomised 63 women with stage I–III endometriosis to either laparoscopic laser ablation or diagnostic laparoscopy alone. At the 6-month follow-up, 62.5% in the laser group were improved compared with only 22.6% in the control group. The response to surgery was poorest in those women with minimal disease. The trial protocol did not permit peritoneal biopsies so it is possible that some of these women did not have endometriosis. When women with stage I disease are excluded from evaluation, the benefits of surgery are seen to improve, with 73.7% of them achieving pain relief at 6 months. In a follow-up of this cohort 12 months after surgery, symptomatic relief continued in 90% of women who had originally responded.[9]

A survey of UK practice published in 2004 [10] indicated that 85% of consultants regularly perform laparoscopic surgery for endometriosis. The vast majority use diathermy to ablate these deposits. While there appears to be evidence for the effectiveness of laser ablation, no similar study has been conducted to assess the use of diathermy, despite its popularity. The popularity of diathermy ablation probably reflects the relative simplicity of the procedure, the cost and the availability of the energy source.

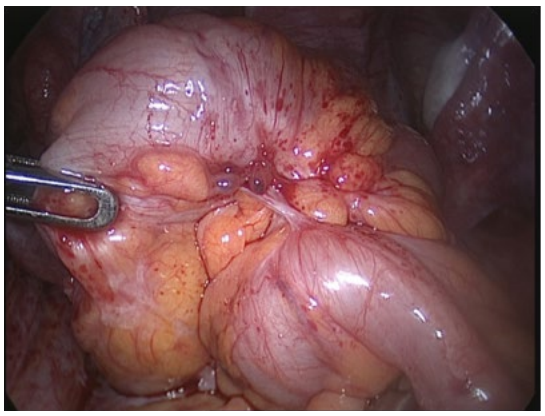
According to current available evidence, only 62.5% of women improve following laparoscopic ablation. One reason for this may be that the disease is deeper than the energy source is able to with deeper peritoneal disease should, therefore, benefit from excisional surgery. penetrate. Women Fewer than 20% of UK consultants performing laparoscopic surgery for endometriosis use excisional methods. This probably reflects the higher level of training required to gain competency in these techniques.

Evidence for the effectiveness of excisional procedures for deeper peritoneal disease is mainly limited to retrospective case series. In a series of 135 women followed up for between 2–5 years following laparoscopic excision of endometriosis, Abbott et al.[11] demonstrated significant reductions in pelvic pain and improvement in quality of life and sexual function. However, 36% of women required further surgery for persistent or recurrent pain. Interestingly, in one-third of these women there was little or no endometriosis visible at laparoscopy.Recurrence rates following laparoscopic excision of endometriosis have also been reported. In a series of 359 women, Redwine12 found that the maximum cumulative rate of recurrent or persistent disease was 19% achieved in the fifth postoperative year.

Abbot et al.[13] have published a placebo-controlled randomised trial examining the effectiveness of laparoscopic excision for all stages of endometriosis. Significant symptomatic improvement was found in 80% of women following excisional surgery compared with 32% who just had diagnostic laparoscopy. Whilst this demonstrates the value of surgery, the fact that 20% of women did not respond despite optimum treatment in a tertiary centre should lead clinicians to continue to search for improvements in surgical techniques and advances in adjuvant therapies. It also demonstrates the powerful placebo effect of laparoscopy, which was not dependent on the severity of disease.

Endometriosis of the bowel and bladder

Rectovaginal disease accounts for at least 5–10% of cases.14 Endometriosis can involve the bowel, including the lower rectum, sigmoid colon, terminal ileum, caecum and proximal ascending colon. (Fig 3 A & B) The depth of involvement can range from serosal to mucosal. Bladder lesions can also extend through the wall into the mucosa and, occasionally, lesions cause such a degree of stenosis proximal to the ureteric tunnel that hydroureteronephrosis and renal destruction result.



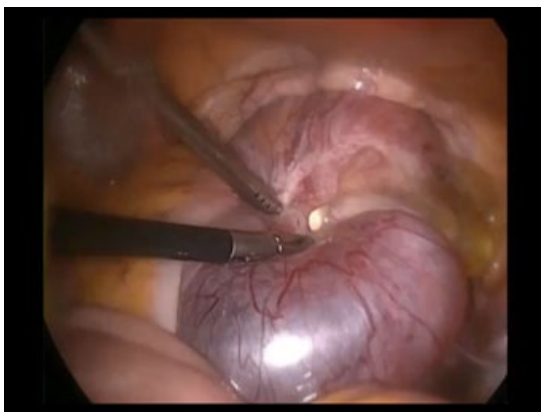


Fig 3 A&B : Endometriosis on bowel

Endometriosis on the surface of the ileum

Medical treatment seems to be particularly ineffective in the treatment of deep disease of the cul-de-sac, even when combined with surgery.[15] Hence, many authors have suggested the complete and radical extirpation of disease, regardless of its site.[16]

Diagnosis and staging are often difficult without laparoscopy but may be aided by transvaginal ultrasound and magnetic resonance imaging (MRI). Digital examination may identify nodules in the uterosacral ligaments or cul-de-sac but the detection of a nodule per se, even one penetrating the posterior fornix, does not necessarily imply true rectal involvement. Assessment in such cases should include an ultrasound assessment of the ureters and kidneys or intravenous urography to detect evidence of ureteric obstruction. In the presence of hydronephrosis, consideration should be given to performing a MAG 3 or DMSA scan to assess individual renal function.

In recent years laparoscopic surgery has led to significant developments in the surgical management of rectovaginal disease by enhancing access to the rectovaginal space and allowing greater accuracy in delineation of disease. Surgical techniques range from debulking of rectal lesions through disc resection to large-scale bowel resections of a kind normally employed for cancer. Unfortunately, there is no current consensus as to the best approach.

In an analysis[17] of the histological findings in a series of rectal specimens removed for endometriosis, disease was present in the muscularis propria in 100% of cases. This implies that simply debulking rectovaginal endometriosis could leave significant disease behind. The same study showed that 62% of endometriotic bowel lesions are multifocal and 38% are multicentric. This would suggest that disc resection also risks leaving residual disease. Bowel resection should remove all the endometriosis but, as it is more radical, the morbidity may be higher.

Evidence suggests that radical extirpation of the disease conveys very real benefits in terms of symptom resolution and fertility, with complete or near-complete resolution of specific symptoms in up to 95% of women.[18] Fedele et al.[19] found that symptomatic disease recurrence within 3 years affected only 25% of women who received conservative (fertility sparing) treatment for rectovaginal disease. Interestingly, they found the risk of recurrence to be higher for younger women and lower if the surgery included segmental bowel resection and anastamosis. In the series published by Redwine and Wright,[20] the recurrence rate was slightly higher, with 23 women (34%) reporting the need for further treatment (13 medical and 10 surgical).

Unfortunately, there is no consistency in the surgical methods described. Until a properly conducted randomised controlled trial is performed it will not be known whether complete resection with disease free margins is necessary, which method has the lowest risk of disease recurrence, or which technique has the highest morbidity in terms of rectal stenosis or fistula.

All of these surgical techniques carry a significant morbidity risk and extensive counselling is,

therefore, mandatory when they are contemplated. Surgery should ideally be performed in centres where there is a multidisciplinary team available with the necessary skills and experience to manage women with these complex issues. At a minimum, such teams must include gynaecological, colorectal and urological surgeons, as well as pain specialists. Indeed, a previous consultant survey in the UK[21] identified the very real need for the development of tertiary centres for the management of advanced endometriosis.

Prevention of gastrointestinal complications

- Prior to Surgery: PV / PR examination
- Trans Vaginal / Trans Rectal ultrasound
- Imaging dynamic / spiral CTS / MRI – bowel preparation?!
- In high risk cases such in severe endometriosis involving the colon and recto-vaginal space and patients with history of previous GIT operation Intraoperative: - Nasogastric tube / mask ventilation (avoid stomach distention)
- Avoid Nitrous oxide - Vaginal packing / uterine manipulator
- To opt for the lateral dissection
- Attention to the electrical current used / bipolar is by far better
-

Bladder endometriosis (Fig 4)

- ***Superficial peritoneal implants:*** On bladder, careful dissection with skinning technique, closure of defect with 3.0 monofilament.
- ***Infiltrative lesions of mucosa in bladder dome***: Partial cystectomy. Close bladder in two or three layers with methylene blue control.
- ***Posterior wall of bladder or trigone:*** Insertion of double J stents 6-8 weeks postoperatively and urinary catheter for 7-10 days.
- ***Adhesions between the anterior uterine wall and the vesico-uterine fold:*** Should be divided before performing partial cystectomy
- ***Control by cystoscopy***

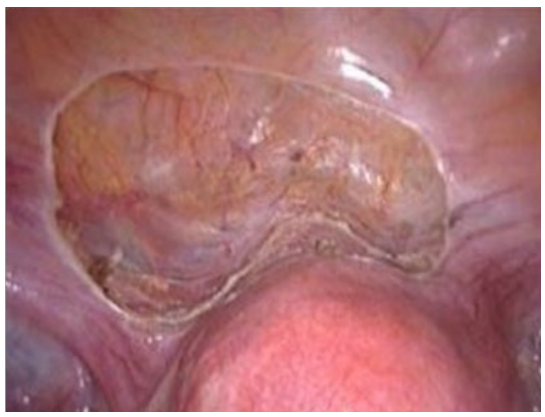


Fig 4: Bladder endometriosis

The role of hysterectomy and oophorectomy

In conservative surgery ,the endometriotic implants are excised or ablated, leaving the reproductive organs in place. Hysterectomy and removal of both ovaries is often offered as a treatment to women who have failed to respond to medical therapy or conservative surgery. Despite the lack of robust scientific evidence to support this practice, it is often described as being the definitive treatment.

As, it is defined as an extrauterine disease, it would appear irrational to remove the uterus when treating endometriosis. However, improvements in symptoms following hysterectomy and oophorectomy are often reported. This could be explained by the presence of associated pathology such as ovulation pain, adhesions, primary dysmenorrhoea or adenomyosis. With this caution in mind, many studies do suggest benefits from hysterectomy if excision of extrauterine endometriosis is performed at the same time. In a follow-up study of women undergoing radical excision of rectovaginal endometriosis at Worthing Hospital,[22] those women who had a concurrent hysterectomy reported better pain scores than those in whom the uterus was conserved.

Debate remains over the benefits of concurrent oophorectomy and there are no randomised controlled trials to help resolve this issue. Results from observational studies suggest that oophorectomy has some advantages. In a series of 138 women undergoing hysterectomy for endometriosis, Namnoum et al.[23] reported that 62% of women had persistent pain when the ovaries were conserved, compared with 10% when the ovaries were removed. The relative risk for repeat surgery in women with ovarian conservation was increased by 8.1%. Whilst oophorectomy does not appear to completely eliminate the symptoms of endometriosis, there does appear to be some benefit. Redwine[24] found that persistent pain was more common following this procedure when invasive disease was present and left in place. Fortunately, for those who remain symptomatic, excision of persistent disease can result in pain relief.

Pelvic denervation

Pelvic denervation can be used to interrupt the sensory nerve supply to the uterus in an attempt to reduce symptoms of dysmenorrhoea. The most commonly described and evaluated procedures are laparoscopic uterine nerve ablation (LUNA) and presacral neurectomy (PSN).

Laparoscopic uterine nerve ablation: Laparoscopic uterine nerve ablation involves dividing the sensory parasympathetic fibres to the cervix and the sensory sympathetic fibres to the uterus contained in the cervical division of the Lee–Frankenhäuser plexus. This is achieved by creating a 1 cm deep and 2 cm wide incision in the uterosacral ligaments close to their point of attachment to the cervix, using a CO_2 laser or electrosurgery.

Presacral neurectomy: Presacral neurectomy involves division of the hypogastric plexus of nerves at the sacral promontory. LUNA can be described as a simple operation that is achievable by most laparoscopic surgeons with minimal training. Because of its proximity to major vessels, PSN has a much higher rate of morbidity and consequently requires much higher levels of skill and training.

Observational studies have supported the use of LUNA for primary and secondary dysmenorrhoea and there is either complete or substantial reduction in menstrual pain in most participants. Unfortunately, success rates have been shown to decline rapidly over time. There are also concerns about anatomical distortion and subsequent uterine prolapse or bladder dysfunction.

Vercellini et al.[25] conducted a randomised controlled trial comparing laparoscopic excision of endometriosis plus LUNA with laparoscopic excision of endometriosis alone. The results showed no difference in the perception of menstrual pain one year after surgery, with 75% in the LUNA group and 74% in the excisional surgery-only group reporting satisfaction over a range of symptoms. The author's conclusion that LUNA does not give any additional benefit in terms of satisfaction or recurrence of pain for women having laparoscopic surgery for endometriosis, is supported by a recent Cochrane review.[26] Interestingly, this review did find that PSN with conservative surgery for endometriosis was more effective than conservative surgery alone. The largest study, by Zullo et al.,[27] reported a 'cure' rate of 86% at one year after excisional surgery with PSN compared with 57% after excisional surgery alone. Whilst these results should encourage further studies to evaluate the effectiveness of laparoscopic PSN, the complexity of the procedure will restrict its use to tertiary centres.

Guidelines to minimize risks and comp-lication

- Patient counselling and pre operative investigation
- Referral centres with Multi disciplinary approach
- Instrumentation and surgical team
- Sound knowledge of pelvic anatomy
- Organ sparing surgery and microsurgical technique
- Documentation of procedure
- Short term and long term follow up
- Check instruments insulation
- Usage of lowest possible power
- Use low voltage (cut) waveform
- Interrupted and not continuous activation
- Do not activate when open circuit
- Do not activate when the diathermy touches another instrument

Conclusion

Laparoscopic ablation of endometriosis for superficial disease and excision of deep disease appear to be effective and offer significant advantages over medical therapy. Laparoscopic surgery should, therefore, be regarded as the 'gold standard' of care. Our understanding of endometriosis, however, is far from complete and many women remain resistant to treatment. Efforts must continue to improve results further.

Efforts should also be made to preserve fertility but when this is not necessary there appear to be benefits from hysterectomy and oophorectomy, provided extrauterine disease is excised at the same time.Whilst surgery remains the best treatment for deep rectovaginal disease, there is no consensus as to the best approach. A multicentre, randomised controlled trial is urgently needed to help resolve this issue.

Developments in the surgical management of endometriosis are almost entirely the result of advances in laparoscopic surgery. So that women suffering from endometriosis receive optimal treatment, we must ensure that there is adequate surgical training in laparoscopic techniques for the management of superficial disease and the organisation of tertiary centres for the management of deep infiltrating disease.

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Medical Management in endometriosis and its role in infertility treatment

DR RUPALI BASSI GOYAL
Senior Consultant
IVF & Laparoscopy
Neelkanth hospital Pvt Ltd , Gurgaon
World IVF Hospital, New Delhi

Endometriosis is an estrogen dependent chronic gynaecological disease, with an overall incidence of 10% in the general population and upto 40 % in patients with sub fertility or pelvic pain. The two primary symptoms of this disorder are pain and infertility. Traditionally the medical management was restricted to the addressing the issues of pain associated with endometriosis.

It requires a life-long personalized management plan with the goal of maximizing medical treatment and avoiding repeated surgical procedures[1]. There are various factors which guide the clinician on the therapeutic modalities available. Various factors need to be assessed before a patient is started on a medical therapeutic modality. The age, extent of the disease, chronicity of pain, need for fertility, contraception and the preoperative or post operative status.

Rationale for medical therapy

It is well known that endometriosis is an estrogen dependent disorder. Endometriotic lesions have shown an increased production and decreased inactivation of estradiol. This is due, in part, to abnormal expression of both aromatase and 17-beta hydroxysteroid dehydrogenase. Common medical therapies used to treat symptoms of endometriosis such as pelvic pain, dyspareunia, dysmenorrhoea and dyschezia target ovarian estrogen production. They produce a hypoestrogenic environment causing decidulization and subsequent regression of implants.

The treatment of endometriosis-associated pain is based on suppressing estrogen production and inducing amenorrhea. This creates a relatively hypoestrogenic environment that inhibits ectopic endometrial growth and prevents disease progression[2].

Ideal Drug for endometriosis[3]

An Ideal drug for endometriosis should be curative rather than suppressive.

- The management of endometriosis usually continues for a long term, therefore the

safety profile of the drug is one of the most imperative features guiding the therapy.
- Cost concerns in long term treatment also form the primary concern of the patients.
- Side effects of the drug should be minimal, allowing the patient for a long term use of the drug.
- The drug should neither have contraceptive action nor interfere with spontaneous ovulation and normal implantation of the endometrium to enhance spontaneous conception.
- There should be no teratogenic potential in case of inadvertent use during the first trimester of pregnancy.
- The drug should suppress the growth of already existing lesions and prevent the development of new ones.
- The drug should help to prevent the complications associated with advanced endometriosis and hence limiting the need for repeat surgery.
- Finally, they should be efficacious for all disease phenotypes, including superficial disease, endometriomas, deep infiltrating endometriosis, extrapelvic disease, and adenomyosis

Therapeutic modalities for management of Endometriosis in patient not wanting to conceieve

The main medical therapeutic options can be classified as (Table 1)

Therapeutic modalities for management of pain

The various options available for management of pain due to endometriosis are pharmacological modalities

I. Non Hormonal

1. Analgesics
2. Neuropathic and Neromodulators
3. Anti Angiogenic drugs
4. Immunomodulators

II. Hormonal modalities

1. Oral contraceptives
2. Progestins – Natural And Synthetic agents
3. Antiprogestins
4. Danazol- oral and intrauterine system
5. Levonorgesterol Intrauterine System LNG - IUS
6. Gonadotropin Releasing hormone agonists
7. Estrogen Receptor inhibitors
8. Selective estrogen receptor modulators (SERMS)
9. Selective Progesterone receptor modulators (SPRMS)
10. Aromatase inhibitors

Efficacy of medical management for pain

Various evaluations have been reported in literature, where the efficacy of medical management in symptomatic endometriosis have been tested.

In recent systematic review of articles showed no reduction in pain were 11%–19%, at the end of treatment and 5%–59% had pain remaining after follow-up of twenty four months. It was observed that 17%–34% had experienced recurrence of pain symptoms after treatment cessation. After median study durations of 2–24 months, the median discontinuation rates due to adverse events or lack of efficacy were 5%–16%. Finally the author concluded that more patient centeric trials need to be performed to evaluate the response[4].

Hormonal management

Oral Contraceptive Pills

Oral contraceptives have been the mainstay of management for endometriosis, especially after surgical ablation, to maintain the status quo and prevent progression or recurrence. First introduced over 30 years ago, the dosages have been significantly reduced and can be administered continuously as a first line of treatment.

There has been no significant difference between various oral contraceptives, but it seems sensible to use preparations with the least possible estrogen content to prevent endometrial proliferation[5].

Mechanism of Action: Suppression of ovarian function prevents ectopic or eutopic endometrial growth for six months reduces endometriosis-associated symptoms.

Advantages: There is a symptomatic improvement of dysmenorrhoea and heavy menstrual bleeding when taking oral contraceptive pills.

In an overview of Cochrane review it was noted that oral contraceptives were as effective as other forms of hormonal treatment, although the level of evidence was low. The evidence is limited, although oral contraceptive pills are commonly used to treat endometriosis-associated pain; they can also serve as contraception, regulate the menstrual cycle, and have a long-term safety profile. Apart from contraceptive benefit, it also helps in regularizing the menstrual cycle.

Prolonged usage may even help in regression of small lesions.

Progesterone and Progestational agents

Progesterones in natural and synthetic forms have now replaced the oral contraceptives as first line of management of endometriosis[6].

Mode of Action: The main mechanism by which progestational agents act is causing atrophy and decidualization of the endometrium.

Routes of administration - Oral and Intramuscular depot oral, subcutaneous, intrauterine device (LNG IUS) and vaginal route.

The most commonly used progestational agents are Norethisterone acetate. Dienogest, is a new synthetic progestational agent increasingly being used in cases of endometriosis. Studies have shown significant symptomatic benefit in term of pain and bleeding, with the use of these agents.

Dienogest

Dienogest is a fourth-generation progestin of 19-nortestosterone derivative.

Mechanism of action: It is well tolerated with no androgenic, glucocorticoid or mineralocorticoid activity. It binds to the progesterone receptor with high specificity, and produces a potent progestogenic effect related to the high circulating levels of the unbound molecule.

It is associated with 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 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 duration of 12-24 weeks.

Dienogest is equally effective in reducing pelvic pain when compared to GnRH agonists. However, dienogest has less hypoestrogenic side effects. There is a little effect on the bone mineral density. It has shown to have a higher incidence of abnormal menstrual bleeding patterns, which usually settles after 90 days of treatment duration and is generally well tolerated by patients[7].

Vercillini P et al recently analysed the overall patient satisfaction in patients with endometriosis comparing Dienogest to norethindrone acetate. He observed that although the tolerability was statistically significantly improved by the use of Dienogest vs Norethidrone but the overall satisfaction with treatment was almost identical in the two cohorts

He further concluded that the use of Dienogest as the first-choice progestin for the medical therapy of symptomatic endometriosis does not offer additional benefits compared with norethindrone acetate in terms of pain relief, health-related quality of life, or sexual functioning[8].

Levonorgestrel Intrauterine Device (LNG-IUD)

The levonorgestrel intrauterine device is an effective treatment modality for endometriosis.

Mechanism of action: The main mechanism of action is by releasing 20 mcg of levonorgestrel per day for up to 5 years. It causes primarily decidualization of the endometrium resulting in decreased menstrual flow. It also acts on endometriotic foci by causing a down regulation of the estrogen receptors. This causes the ectopic foci of endometrium to reduce in size, allowing the uterus to contract more efficiently, reducing menstrual blood loss, and resulting in decreased prostaglandin production, improving dysmenorrhoea and the pain scores.

Side effects: few patients with adenomyosis and intrauterine LNG can have heavy menstrual bleeding, persistent irregular bleeding and expulsion of the IUD after 2 months.

There is a documented improvement in symptoms of heavy menstrual bleeding and dysmenorrhoea, alongwith a discernible change in the radiologic changes following the insertion of the LNG-IUD.

Radiologically, there was a reduced uterine volume, significant reduction in junctional zone thickness. This further resulted in significant increase in haemoglobin, hematocrit and serum ferritin one year after of usage.

In a randomized, controlled multicenter study involving 83 patients with endometriosis performed by Petta and colleagues in 2005, the Levonorgestrel-releasing intra-uterine system was compared with monthly leuprolide acetate. After 6 months of treatment, both groups had significantly reduced visual analogue pain scores, but no difference was found between the groups [9].

It was observed that there was an overall patient satisfaction rate was 72.5%. They concluded that the LNG-IUD is effective at reducing uterine volume with improvement of vascularity and patient's symptoms; however the beneficial effects would appear after a minimum of 2 years post insertion.

Selective Progesterone Receptor modulators (SPRMS)

It has been observed that the endometriotic lesions produce significant quantities of progesterone, although they contain strikingly lower levels of progesterone receptor (PR) with endometrium. It has been observed that SPRMs interact with the PR, allowing the binding of antiprogestins with mixed agonist and antagonist properties (SPRM), therby reducing endometriosis associated pelvic pain.

Mifepristone (RU486): It being the most clinically studied SPRM, has been used mostly for the induction of medical abortions. Mifepristone was shown by the same group to have a positive effect on pain symptoms; it is interesting that it induced amenorrhea without causing hypoestrogenism in 16 patients with endometriosis. However, these findings have not been substantiated in an RCT compared with placebo or other hormone alternatives.

Ulipristal acetate: It is another member of the same family. Ulipristal acetate is approved for clinical use as an emergency contraceptive in the United States and for the treatment of fibroids in Europe and Canada. It has been observed that Ulipristal also lead to the regression and atrophy of endometriotic lesions in rats through its proapoptotic effects. In addition, treatment with Ulipristal reduced cellular proliferation, as indicated by a decrease in Ki-67 expression, and has an anti-inflammatory effect, as shown by a decrease in cyclooxygenase-2 expression. The feasibility of Ulipristal acetate for the treatment of endometriosis has yet to be determined.

Asoprisnil: It is another SPRM, was shown to statistically significantly reduce non-menstrual pelvic pain but further studies need to be conducted before it can be used freely[3].

Tanaproget: It is a newly developed SPRM used to down-regulate endometrial matrix metalloproteinase expression in vitro and regress experimental endometriosis in vivo. Tanaproget effectively down-regulated matrix metalloproteinase expression in vitro and induced a statistically significant reduction of lesions in mice with disease established by tissues from endometriosis patients. The feasibility of using tanaproget in humans has yet to be evaluated [3].

Danazol

Danazol can be given by Routes – Oral and Danazol loaded intracervical injections and intrauterine devices. Danazol acts by suppressing pituitary release of FSH and LH and therefore causes atrophy of both normal and ectopic endometrial tissue. Systemic treatment with Danazol has been shown to decrease expression of aromatase cytochrome P450 in disease eutopic endometrium; this may contribute to improvement of symptoms and reduced uterine size.

Route of administration

Oral - It is not well tolerated by many patients because of its side effect profile which can include acne, depression, deepening of the voice, hirsutism, hot flashes, decreased high-density lipoprotein levels, increased liver enzyme concentrations, oily skin, muscle cramps, reduced breast size, and weight gain.

Intrauterine injections and device- Novel ways of treating endometriosis with Danazol are being studied such as intracervical injections and with Intra Uterine devices. These methods allow local delivery of hormones in an attempt to minimize systemic side effects. It was observed that the Danazol IUD/ and injections did not cause any of the side effects typically observed with oral therapy. There was a significant symptomatic relief and an immediate return of the fertility after withdrawing the administration of Danazol.

Side Effects Danazol is not suitable for prolonged treatments, mainly owing to androgenic-type adverse effects (seborrhoea, hypertrichosis and weight gain) and unfavourable effects on serum cholesterol lipoprotein distribution (HDL levels decrease, and LDL levels increase).

Selective Estrogen Receptor modulators SERMS

Selective estrogen receptor modulators example Tamoxifen, Raloxifene etc may be preferred agents in management of Endometriosis due to their differential ER expression in a given target tissue. This results in differential expression and binding to the ER coregulator proteins. Ideal SERM should have an antagonist estrogenic activity on endometrium with an agonist activity in the bone and serum.

Raloxifene: Studies have shown that Raloxifene in doses of 10.0 mg/kg produced statistically significant implant regression. Although, there have been a few studies but a short placebo controlled trial of six months was prematurely terminated due to significant pain and second surgery in the Raloxifene group.

Bazedoxifene: Bazedoxifene is a third-generation SERM, effectively antagonizes estrogen-induced uterine endometrial stimulation without countering estrogenic effects in bone or the central nervous system. It is known to reduce the size of endometriosis lesions, with experimental evidence of an antiproliferative effect in rat models[3].

Antiprogestins (Gestrinone)

Anti progestational drugs like Gestrinone (ethylnorgestrienone) have been used for treatment of endometriosis. The mechanism of action includes a progestational withdrawal effect at the endometrial cellular level and inhibition of ovarian steroidogenesis. Long Term use of Gestrinone has shown to cause androgenic side effects, so has currently not been used for the same.

GnRH Agonists

GnRH agonists cause a suppression of pituitary gonadotropins and thus induce ovarian quiescence, resulting in a medical menopausal, hypoestrogenic state thereby reducing the manifestations of endometriosis.

Mode of Administration: Subcutaneous injections or Intranasal spray.

Effect: Studies have shown that patient's symptoms of heavy menstrual bleeding and dysmenorrhoea completely resolved and her uterine volume decreased. Cochrane analysis found that GnRH-analouges were more effective than placebo for endometriosis pain relief but were similar to the LNG-IUS and Danazol. A long-term follow-up study of patients treated with a GnRH-a alone for 6 months revealed a 53% recurrence of disease/ symptoms 2 years after treatment.

Side Effects: Primarily the hypoestrogenic adverse effects (for example, vasomotor symptoms, genital hypotrophy and mood instability), and a negative calcium balance with increased risk of osteopaenia, although bone loss seems to be reversible if treatment is limited to a few months. The initial flare effect seen following administration of the depot in some patients causes aggravation of symptoms. The add-back therapy should be started at the same time as the agonist rather than delaying until a period of hypoestrogenism has occurred. This approach has been shown to decrease bone loss and improve vasomotor symptoms and compliance.

GnRH Antagonists

Mode of action: GnRH Antagonists Gonadotropin-releasing hormone antagonists prevent binding of endogenous GnRH to its pituitary receptors, which are not down-regulated. Thus, titrating GnRH antagonists dosage allows modulation of inhibition of ovarian E2 synthesis. Several phase 3 trials have recently been published demonstrating the dose dependent superiority of **Elagolix**, an oral, nonpeptide, GnRH antagonist, over placebo in reducing endometriosis-associated dysmenorrhea and nonmenstrual pain[3].

Side Effects: There is a dose-dependent reduction in bone mineral density, apart from the usual side effects of using GnRH analouges. Further research is required to determine the duration of GnRH analogue treatment that will result in symptomatic improvement while minimizing risk of long-term side effects and delay in patients wanting to conceive.

GnRHAnalouges in Infertility

It has been stated in the Cochrane reviews that a pretreatment with a gonadotropin-releasing hormone (GnRH) agonist for 3- 6 months before in vitro fertilization (IVF) has shown to improve clinical pregnancy as compared with controls. However, NICE 2017 guidelines do not support the

use of pretreatment Gnrh Analogues in patients wishing to conceive. Similarly, the Royal college of UK and Cochrane database did not find any significant difference with the use of with ovulation suppression agents (Medroxyprogesterone, Gestrinone, combined oral contraceptives and Gonadotrophin-releasing hormone agonist), in improving clinical pregnancy rates in women with endometriosis associated infertility compared with no treatment. or Danazol Postoperative use of GnrH analouges in patients with infertility has been advocated in cases to reduce the size and volume of the residual lesion. Once given in the postoperative phase they can further help in eliminating the disease.

GnRH analogue recommended in women with pelvic pain symptoms who undergo laparoscopic conservative surgery for endometriosis stage III–IV.
Dose: Single dose of depot injections per month for the 3 months, starting in the postoperative period. It can be given as a single 3 monthly injections as well.

Aromatase Inhibitors
Aromatase cytochrome P-450 converts androgens to estrogens. 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. Aromatase inhibitors (AIs) inhibit local estrogen production in endometriotic implants, the ovary, the brain, and adipose tissue.

Aromatase inhibitors are usually used in cases of severe, intractable endometriosis associated pain in combination therapy with oral contraceptive pills, progestins, and GnRH analogues.

Various studies demonstrated that AIs combined with either progestins or Oral contraceptives reduced the severity of endometriosis-related pain, lesion size and improved quality of life[10].

Dose: Letrozole can be used at 2.5 mg daily, whereas anastrazole is used in a dose of 1 mg daily. Letrozole's effect is comparable to oral contraceptive pills in endometriosis-related pelvic pain.

Although Individual studies have reported a 75% reduction in the endometrioma volume and pain with a three month usage of the drug, but the patients should be counselled about the off-label nature of its use for endometriosis-associated pain[11].

Nonhormonal

Management Analgesics
The management of pain in most cases of endometriosis is initially empirical. It has been observed that the women experience symptom improvement by taking non-steroidal anti-inflammatory drugs, which inhibit cyclooxygenase, the enzyme involved in the production of prostaglandins. Although, the effectiveness of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating endometriosis-associated pain is not well established because of the lack of studies but still they form the first line in management of endometriosis related pain. Various other pain relieving agents like Naproxen sodium (275mg, 4 times per day) Cox2 inhibitors, oral cyclooxygenase (COX)-2 inhibitor (Rofecoxib) have been studied, but there was no significant evidence of a moderate to excellent pain relief following the use of these agents.

Anti angiogenic drugs [12]
One of the key processes involved in the pathogenesis of endometriosis is development of new blood vessels from the pre-existing ones, known as angiogenesis. These include growth factor inhibitors, endogenous angiogenesis inhibitors, Fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists and peroxisome proliferator-activated receptor agonists. These agents have been proven in experimental studies to induce the regression of endometriotic lesions by targeting their blood supply. However, clinical evidence for the efficacy of anti-angiogenic treatment strategies in endometriosis is still lacking. These drugs are paving a way for development of novel therapeutic regimens of endometriosis, with fewer side effects and increased efficacy.

Immunnomodulators
Tumor necrosis factor-α, a proinflammatory cytokine able to initiate inflammatory cascades, is increased in the peritoneal fluid and serum of women with endometriosis. It has been implicated in the pathogenesis of endometriosis. In a RCT using a baboon model, a TNFα blocker (**Etanercept**) was evaluated. It led to a statistically significant decrease in red lesion surface area in the treatment group with a trend toward a decrease in the absolute number of red lesions. There is still a need to conduct studies on larger scale on human beings, considering the potential of this form of therapy[3].

Non Pharmacological Methods

Dietary supplements, transcutaneous nerve stimulation, traditional Chinese medicine, and acupuncture have not shown to be effective for the management of endometriosis. Few other modalities like the herbal medicine, sports and exercise. However, the ESHRE guideline development group acknowledges that women with endometriosis who seek complementary and alternative medicine to treat their pain symptoms may benefit from it.

Current status of medical management in infertility

SOGC Guidelines[13]

1. If a patient with known endometriosis is to undergo IVF, GnRH agonist suppression with Hormonal Therapy addback for 3 to 6 months before IVF is associated with an improved pregnancy rate.
2. Medical management of infertility related to endometriosis in the form of hormonal suppression is ineffective and should not be offered.

Cochrane Review 2014[14]

In women with endometriosis undergoing assisted reproduction, three months of treatment with GnRH agonist improved pregnancy rates.

There was no evidence that medical treatment improved clinical pregnancy rates

Medical management for pain related symptoms of Endometriosis is an effective modality. Studies have shown that gonadotrophin-releasing hormone (GnRH) analogues, levonorgestrel-releasing intrauterine system (LNG-IUD), danazol and progestagens and anti-progestagens have been used in various studies. Laparoscopic surgical interventions also appeared to be effective for pain.

National Institute for Health and Care Excellence (NICE) Guidelines 2017[15]

A short trial of paracetamol or a non-steroidal anti-inflammatory drug (NSAID) alone or in combination for first-line management of endometriosis-related pain.

Do not offer hormonal treatment to women with endometriosis who are trying to conceive, because it does not improve spontaneous pregnancy rates.

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.

Europeon Society of Human Reproduction and Embryology (ESHRE) 2013[16]

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility.

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.

Postoperative GnRH therapy for improving endometriosis outcome in infertility is not recommended

In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates

American Society of Reproductive Medicine (ASRM)[17]

According to the American Society of Reproductive medicine 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.

At present, there are insufficient data to evaluate the efficacy of aromatase inhibitors, selective estrogen receptor modulators, progesterone antagonists, or selective progesterone receptor modulators in the medical management of endometriosis for fertility.

Hormonal treatment does not improve the fecundity of infertile women with Stage I/II

endometriosis.

Key Message

- Endometrisis is an disorder with no curative treatment.
- All the medical modalities available are based on suppressive therapy rather than cure of the disease.
- There is a need to develop newer, more forms of treatment.
- Medical for pain is initially based on diagnosis in mild disease and is a long term treatment.
- Progestogens have now replaced oral contraceptives as a first line of therapy in endometriosis.
- Dienogest, a synthetic progesterone although has shown a better tolerability but due to higher costs has similar patient as compared to Norethidrone acetate. .
- There is no role of hormonal therapy in women with endometriosis who are trying to conceive, as it does not improve spontaneous pregnancy rates.
- Intrauterine insemination with controlled ovarian stimulation is preferred in early stages of endometriosis instead of expectant management, as it increases live birth rates.
- In Vitro is the treatment of choice in cases of

Table 1: Medical Management of Endometriosis

Medical management of Endometriosis

Pharmacological Methods		Non Phramacological Methods
Non Hormonal	Hormonal	1. Diertary Supplemets 2. TENS 3. Chinese Med 4. Accupunture
1. Analgesics 2. Neuropathic & Neromodulators	1. Oral contraceptives 2. Progestins – Natural And Synthetic agents 3. Antiprogestins 4. Danazol- oral and intrauterine system 5. Levonorgesterol Intrauterine System LNG - IUS 6. Gonadotropin Releasing hormone agonists 7. Estrogen Receptor inhibitors 8. Selective estrogen receptor modulators SERMS 9. Selective Progesterone receptor modulators SPRMS 10. Aromatase inhibitors	

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The Dilemma of Endometriosis Management in Infertile Women

DR SUSHMA P. SINHA

MD, MRCOG (UK), FRCOG(UK), FICOG, FIMSA
Academic Co-ordinator & Senior Consultant Obst & Gynae and IVF
Laparoscopic & Robotic Surgeon
Indraprastha Apollo Hospital, New Delhi

Endometriosis is one of the most challenging clinical entities for gynaecologists. Although, a benign gynaecologic disease, it is a complex one, enigmatic and has varied manifestations. There are challenges faced at every step of endometriosis management, at diagnosis, at communicating with the patients, at taking a decision for the treatment and choosing the type of surgery etc.

Prevalence

It is hard to know the exact prevalence of endometriosis because surgery is needed for accurate diagnosis and asymptomatic patients may decrease the prevalence.Literature quotes it to be upto 10 % in reproductive age group.(1)

Prevalence is higher in women with
Dysmenorrhea: upto 60%
Dyspareunia: upto 44%
Pelvic Pain: upto 80%
Subfertility: upto 20-30%

Age of the Diagnosis: Different age group has got different incidence of endometriosis. (Fig 1)

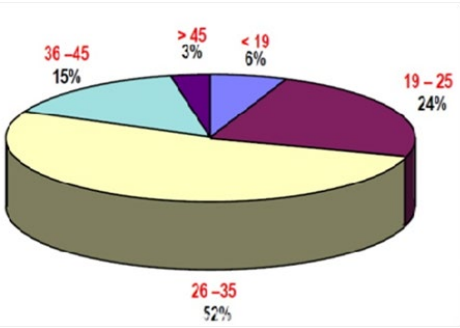


Fig 1: Age of Diagnosis

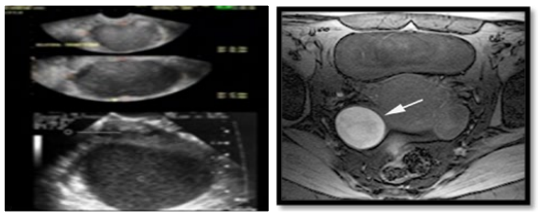
Some of the challenges faced in the management of Endometriosis will be discussed here.

1. Endometriosis - a diagnostic dilemma:

It takes years before this disease gets diagnosed. Dilemma in diagnosis is because the clinical examination is mostly poor, non-informative. There are many techniques of imaging available

but none of them is always conclusive. Small peritoneal implants are not visible on Transvaginal Ultrasonography (TVS), CT, and MRI etc. (Fig 2 A & B) Ovarian Endometrioma can mimic a haemorrhagic cyst or luteal cyst. The lack of specific biomarker significantly contributes to the delay of diagnosis.

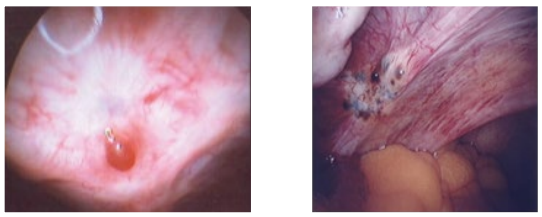
Fig 2 (A& B) Imaging in endometriosis



Delay to diagnosis of 8-10 years is the RULE. Studies have reported a delay of 10 years in Germany and Austria (2), 8 years in the UK (3) and Spain, 7 years in Norway and Italy, 4-5 years in Ireland and Belgium. We have no data about India but definitely it might be no less than that in other countries.

Only test for certain diagnosis is the laparoscopy with histological confirmation.(Fig 3 A&B)A gold standard procedure but invasive one with inherent risks and involves the use of anaesthesia with its own treated for chronic pelvic pain or infertility for years with medicines which may have side effects as well, before being offered diagnostic laparoscopy. Yet the other side is that she may be having some other cause of pain not the endometriosis risks. One has to balance the situation protecting the patient and avoiding doing harm with the utility of potential benefits of diagnostic laparoscopy. The laparoscopy too if performed by a less experienced or untrained person can miss a significant number of cases.

Fig 3 (A&B): Laaroscopic picture of endometriosis



Sometimes dilemma of diagnosis exists even after diagnostic laparoscopy by an experience one in view of varied presentations and as all the cases cannot be proven by histopathological examination. In a retrospective analysis (Canadian task force classification11-12) only 56 % cases could be proven by histology (4). Even when the condition is strongly suspected, there are challenges faced by the clinician while communicating the probable diagnosis to the patient and due to multiple ethical issues as well. (5)

2. Dilemma faced at communication

Just to achieve the diagnosis, offering the invasive procedure without offering at the same time, a cure is one of the biggest challenges.It is clearly evident that endometriosis is a significant cause of infertility but the impact on infertility not being always obvious and the mechanism being hypothetical and many cases conceiving spontaneously, dilemma of how to communicate to the patient about this disease as cause of her infertility is really difficult.

In case of infertility the dilemma of communication exists between, communicating only to the patient in view of her right to confidentiality or to the couple as the partner's right to have access to information as it is a case of infertility. When the disease is explained to the patient as a chronic one with a high risk of recurrence, the patient can perceive the disease as incurable as cancer leading to the feeling of despair and helplessness.

Then, there is this challenge whether to start the drug first for a trial for the management of pelvic pain or to go for the diagnostic laparoscopy straight away. Medical management may suppress the implants but do not necessarily remove them. Not only that, while advising diagnostic laparoscopy one may have to handle the issue of why I have been given drugs after drugs and not offered diagnostic laparoscopy before, by your fraternity?

Recommending a radical surgery in case of severe debilitating pain to nulliparous women is another challenge.

To establish the proper balance between the risks and the benefits for the patients to find a best way of achieving the maximum good to her is the goal which is no less difficult to achieve.

3. Difficulty in decision making- Another dilemma:

There are always difficulties in correctly and fully informing the patient about the decision for the treatment. Medical management can suppress the pain but does not necessarily eliminate the disease. Explaining the surgery while offering it to the patient is difficult too.What do you expect? The intra-operative reality and extension of the lesions may be different from the diagnosis established before starting the surgical procedure. Surgeons are often tempted for going beyond the wishes of the patients expressed in the signed informed consent sheet as surgeons would like to do the best for the patient and would try to avoid second surgical interventions.

Informed written consent has to be always taken for both diagnostic as well as therapeutic procedure. Thorough counselling of the patient before surgery is a must, informing them of not only the type of procedure but also the therapeutic limits.The consequences and probable complications- small likelihood of injury to bowel, ureter, bladder, vessels etc. have to be explained in detail. Need for ureteral stenting, involvement of urologist or general surgeon as and when required, have to be explained prior to the surgery very carefully.

In case of infertility, where laparoscopy is being done to check for the tubal patency if one encounters extensive peritoneal endometriosis and fibrous adhesions, (6) it becomes difficult to choose one out of these two options of merely diagnosing the lesion without removing them leaving her to undergo another surgery in future or maximizing the patient's benefit by removing all the endometriotic lesions without patient's prior consent. In the later we are going against the wishes of the patient as well as subjecting her to the risk of bladder or bowel injuries and subjecting ourselves to the risk of litigation in this era.

A 18 years old teenager had ultrasound done in view of acne on the advice of her dermatologist. Ultrasound reported a 6cm size endometrioma in her right ovary. She is referred to a gynaecologist who finds that she had no history of pain so far, endometrioma being an incidental finding.This is an example of challenges faced by the medical professional not only for diagnosis as patient being asymptomatic not giving a clue about the condition, but also for communicating the diagnosis to the patient and the parents and deciding for the surgery.

4.Therapeutic challenges in Surgery

Some of the challenges faced in day to day medical practice while managing endometriosis are-

Dilemmas in therapeutic decision making

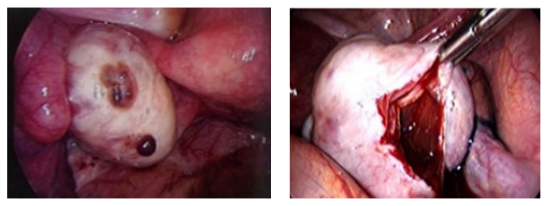
- Restoration of disrupted pelvic anatomy is the goal of surgical management in infertility but where there is no anatomical distortion is not surgery questionable?
- Is cystectomy the ideal treatment for endometrioma?
- Is laparoscopy really needed for infertility management? Has IVF superseded the need?
- Does surgical treatment before IVF improve success?
- Whether to go for ovarian stimulation with natural conception or IUI in minimal to mild endometriosis and should they be tried before a laparoscopic evaluation or after that?
- Should endometrioma aspiration ever be done?
- How much is the role of adjuncts in endometriosis management?
- What to do in recurrent endometriosis in patient with Infertility?
- Should asymptomatic deep infiltrating endometriosis be treated while encountered during diagnostic procedure for Infertility?
- How much is the role of medical treatment in case of symptomatic endometriosis.

Should endometrioma be operated?

Ovarian Endometrioma affects 17-44% of women with endometriosis. (Fig 4 A&B) Surgical treatment of endometrioma is no less a controversial procedure.A Meta-analysis in 2009 showed no statistically significant difference in pregnancy rate per cycle after IVF between patients undergoing surgery for endometrioma and women with endometrioma receiving no treatment. (7)

In women with chocolate cyst larger than 3 cm there is NO evidence that cystectomy prior to treatment with ART improves pregnancy rate. (Grade A Recommendation, ESHRE guideline 2014) (8)Cystectomy prior to ART to be considered only to improve endometriosis associated pain or if difficulty in oocyte retrieval.

Fig 4 (A&B) : Endometrioma



Study by Fauconnier and Chapron (9) reported that only 19 out of 1785 patients (1.06%) had ovarian endometriomas without any other pelvic

endometriosis. Ovarian endometriomas did not contribute to chronic pelvic pain, but are highly associated with deep infiltrating endometriosis, which is known to cause chronic pelvic pain. Ovarian endometriomas can be further complicated by the formation of adhesions that can fixate the pelvic organs. Fixation of the pelvic organs may distort the anatomical locations and reduce natural fertility.

Arguments in favour of removing endometriomas- are that it may interfere with ovarian stimulation, may impose difficulties during oocyte retrieval, may be responsible for producing substances that are toxic to maturing oocytes affecting cleavage after fertilization, may compromise ovarian reserve by destroying ovarian tissue through their expansion, without laparoscopic evaluation the diagnosis of malignant transformation might be delayed and may be associated with the occurrence of pelvic abscess or rupture and acute abdomen. Studies have established a link between Endometriosis and ovarian cancer. According to the literature "Endometriosis patients have an increased risk for ovarian cancer odd ratio varying from 1.2 to 8. (10)

Arguments against removing endometriomas - there is support from retrospective studies that IVF in the presence of endometriomas is not associated with a compromised outcome, surgery for ovarian endometriomas may damage ovarian reserve, potentially resulting in poor ovarian response to COS.

Excision or Drainage/ Ablation of endometrioma?

It has always been an issue for discussion. Although now excision of endometrioma capsule is the recommended treatment in infertile women with ovarian endometrioma undergoing surgery, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart, et al., 2008) (11) a grade A recommendation by ESHRE 2014.But decrease in ovarian reserve are statistically significantly more frequent in cystectomised ovaries than in coagulated ones.

Ovarian reserve may be badly compromised while stripping the cyst as normal ovarian tissues are also removed whereas drainage and ablation have high recurrence rate. Benefits in terms of pregnancy rates and pain relief are largely dependent on surgical skill and experience. Hence, current guidelines stipulate that the Endometriosis patients should be managed by an endometriosis expert. A very meticulously done surgery does not guarantee the best function since complete excision may leave the patient with poor ovarian reserve.

Complete resection of Endometriosis?

Even while being operated by the expert endometriosis specialist certain difficult areas may not be treated in view of ethical principle of not doing harm leaving the patient to suffer. Evidence that endometriosis surgery needs to be 100% complete is lacking. Maximizing the patient's benefits by removing all endometriotic lesion may not apply all the time.

Advanced Endometriosis- Surgery or ART?

There is an argument about the use of treatment of advanced stage of endometriosis. Most of the people prefer to offer IVF and sometimes Egg donation rather than going for laparoscopic evaluation and treatment in case of infertility. There is no randomized controlled trial comparing assisted reproduction with surgery. Some may argue in favour of Assisted Reproduction while others would like to combine both. In one study after laparoscopic treatment 76% patients achieved pregnancy.(12)

There are many questions which come to mind while dealing with endometriosis and ART. Here is this example - A 26 years old female with 5 years of unexplained infertility had 6 cycles of ovarian stimulation with Clomiphene Citrate and 4 cycles of IUI but failed to conceive. Now after Diagnostic Laparoscopy grade 2 Endometriosis is detected but already recommended treatments have been tried.What next? IVF could have been offered even without Diagnostic laparoscopy. Then why to subject her to surgery?

Recurrent Endometriosis – Two concerns: Ovarian reserve Vs repeat surgery?

Decision to proceed with surgery is all the more difficult in recurrent endometriosis. Overall recurrence rates range between 6 to 67% according to the criteria that are taken into consideration. Repeat surgery is always more difficult in view of adhesions and increased risk of complications such as injuries to bowel, bladder, ureter and vessel and intraoperative bleeding is much higher.

Not only that, the risk of reduced ovarian function due to repeated surgery and the possible loss of the ovary always existed. AMH level (13) and antral follicle count have been found to be significantly lower after repeat surgery. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery. Clinicians should counsel women with endometrioma regarding these risks in detail.

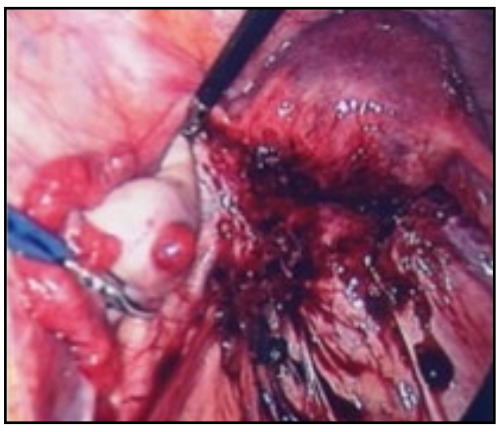
Mrs RS, a 34 years old software engineer, attempted for pregnancy for two years. She had a previous laparoscopic surgery for ablation of visible implants plus resection of a 4 cm endometrioma a year ago. Prior fertility testing reports had an occluded left Fallopian tube on hysterosalpingogram and her partner's history was significant for a semen analysis that demonstrated 6 million sperm with 10% motility.At RS's initial infertility evaluation, a transvaginal ultrasound demonstrated suspected bilateral recurrent endometriomas measuring 5 and 7cms. Her anti-mullerian hormone (AMH) level was reassuring then at 1.6 ng per mL.

Management options where discussed including proceeding directly to in vitro fertilization (IVF) versus resection of the endometriomas. She was asymptomatic, but given the size of the endometriomas, repeat laparoscopy and resection of the endometriomas was done.Four months postoperative, RS's AMH was undetectable. Thereafter, she underwent an IVF. Despite an aggressive 15 days stimulation with a high dose of gonadotrophins no oocytes were recovered. Her AMH remains undetectable. She is now considering use of donor oocytes.

Deep Infiltrating Endometriosis – Should it be operated?

The effectiveness of surgical excision of deep nodular lesions before treatment with assisted reproductive technologies in women with endometriosis-associated infertility is not well established with regard to reproductive outcome. (14,15)

Fig 5 Deep Infiltrating endometriosis



However, these women often suffer from pain, requesting surgical treatment. For symptomatic deep infiltrating endometriosis the stress has been on visually complete surgery. (Fig 5) To avoid recurrence systemic resection of the posterior vaginal fornix is proposed but a recent review shows that low rectal resection has a high complication rates (16) hence, one may have to rethink about the decision to go for a meticulous surgery.

Conclusion

Endometriosis is a complex disease of great variability and presentations which causes significant health problems in women of reproductive age. It is the commonest cause of chronic pelvic pain and important cause of infertility. There is dilemma at every aspect of endometriosis management, no clarity being in the relationship between the extent of the disease and degree of symptoms, effect on fertility as well as the most appropriate treatment. Medical treatment is based on suppression of disease activity and not eliminating the disease. Surgery and ART are the mainstay of the management. Therapeutic challenges are faced at every step by the clinician while managing the disease. It is really difficult to come to a consensus on management with this enigmatic disease.

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Endometriotic Fertility Index (EFI) and its clinical significance in infertile women

DR SWETA GUPTA

MBBS, MD (Obs & Gynae, Delhi)
MRCOG (London, UK), DFSRH (UK)
MSc (Reproduction & Development, UK)
Fellowship in Reproductive medicine & ART (London, UK)
Sr Consultant & Clinical Director, Reproductive Medicine and IVF
Medicover fertility, Delhi, India

Endometriosis is the presence of ectopic endometrium which create a microvascular environment around itself[1]. The main symptoms are infertility and pelvic pain. The commonly used classification was the revised American Fertility Society (r-AFS) classification (1985). This classification mainly depends on the morphological description. It predicts the recurrence potential of endometriosis after surgery. The limitation of this classification is the limited predictive ability for pregnancy after surgery. Studies have shown no association between the endometriosis stage, lesion type, lesion site and cumulative probability of pregnancy.[2]

Endometriosis Fertility index (EFI) and its calculation

Endometriotic Fertility index is calculated as shown in Figure 1. The historical factors evaluated in preliminary analyses included age, duration of infertility, and pregnancy history which repeatedly have been shown to be predictive of pregnancy.

The functional score was determined by the surgeon for each of the tube, fimbria and ovary bilaterally where 0 ¼ absent or nonfunctional; 1, 2, and 3 ¼ severe, moderate, and mild dysfunction, respectively; and 4 ¼ normal with respect to the capacity of the organ/structure

to affect its purpose in the reproductive process. The functional score measures the ability of the tube to move over the ovary, to be the passage for the sperm from the uterus, to provide the early environment for the egg and embryo, and to enable transport of the embryo to the uterus; the ability of the fimbria to move over the ovary and to pick up an egg; and the ability of the ovary to house eggs, develop follicles, ovulate eggs, and allow them to be picked up by the fimbria.

The EFI score ranges from 0–10, with 0 representing the poorest prognosis and 10 the best prognosis. Half of the points come from the historical factors and half from the surgical factors. Uterine abnormality was not included in the score.(Fig 2)

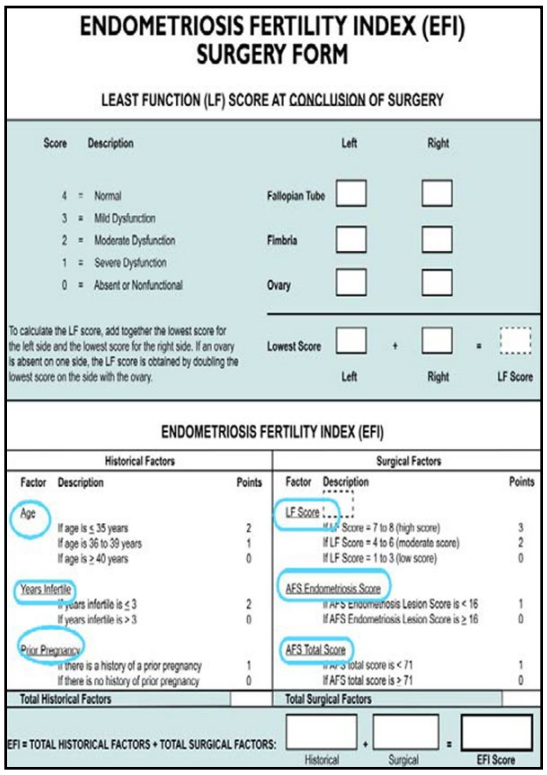

Figure 1: The newer scoring system, Endometriotic Fertility Index (Adamson and Pasta, Fertil Steril 2010).

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 minimal 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

Figure 2

Advantages of EFI

EFI has more predictive power for IVF outcomes in endometriosis patients than the r-AFS classification. The clinical pregnancy rate was higher in patients with EFI greater than or equal to 6 score than with EFI lower than or equal to 5 score.[3]

Data suggested by Wang et al.[4] shows that the r-AFS classification has limited potential in predicting the pregnancy outcome. EFI score maybe more sensitive in predicting pregnancy because it not only considers the size and number of lesions and the degree of local adhesion but also consider other reproductive factors, such as age, infertility duration, or fallopian tube and ovarian function.

In 2002, Fujushita et al[5] modified the AFS classification of endometriosis by adding the TOP score, fallopian tubes, ovaries, peritoneum, and other factors. However, the patient's age or other factors affecting pregnancy as not considered.

Adamson and Pasta (2010) further revised and updated the AFS classification system.[3] They prospectively collected detailed clinical and surgical data of 579 patients with endometriosis and analysed 275 variables associated with pregnancy, thereby establishing the EFI. In addition, they confirmed that the EFI had a close correlation with pregnancy rate in 222 patients.

In 2013, Tomassetti C et al[6] suggested that the EFI could be used clinically to counsel infertile endometriosis patients receiving reproductive surgery in specialized centres about their post-operative conception options. Unlike the r-AFS classification, the EFI objectively evaluates factors closely associated with female fertility, such as fallopian tube, tubal fimbria, and ovarian function. It incorporates the LF score which can evaluate the reproductive potential of pelvic organs and comprehensively includes several objective factors such as patient's age, duration of infertility, and pregnancy history.

Jayakrishnan N et al[2] compared endometriotic Fertility Index (EFI) and r-AFS, in patients with surgically documented endometriosis, attempting conception. Unlike the r-AFS classification, the EFI objectively evaluated factors closely associated with female fertility, such as fallopian tube, tubal fimbria, and ovarian function. According to them EFI incorporates the LF score which can evaluate the reproductive potential of pelvic organs and comprehensively include several objective factors, such as patient's age, duration of infertility, and pregnancy history. The EFI also incorporates all the components of the r-AFS scoring systems.

Xin Le et al[7] in 2017 published EFI as a reliable staging system to predict the spontaneous pregnancy rates (PR) of patients. The least function score was the most influential factor to predict the spontaneous PR. Patients with an EFI score ≥5 after 12 months from surgery are recommended to receive IVF-ET to achieve a higher PR. The life table analysis showed a significant relationship between EFI score and time to achieve spontaneous pregnancy (Figure 3).

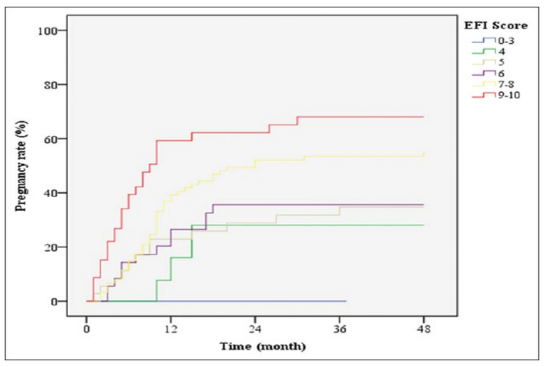

Figure 3: Probability of pregnancy classified by EFI scores during a 48-month follow-up of 234 infertile patients without IVF-ET ($\chi 2 = 29.945$, $P < 0.001$). EFI: Endometriosis fertility index; IVF-ET: In vitro fertilization and embryo transfer. Xin Le et al[7].

According to the newly published (2015) guidelines from the Chinese Medical Association[8], Obstetrics and Gynecology branch, endometriosis cooperation group, women with an EFI score of 4 or lower should undergo IVF-ET treatment directly after surgery. Thus, the EFI score enables targeted and individualized infertility treatment. Further research should be performed to define the optimal timing for IVF in patients with different EFI scores.

Xin Le et al[7] demonstrated that the EFI staging system is very effective to predict reproductive performance after laparoscopic endometriosis surgery. Secondly, they proved that the least function score offers the greatest contribution to predict the pregnancy rates in patients who are attempting to conceive spontaneously. They suggested that patients with an EFI score ≥5 should be allowed to attempt conception naturally for at least 12 months after surgery. If the attempt fails, IVF-ET should be considered for these patients.

Garavaglia et al[9] suggested EFI score is a reliable scoring system to predict non-ART and ART pregnancy outcome after surgery for endometriosis. In 104 women with endometriosis, EFI score was calculated based on a prospective database, cumulative pregnancy rates curves were calculated using Kaplan-Meier (K-M) product limit estimate and log-rank test was used to evaluate differences between EFI groups. The best cut-point for pregnancy was calculated to be 5.5.

Kumi Ohuchi et al[10] showed that post-operation pregnancy rates were 55% and 76% for EFI ≤ 5, and EFI ≥ 6, respectively. Rates of non-ART pregnancy within 1 year post-operation (timed intercourse or artificial insemination with husband's semen (AIH)) were 9% and 47% for EFI ≤ 5 and EFI ≥ 6, respectively. There was no non-ART pregnancy in patients with EFI ≤ 3. They concluded there was a higher tendency for pregnancy in non-ART cases with a larger EFI. There was no non-ART pregnancy in patients with EFI ≤ 3, thus, ART is suggested for this population. EFI may have a role in deciding the treatment methods for patients with endometriosis.

Limitations of EFI

The EFI is useful only for infertility patients who have had surgical staging of their disease. It is not intended to predict any aspect of endometriosis-associated pain[2].

One factor found to predict pregnancy that is not included in the EFI is uterine abnormality. Severe uterine abnormality that is clinically significant was omitted because it is so uncommon in infertile patients with endometriosis. Deficiencies in the reproductive function of the gametes or uterus will obviously affect the prognosis and must be considered separately as fertility factors, just as they would with any patient with any other type of disease[2].

The least function score is subjective for any given surgeon and for different surgeons. Although true, the least function score in fact is a robust measure of pelvic reproductive potential because the categories are fairly clear, any subjective differences in assessment tend to be averaged through the calculations on one side and then the other and the least function score represents only 30% of the EFI[3].

Another limitation of the study was that, the stimulation protocols used in assisting conception, were not included as a part of the study.

Conclusion

"The EFI is a simple, robust, and validated clinical tool that predicts pregnancy rates for patients after endometriosis surgical staging. It provides reassurance to those patients with good prognoses and avoids wasted time and treatment for those with poor prognoses"3 (Fertil Steril_ 2010;94:1609–15. _2010 by American Society for Reproductive).

EFI is an important tool in individualizing treatment plan for sub fertile endometriotic patients receiving surgery and in counselling about their postoperative conception options.

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Management of Endometriotic Cysts Associated With Infertility

DR SURVEEN GHUMMAN SINDHU

Director & Head
IVF & Reproductive Medicine
Max Multispeciality Hospitals
Panchsheel, Saket, Patparganj, Delhi and Vaishali

The ovary is one of the more frequent sites of pelvic endometriotic lesions. Management of ovarian endometriosis, though a frequent problem, still has many grey areas with unresolved debates. Its pathophysiology, correlation with symptoms and stage and the optimal treatment are still controversial. Ovarian endometriomas are identified in around 20 % of patients with endometriosis, associated with subfertility or pelvic pain.

An ovarian endometrioma, of 3 centimeters size, leads to an AFS score of stage III, or moderate endometriosis. A spontaneous conception rate of 22 % is associated with this stage. Controversies exist about co- relation of this classification with fertility outcomes. Predictive value of this classification is still very controversial. After surgical treatment of ovarian endometriomas the reported conception rates are in the range of 50 %. These findings suggest that an ovarian endometrioma might impair fertility. However this effect has not been backed by a randomized controlled trial. Medical treatment is not recommended for endometrioma as it is not effective.[1]

Removal of lesions is indicated, for endometrioma of at least 4 centimeter size, especially more when pain is associated. In case of infertility, the main objective of the treatment is to improve the fecundity. Removal of cyst also provides a histological proof of the nature of the whole cyst. Other treatment options have been tried.

1. Expectant

Endometriomas, less than 4 cm in size, do not have a significant effect on fertility. These young women can be treated expectantly with a regular ultrasonography of the cyst.

2. Hormonal suppression

Hormonal suppressiondoes not show a benefit asmedical treatment has little impact on ovarian endometriomas. A decrease in size of the cyst after medical treatment has been observed in some but with a high recurrence rate after 6 to 12 months. Medical treatment prior to and after surgery showed no benefit.

3. Surgical treatment

Surgery is the treatment of choice for a large endometrioma. The laparoscopic approach is preferred. Two main techniques are used: cystectomy or ablation. It is important to avoid excessive destruction of ovarian tissue in the infertile patient justifying under treatment of these patients.

Superficial small ovarian endometrioma: Superficial endometriosis of the ovary usually presents as small dark, punctuate lesions immediately beneath the cortical surface. Tiny surface lesions can be vaporized or coagulated by bipolar cautery. Layer by layer vaporization can be done by short bursts of laser. Occasionally the visible lesion may be a tip of a larger deeper lesion. If a deeper lesion is suspected with a superficial endometrioma the implant should always be excised and the ovary explored

Moderate endometriomas: There may be difficulty in stripping the pseudocapsule and it may often have to be excised. Laser coagulation helps in achieving hemostasis.

Large Endometriomas: Large endometriomas may be adherent to the adjoining tissues. They are difficult to remove because of extensive adhesions and care must be taken in identifying the ureter. If extensively adherent an aspiration is done. It is associated with recurrence which can be reduced by injecting the empty cyst with various sclerosing or cytotoxic agents, such as methotrexate, ethanol or tetracycline.[2]

Cystectomy vs Ablation for patients desiring pregnancy

A randomized control trial showed lower reoperative rates 6 % vs 23% and higher pregnancy rates 59% vs 23% with laparoscopic ovarian cystectomy in comparison with fenestration and coagulation. Cystectomy was found to be superior in terms of risk of recurrent symptoms, cyst reoperations and pregnancy rates and was strongly recommended especially in infertile patients.[3], a view supported by Cochrane review 2010[4] Intracystic vapourization offers a better chance of preserving Oocyte stock. The difference in the two techniques in terms of ovarian function in an IVF stimulation protocol is 10% more harvested oocyte with cyst vaporization.[5] Cystectomy is preferred if feasible and intracystic vapourization or coagulation if cystectomy is not possible.

Post operative problems

There are some major postoperative problems which need to be tackled

1. ***Major complications:*** Major complications can occur as it is a difficult surgery– bowel injury, ureter and bladder involvement, bleeding
2. ***Post operative adhesions:*** Post operative adhesions are frequently encountered after surgery.
3. ***Recurrence:*** Recurrence after surgery varies from **0 to 30 %** depending on the surgical procedure, the definition and the length of follow-up. Medium-term recurrence of lesions was observed in 20% of the cases, 25% of the women underwent repetitive surgery.[6]

Cystectomy seems to lead to fewer recurrences, as demonstrated by randomized controlled studies. Recurring ovarian endometriomas should not be systematically removed before performing an IVF. Iterative surgery may impair ovarian reserve and the presence of the ovarian endometrioma does not impair the expected results of IVF.

4. ***Impact of surgery on ovarian function and ovarian reserve:*** Raised FSH levels have been found in patients after surgery as there may be removal of healthy tissue leading to a decreased ovarian reserve.[4] It was shown that 65 to 80% of women who underwent cyctectomy had ovarian tissue in the wall of the removed cyst.[7] However none of the tissue had follicles. Most endometriotic cysts are not true cysts. They are formed by invagination of the ovarian cortex. Oocytes may be lost by removal of the ovarian cortex that forms the pseudocyst. CO2 laser vaporizes the cyst wall layer by layer with superficial depth and prevents excessive destruction of the cortex. With cautery, damage may be more widespread as there is scattering. Scissor excision may have a role as it gives a tissue feel. However, it can be argued that since the ovarian cortex invaginates, it is unavailable for external ovulation and removal causes no harm. Excision also provides histopathological specimen for diagnosis. Ovarian response was reduced during IVF-ET cycles in patients with history of severe endometriosis and laparoscopic excision of endometriomas compared to women with mild or minimal endometriosis without ovarian surgery.[8]There was a metanalysis which included eleven studies where they found a statistically significant reduction of serum AMH level after surgery. The magnitude of the decline was more evident in women operated on for bilateral endometriomas.[9] In a study it was shown that serum AMH decreased significantly at the sixth month (61%) postoperatively. The AMH decrease was more in bilateral compared with unilateral endometriomas (67% versus 57%, respectively). Basal AMH level was the only independent factor affecting the AMH decrease (odds ratio, 3.68). Bipolar cauterization plays a role on ovarian damage.[10] Surgeons skill is important hence, cannot have blanket rule

Fertility preservation

Patients with endometriosis should be informed about fertility preservation options, especially in the presence of bilateral endometriomas or prior to surgery.

Recurrence

It is not recommended to reoperate on endometrioma in infertile women, unless indicated for pain.

4. IUI/IVF

About 50 -80 % of patients do not conceived after surgery with IUI and need IVF. Ovarian endometrioma does not affect results of IVF and its presence is not a contra- indication to perform an IVF. A higher dose of gonadotropins for ovarian stimulation may be required where patients have had surgery because of effect on ovarian reserve, but no effect on pregnancy rates was seen. Aspiration of an ovarian endometrioma, incidentally

identified during ovarian hyperstimulation or ovum pick up for IVF, is not required and may lead to infection and abscess formation. If found accidentally during IVF cycle stimulation it should be ignored and cycle continued. Unexpected puncture of an ovarian endometrioma during ovum pick up has no impact on the results of IVF, but bears a risk of infection. Presence of chocolate fluid (hemosidderrin) in follicular puncture does not impair quality of oocyte.[11] It is not necessary to operate on endometriomas before IVF.[12] Endometrioma does not impact quality of oocyte although there are studies which have shown otherwise. Endometriomas do not cause any complications in pregnancy resulting from IVF.

Risk of conservative management

Various risks of conservative management of endometrioma in a patient undergoing IVF is enlisted in Table 2. These enlisted events are uncommon and the number of women needed to be treated would be exceedingly high and would not justify the costs and risks of the intervention.[13]

Risk of contamination.

In a study done on 314 women 19 had contamination of endometriotic fluid on oocyte retrieval. (6.1%,). Number of embryos and top quality embryos were significantly higher in exposed women - 3.1±2.0 versus 1.7±1.2 and 1.9 vs 1.1 respectively, but chances of pregnancy were lower aRRs - 0.63. Live birth were OR - 0.60 They concluded that accidental contamination of the follicular fluid with endometrioma content is an uncommon but possible event. This situation may affect IVF outcome but does not justify systematic surgical removal before the cycle.[14]

Table 2. Risk of conservative management of endometrioma before ART[13]

1.	Difficulty in retrieval of oocyte: If not possible surgery must be done before IVF
2	Follicular fluid contamination with the endometrioma content
3	Interfere with ovarian responsiveness and oocyte competence – Not proven
4	Higher pregnancy complications - usually not seen
5	Disease progression during IVF procedure
6	Chemical peritonitis
7	Infection in endometrioma
8	Risk of missing occult malignancies with cancer development later in life very rare

Impact of endometriosis on the outcome of ART

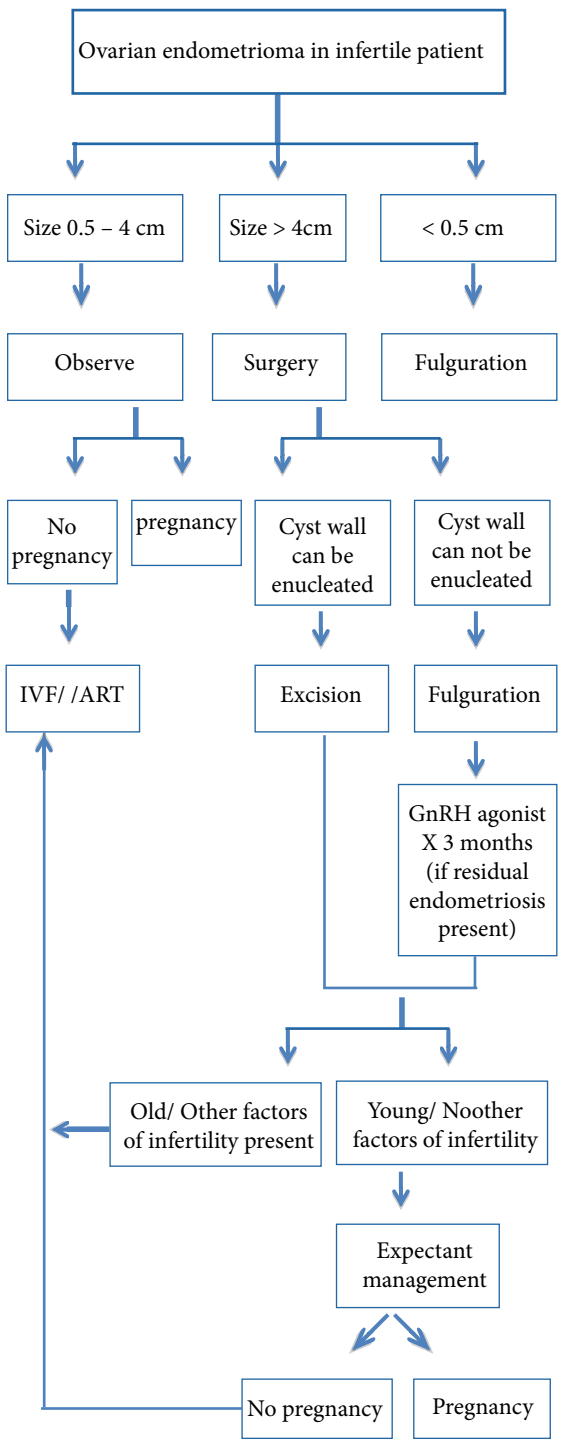
Impact of endometriosis on the outcome of ART is controversial. There are many studies which say that endometriosis impacts oocyte embryo quality and endometrial receptivity. A recent metanalysis showed that although women with endometriosis generate fewer oocytes, fertilization rate is not impaired and the likelihood of achieving a live birth is also not affected. A total of 22.416 women were included (3.583 with endometriosis and 18.833 in the control group). (Table 3) Studies examining the basic morphology of oocytes and embryo development in women with and without endometriosis have not found any differences in the two groups.

Table 3: Outcome of IVF in endometriosis [15]

	Controls	Endometriosis
Age	34.6	34.1
Number of oocytes recovered	9.86	8.89
Cancellation	2.95	3.94
Fertilization rate	59.4	60.2
Number of oocytes transferred per ET	2.22	2.15
Pregnancy rate	23.7	24.3
Miscarriage rate	5.86	5.7
LBR	23.3	23.8

Figure 1 shows the algorithm for treatment of endometrioma in infertility

Fig I: Treatment of Ovarian Endometrioma in Infertility



Thus, indications of surgery before IVF are if endometrioma is very large and it obstructs retrieval, there is intractable pain or laparoscopy is indicated for other reasons. Its presence does not impact IVf results.

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Management of Adenomyosis in women less than 35

DR LEENA WADHWA

Professor
Deptt of Obst & Gynae, ESI-PGIMSR, Basaidarapur, Delhi

DR SHUBHI YADAV

Senior Resident
Deptt of Obst & Gynae, ESI-PGIMSR, Basaidarapur, Delhi

DR SRISHTI PRIYADARSHINI

Post Graduate Student
Deptt of Obst & Gynae, ESI-PGIMSR, Basaidarapur, Delhi

Adenomyosis is a benign disorder which is characterized by the presence of heterotrophic endometrial glands and stroma in the myometrium. On the basis of myometrial invasion extension, it can be either diffuse or focal [1]. Adenomyosis has a negative impact on the fertility of women. The spontaneous abortion rate was higher in women with a diffusely enlarged uterus on ultrasound imaging without distinct uterine masses compared with those with a normal uterus [2]. It is also proposed that an increase in junctional zone diameter is inversely correlated to implantation rate [3]. Approximately 20% of cases of adenomyosis involve women younger than 40 years. Treatment of adenomyosis in women less than 35 can be either medical or conservative surgical management.

Medical treatment of Adenomyosis

Medical treatment is aimed at reducing the production of endogenous estrogen or inducing endometrial differentiation with progestins. The objectives of medical treatment are the inhibition of ovulation, abolition of menstruation, and achievement of a stable steroid hormone milieu, based on the concept that the responses of the eutopic and ectopic endometria are substantially similar.

GnRH Agonists

GnRHa is the first drug used for this purpose. They act by binding to GnRH receptors in the pituitary gland, resulting in down-regulation of GnRH activity. This creates a reversible state of medical menopause [4]. It also decreases expression of aromatase cytochrome p450 and of nitric oxide synthases which is over expressed in the eutopic endometrium of women with adenomyosis and endometriosis. There is a reduction in uterine volume and amenorrhea, and relief of severe dysmenorrhea .Women seeking pregnancy GnRH-a also promotes uterine and endometrial receptivity. However, discontinuation of therapy prompts re-growth of the uterus and results in recurrence of symptoms . Use of the drug is limited for a period three to six months because of adverse effects, including hot flashes and decreased bone mineral density, but with the advent of add-back therapy, the duration of usage has substantially increased. .Goserelin and leuprolide are two commonly used GnRH agonists. Goserelin is used in doses of 3.6 mg once every 4 weeks or 10.8 mg once every 12 weeks, and is injected subcutaneously. Leuprolide can be given as a daily dose of 0.5 to 1 mg or monthly depot of 3.75 mg or even can be given 3 monthly in a dosage of 11.25 mg. It can be injected subcutaneously or intramuscularly. Various studies show successful use of GnRH agonist alone in the conservative treatment of adenomyosis. Long-term use of GnRHa resulted in spontaneous pregnancy in all three studies (6 of 7) within24 months of cessation [5, 6].

Progestogens

Women with adenomyosis are characterized by a lower expression of progesterone receptors (A and B) in endometrial lesions, but also in the outer and inner layers of myometrium. The treatment of adenomyosis with progesterone may be restricted owing to the abnormal expression of progesterone receptors.. A Cochrane database systematic review showed that the progestogens (100 mg medroxyprogesterone (MPA) daily) more effectively reduced the symptoms during a period of 12 months follow-up (mean difference 0.70, 95% confidence interval 8.61 to 5.39; $p < 0.00001$) compared with placebo (moderate-quality evidence). Norethisterone acetate (2.5 mg per day) is associated with a marked degree of pain relief, progressively better over a longer duration of use . A drawback of progestin therapy are break through bleeding, fluid retention, mood changes, breast tenderness and weight gain [7].

Dienogest

Dienogest (progestin) has been used to treat adenomyosis pharmacologically. Dienogest directly inhibited cellular proliferation and induced apoptosis in human adenomyotic stromal cells. Two nonrandomized studies on a small number of patients have been published, but neither refers to the patients' fertility. The first study compared 2 groups of approximately 20 subjects treated with danazol and dienogest for adenomyosis. That study did not clearly describe the effectiveness of the therapeutic protocols. Adenomyosis patients treated with dienogest are at higher risk of discontinuation owing to uterine bleeding. The second study presented a correlation of 3 factors: age younger than 38 years, lower hemoglobin levels before the starting point of the therapeutic protocol, and estradiol levels after 3 months of dienogest therapy [8, 9].

Selective Progesterone Receptor Modulators (SPRMs)

It is well known that lesions in adenomyosis not only produce significant quantities of progesterone, but also contain lower levels of endometrial progesterone receptors. Selective progesterone receptor modulators reduce adenomyosis associated pelvic pain, and are possibly more effective than progestins. The reason may be progesterone resistance of adenomyotic lesions, secondary to low receptor density. Two SPRMs are currently prescribed are mifepristone and ulipristal acetate (UPA). In a study, subjects who were prescribed 50-mg of mifepristone daily were found to have improved pain symptoms, as well as regression of adenomyosis. It is possible that mifepristone induces apoptosis of endometrial cells by activation of caspase-3 expression [10]. Further studies are warranted to confirm the mechanism of action and long term effects of SPRMs on endometrium.

Ulipristal Acetate (UPA)

UPA induces amenorrhea and also has a direct effect on adenomyotic foci, so it could potentially be of use in adenomyosis-related heavy uterine bleeding without suppressing follicular growth, maintaining normal FSH and estradiol levels within follicular phase levels. Prolonged treatment with UPA has shown to induce non-physiologic changes in the eutopic endometrium (progesterone receptor modulator associated endometrial changes [PAEC]) Adenomyosis is characterized by a reduction of progesterone receptors in the eutopic and ectopic endometrium and the myometrium, which could lead to a reduced efficacy of SPRMs.. It is currently not known what effect UPA have on ectopic endometrial foci and whether PAEC might also be induced in ectopic foci.UPA is given in a dose of 5mg to 10mg daily dose. The treatment courses should each not exceed 3 months as the risk of adverse impact on the endometrium is unknown if treatment is continued without interruption Repeated intermittent treatment has been studied up to 4 intermittent treatment courses.

Danazol

Danazol is an isoxazol derivative of 12 a-ethinyl testosterone, and has a complex mechanism of action involving inhibiting steroid genesis, lowering the mid-cycle luteinizing hormone surge, and increasing serum free testosterone levels. Danazol use results in an androgenic and hypo estrogenic environment; due to this effect on adenomyotic lesions they are helpful and reduce

pain during and after therapy, and the latter may have an indirect effect on adenomyotic lesions, contributing to relieving pain and resulting in clinical improvement in 55-93% of women treated for 6 months.

Oral contraceptives

OCP's suppress endometrial growth and retrograde menstrual flow. As no difference has been found between efficacies of various OCP's, it is judicious to use pills with low estrogen content, to minimize side effects. Continuously administered monophasic low dose OCP's with withdrawal bleed every 4-6 months are effective in relieving menorrhagia and dysmenorrhea, also have the advantage of being effective with low cost and high patient compliance, and minimal side effects.. Medical therapy with OC enables satisfactory long-term pain control in two-thirds of women with symptomatic adenomyosis. Continuous combined oral contraception and high-dose progestins, such as continuous oral norethindrone acetate or subcutaneous depot medroxyprogesterone, have been found to induce regression of adenomyosis temporarily. Nausea, breast discomfort and breakthrough bleeding are common side effects observed with oral contraception and progestins.

Hormone containing IUD'S

Levonorgestrel intrauterine system (LNG-IUS) is approved for treating women with adenomyosis who have completed their childbearing. Levonorgestrel intrauterine system treatment is accompanied by decreased pain and heavy uterine bleeding, which could be explained by the following mechanisms: (i) a progestogenic influence on adenomyosis foci; (ii) atrophy of the eutopic endometrium; and (iii) controlling of endometrial factors that changed during adenomyosis. A study described decreased expression of growth factor and the related receptors in women with heavy bleeding and adenomyosis after LNG-IUS treatment [11]. LNG-IUS reduces abnormal uterine bleeding secondary to endometrial dysfunction more than OC, luteal-phase oral progestins, or nonsteroidal anti-inflammatory drugs, and that antifibrinolytics are more effective than placebo.

Danazol-loaded devices

Danazol-loaded intrauterine devices induce remission of dysmenorrhea, reduced menstrual bleeding and spontaneous conception after removing the IUD. Two case series reports evaluated the use of a danazol-loaded intrauterine device or a vaginal ring in patients with adenomyosis requiring fertility preservation. The combined pregnancy rate after insertion and removal of these devices was41% [12].

Aromatase inhibitors

The rationale for treating adenomyosis with aromatase inhibitors is related to their effect in inhibiting the enzyme aromatase P450, which is expressed in the ectopic endometrium. Aromatase is the enzyme responsible for the transformation of androgens, androstenedione, and testosterone, into estrogens, estrone, and E2, respectively Aromatase is an excellent target for inhibition of the E2 synthesis because it is the final step in steroid biosynthesis; therefore, there are no important downstream enzymes to be affected. Joint and muscle pain are common side effects of aromatase inhibitors. In addition, loss of bone density, which leads to higher rates of osteoporosis and bone fractures, and hot flashes are reported. In a study, it was confirmed that aromatase inhibitors are as effective as gonadotropin-releasing hormone agonists in reducing adenomyoma volume and improving symptoms [13].

Bromocriptine

Vaginal bromocriptine, a dopamine agonist, is currently under study in women with MRI diagnosed adenomyosis. The investigators have planned to assess the effect of a 6-month treatment on the extent of the disease evaluated by pelvic MRI and on the severity of adenomyosis-related symptoms.

Anti Angiogenic

Neovascularization that supports the growth of the ectopic implants has been reported in women with adenomyosis one of the mechanisms implicated in the pathogenesis of adenomyosis is the estrogen-induced invasive properties by endometrial cells and their pro-angiogenic effect within the myometrium. Adenomyosis could be an epigenec disease with, amongst others, hypermethylaon of PR-B in ectopic endometrial stromal cells but not in eutopic stromal cells . The treatment of stromal cells with an HDACi or a demethylaon agent induces an increase in the PR-B gene and protein in ectopic endometrial stromal cells.

Valproic Acid

In a pilot study in 3 symptomatic women with adenomyosis, VPA at a dose of 500 mg t.i.d. for 3 consecutive months relieved dysmenorrhea substantially and reduced the uterine volume and ii) in a case series of 12 women with adenomyosis, a 3-month administration of VPA 500 mg t.i.d resolved dysmenorrhea, reduced menstrual bleeding and led to a shrinkage to one-fourth of the uterine size. VPA treatment was overall well tolerated with no major side-effects. There are currently no ongoing clinical trials on the use of VPA in the treatment of adenomyosis.

Exploring Surgery Treatments and Pregnancy Rates

Conservative uterine-sparing surgery are considered difficult in managing patients, partly because it is not easy to determine the extent of the adenomyosis involved and how much of the tumor should be removed, and secondly adenomyosis foci frequently mix with the surrounding normal myometrium, making it nearly impossible to completely resect uterine adenomyosis using conservative uterine-sparing surgery.

Conservative Surgery Alone

The results of conservative surgery, which consists of laparoscopy or laparotomy, are based on few studies in women with a diagnosis with adenomyosis. Two studies reported birth rate and one reported pregnancy rate. The surgical techniques presented in all the studies consisted of excision of the adenomyoma and hysteroplasty using laparoscopy or laparotomy. The overall average birth rate reached 36.2% (21 of 58) in women who had this surgery [14, 15].

Classification

Classification of conservative uterine-sparing surgery for adenomyosis can be made based on the extent of removal of adjacent healthy myometrium and the preservation of the integrity and possible function of the uterus. This includes

Type I: Complete and total resecection of adenomyosis, complete resection of adenomyosis (also called adenomyomectomy).

Type II: Cytoreductive surgery of adenomyosis Many modifications are used in the conservative uterine sparing surgeries. Fujishita and colleagues used a transverse H-incision technique to perform this procedure for adenomyosis . The main components of the three interconnecting "H" incision are a vertical incision with a 5-mm resection of the uterine serosa, myometrium layer and two transverse incisions perpendicular to the vertical incision along the upper and lower edges of the uterus, which extend down both to the right edge of the uterus up to the line connecting the right corners of the upper and lower transverse incisions and to the lower edge of the uterus connecting the lower corners of the upper and lower transverse incisions.

Another classic method used to finish uterine-sparing surgery for adenomyosis is very similar to myomectomy, the resection must be done piece by piece, with preservation of as much of the adjacent normal myometrium as possible . The laparoscopic approach might be possible, although laparotomy is much more feasible that the surgeon can palpate and recognize the adenomyomectomy lesions intraoperatively.

Comparison of 2 Surgical Techniques

A retrospective study of 104 patients undergoing conservative surgery compared the classical adenomyomectomy with the H-incision surgery. The classical technique was performed in 5 women with adenomyosis who were selected retrospectively among 104 patients. The newer technique was used in 6 of 83 patients who desired to preserve fertility. The classical technique involves incision of the uterine wall and a stepwise resection of adenomyomatic tissue. The other technique consists of an H-shape incision and excision of the adenomyomatic tissue. In this study, H-shaped incision technique resulted in one spontaneous pregnancy 4 months after operation compared with no pregnancy in women undergoing the classical technique. Classical technique pregnancy rate, 0.14, 95% confidence interval. Time between surgery and pregnancy was 4 to 6 months followed by a live birth, with one continuing pregnancy at the time the study finished [16].

Uterus-sparing surgery for adenomyosis-associated sub fertile women was also demonstrated by Kishi et al. In the group aged younger than 39 years, 60.8% of women with a history of IVF failure achieved pregnancy after surgery, although there was no clear benefit of surgery on fertility outcomes for patients older than 40 years. Wang et al. also suggested that laparoscopic cytoreductive surgery might be suitable for women with localized adenomyosis

Adenomyomectomy

When women experience the severe symptoms of advanced adenomyosis, hysterectomy has been advised. However, the more conservative adenomyomectomy preserves the uterus. One study reported that from a pool of 103 patients, 55.34% presented with infertility, and of those, 16.50% had IVF failure, 8.74% had recurrent miscarriages, and 19.42% had abnormal uterine

bleeding. Of the 103 patients, 70 attempted pregnancy, 21 naturally through intercourse, and 49 through IVF. Pregnancy outcomes were 30% pregnancy, with 23% live births. The symptoms of dysmenorrhea/hyper menorrhea lessened after surgery. Only one patient had a recurrence of adenomyosis [17].

Medical or Surgical Therapy in sub fertile women.

Case reports or small series report adenomyosis treated with gonadotropin-releasing hormone (GnRH) analog alone, conservative surgery, or combined therapy. Patients were treated with GnRH for a period of 3 to 6 months and interval from completion of treatment to spontaneous conception varied from 1 to 18 months [18]. A live birth rate after treatment with GnRH agonist (GnRH-a) for 5 months was reported. In a case study , the patient with histologically diagnosed adenomyosis who underwent a long-term course of GnRH-a conceived shortly after cessation of treatment. It was also reported that 2 cases of adenomyosis were conceived within 6 months after a short course of GnRH therapy with buserelin [19].

Conservative surgery or combination treatment in sub fertile women with adenomyosis also had significant benefits for not only controlling symptoms but also for increasing the pregnancy rate compared with GnRH-an alone. The cumulative 3-year clinical pregnancy rate and final successful delivery rate were higher in adenomyotic women who underwent conservative surgery with or without GnRH-a compared with those who received GnRH-a alone for 6 months.

Effect of Adenomyosis on Reproductive Outcome after Endometriosis Surgery

A significantly higher pregnancy rate was recorded in women with endometriosis, but without adenomyosis, compared with those with concurrent endometriosis and adenomyosis after laparoscopic excision of deep, infiltrated endometriosis. Presurgical hormone treatment (GnRH agonists for3months) was used in 2 studies. Surgery was performedin 3 studies with laparoscopy and with laparotomy or laparoscopy in 2 studies [20].

Adenomyosis and ART

There are different conclusions of various studies pertaining to the results of ART in adenomyosis relating to the type of protocol used. Thalluri and Tremellen conducted a retrospective study in women with adenomyosis undergoing IVF cycle with an antagonist stimulation protocol. . Their results show reduced clinical pregnancy rates in the adenomyosis group compared to the group without adenomyosis. A study used a long agonist stimulation protocol in ART cycles. found no difference in live birth rate per cycle between women with adenomyosis and controls. The use of GnRH down regulation in the study could have had an effect on the endometrium, correcting endometrial alterations related to the presence of adenomyosis and thus increasing live-birth rates [21].

Oocyte Donation

In a retrospective cohort study, oocyte recipients with adenomyosis; implantation rates after were comparable to those of women with endometriomas or controls without endometriosis adenomyosis. Early miscarriage rates were higher in women with adenomyosis compared to women with endometriosis or controls they postulate that the disruption of the JZ in adenomyosis could alter initial stages of embryo invasion and later placentation [22].

Pretreatment in frozen-thawed embryo transfer cycles

It is also suggested that long-term pituitary down regulation before frozen-thawed embryo transfer (FET) cycles could improve pregnancy outcomes in women with adenomyosis. The implantation, pregnancy and ongoing pregnancy levels were significantly higher compared to the group without pretreatment with leuprolide acetate [23].

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FERTIVISION **2017**

The 13th Annual conference of Indian Fertility Society "FERTIVISION 2017" was held in Hotel Pullman, New Delhi from 8th, 9th & 10th December 2017.
There was a cutting edge scientific program delivered by renowned 16 international faculties and many Indian stallworts.
Total of 11 pre-congress workshops were conducted on 8th December covering wide variety of infertility related topics.
The scientific program on 9th & 10th December had 4 orations and 7 panels attended by 1350 delegates.
FERTIVISION 2017 has set a BENCH MARK FOR ITS ACADEMIC CONTENT, which is appreciated by the excellent feedbacks from International & National Faculties and Delegates.
Dr. K D Nayar
Organising Secretary

WORKSHOP No 1
IVF VIDEO WORKSHOP


WORKSHOP No 2
SEMENOLOGY VIDEO WORKSHOP

WORKSHOP No 3
REPRODUCTIVE ULTRAS1OUND - HANDS ON 3D & 4D SIMULATORS

WORKSHOP No 4
FERTILITY ENHANCING PELVIC ENDOSCOPY

WORKSHOP No 5
PGS & PGD WITH LIVE DEMONSTRATION



WORKSHOP No 6
CRYOBIOLOGY WORKSHOP WITH DEMONSTRATION

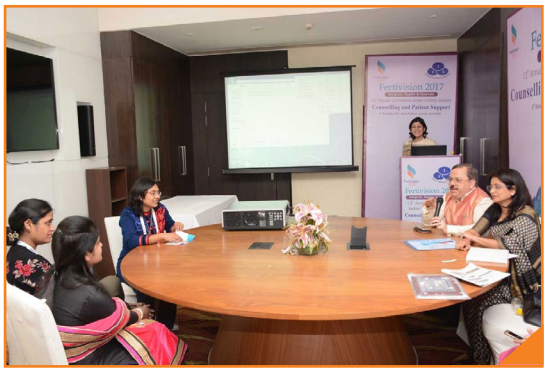


WORKSHOP No 7
QA, QC & DATA MANAGEMENT IN ART CENTRE


WORKSHOP No 8
IFFS WORKSHOP OVULATION / OHSS / COST EFFECTIVE STIMULATION


WORKSHOP No 9
HOLISTIC MEDICINE (YOGA & ACUPUNCTURE)

WORKSHOP No 10
COUNSELLING & PATIENT SUPPORT



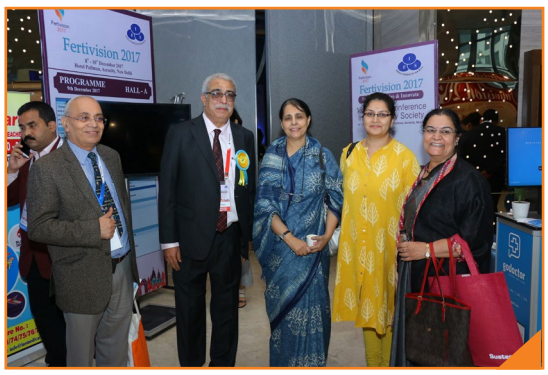
WORKSHOP No 11
WORKSHOP ON RESEARCH METHODOLOGY & PAPER WRITING

FACULTY DINNER
8TH DECEMBER, 2017

FACULTY DINNER
8TH DECEMBER, 2017

INAUGURATION
9TH DECEMBER, 2017

SCIENTIFIC SESSION
9TH DECEMBER, 2017



BANQUET
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BANQUET

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9TH DECEMBER, 2017



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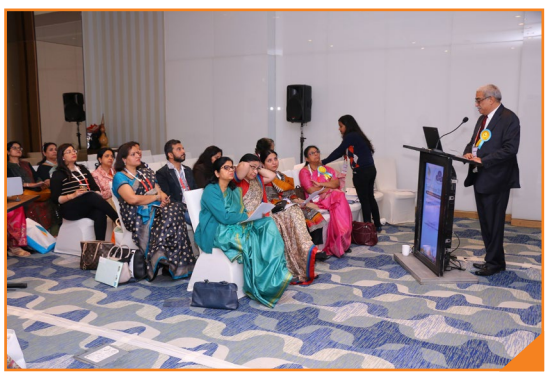







SCIENTIFIC SESSION

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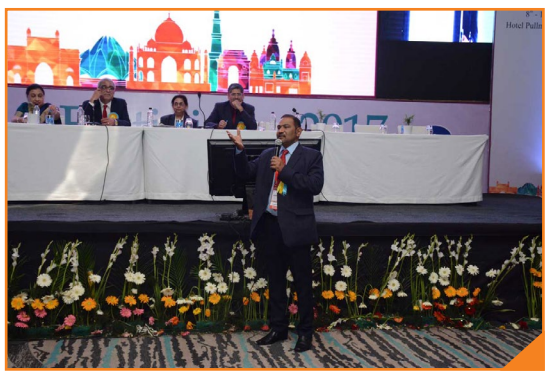
SCIENTIFIC SESSION
10TH DECEMBER, 2017

VALIDICTORY



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CHAPTER ACTVITIES

GUJRAT CHAPTER

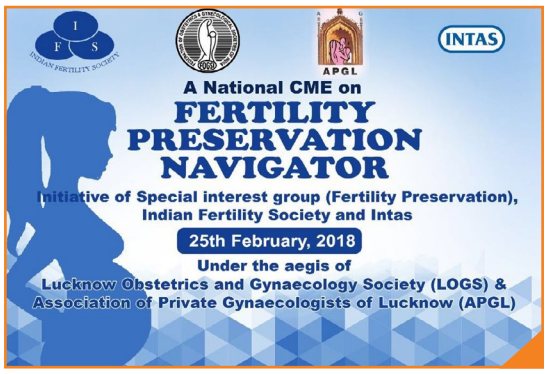
The 1st inaugural meeting of "Fertility Preservation Navigator - an initiative of Special Interest Group" under the banner of Indian Fertility Society (IFS) was held on 11th Feb 2018 at Novotel, Ahmedabad.

The event was organized under the guidance of Dr. Pankaj Talwar (SIG Convener)
and organizing team of IFS including local organizing chairperson – Dr. Jayesh Amin

UP CHAPTER

2nd meeting was held at Lucknow on 25th February 2018 at Hotel Clarks Avadh.

Fertility Preservation NavigatorInitiative of special interest group (Fertility preservation) Indian Fertility Society and Intas.



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Entrance Examination Syllabus: Clinical Reproductive Biology, Physiology, Anatomy, Endocrinology, Basic Embryology and Andrology. Clinical Genetics.

DIPLOMA IN CLINICAL EMBRYOLOGY

Eligibility: MBBS/Postgraduate in Medical Sciences or M.Sc./Ph.D in Life Sciences or Veterinary Sciences (Regular Course) from recognised institute in India.

Entrance Examination Syllabus: ICMR Guidelines, Basic Human Embryology, Human Cell culture, Genetics, TQM, Basic Semenology, Anatomy, Physiology & Pathalogy of Reproductive Biology.

Enterance Examination on 3rd June, 2018

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