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ENDOMETRIOSIS

VISION

PROTOCOLS FOR PRACTICE

By Dr. Nandita Palshetkar

SURGICAL MANAGEMENT OF ENDOMETRIOSIS

ENDOMETRIOSIS ASSOCIATED WITH FERTILITY





Dear FOGSIans,

Greetings !!

Endometriosis has a highly unpredictable nature that makes it very difficult to diagnose and treat. Moreover, infertility due to endometriosis can occur at any stage of the disease. In such cases, the quality of life is a priority for such patients.

We for Stree FOGSI campaign aims at prioritizing the management of this disease and easing the life of every woman suffering from Endometriosis and its complications.

FOGSI thanks Bayer for bringing forth the deeper challenges associated with Endometriosis and providing evidence based solutions under the guidance of FOGSI.

I am sure this book will add a great value to decision making when you encounter any case of Endometriosis. So, follow and practice. Lets promise a beautiful life for every suffering woman.

Best wishes!

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ENDOMETRIOSIS VISION

19th Feb 2019 - Mumbai meeting -
VISIONaries of **VISION** Endometriosis



Gynaec Stalwarts from across
India meet at Mumbai on 19th
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236 THINK TANKS across
India voicing their opinion on
ENDOMETRIOSIS contributing
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ENDOMETRIOSIS VISION

Ahmedabad – 3rd April, 2019



Ahmedabad

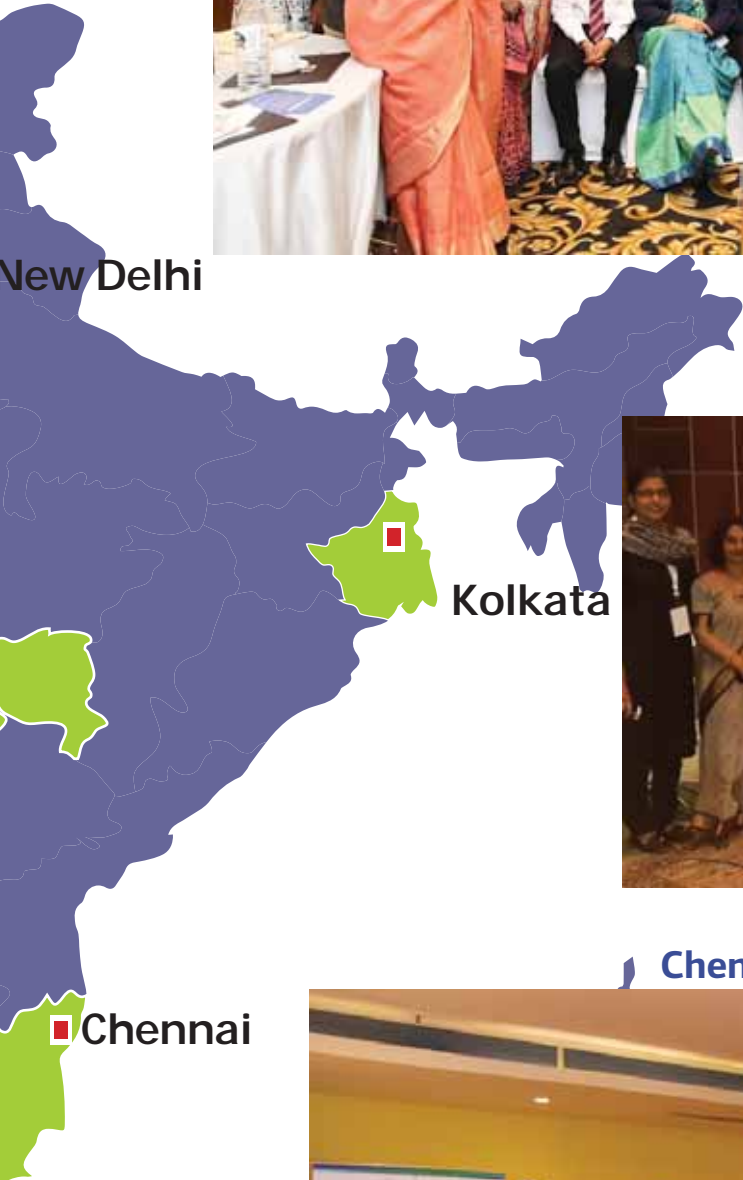
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SURGICAL MANAGEMENT OF ENDOMETRIOSIS

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SURGICAL MANAGEMENT OF ENDOMETRIOSIS

Introduction

- Surgery is the mainstay for the diagnosis of endometriosis.
- Surgery may be used primarily or when medical therapy fails, and also whenever there is recurrence not responding to medical treatment.²
- Surgical management of endometriosis may benefit women who suffer from severe disease and failed medical therapy.¹
- Surgical intervention has been an adjunct to medical management in the treatment protocol for endometriosis and chronic pelvic pain (CPP).
- A patient should be counselled about the risks involved with the surgical intervention and a balance of symptom relief, and complication risk must be weighed. (Table 1).

Table 1. Patient counselling

- Risk of recurrence
- Diminished ovarian reserve
- Risk of injury to adjacent organs
- Infection
- Conversion to laparotomy
- Post-operative medical treatment
- Incidental findings which do not have impact on treatment will not be tackled

- Laparoscopy is the gold standard in both diagnosing and managing endometriosis lesions and implants. It is the mainstay of surgical intervention due to decreased postoperative recovery time, pain, and infection rates over laparotomy.
- Laparotomy conversion is considered if there is difficulty in visualization due to extensive disease, and if there is involvement of multiple complex procedures involving other organ structures.
- Conservative therapy is fertility sparing and involves ablation or excision of peritoneal implants, resection of deep infiltrating implants, and removal of endometriomas.
- Hysterectomy with or without oophorectomy may be considered according to patient's needs.

The aims of current approach to managing endometriosis are treating symptoms of pain and infertility, while targeting disease progression, and preventing recurrence.

For women with severe disease who desire fertility, surgery followed by ART is a reasonable option.

Goals are to restore anatomy, excise or destroy lesion in-situ, remove adhesions, and prevent of recurrence.

Management goals

- Endometriosis affects about 5%–10% of women of reproductive age, hence there is a large population of patients undergoing surgical management.³
- Surgical intervention for endometriosis related pelvic pain may significantly reduce postoperative pain.⁴
- If there is the presence of rectovaginal adenomyotic nodules, surgery must be considered as first-line therapy, medical therapy being relatively inefficient.⁵
- The aims of current approach to managing endometriosis are treating symptoms of pain and infertility, while targeting disease progression, and preventing recurrence.
- Management goals may vary for the patients, young patients with mild disease not desiring children can benefit with medical suppression to control symptoms and minimize surgical intervention.
- For women with severe disease who desire fertility, surgery followed by assisted reproductive technology (ART) is a reasonable option.
- Goals are to restore anatomy, excise or destroy lesion in-situ, remove adhesions, and prevent recurrence.

Indications for surgical treatment

- The indications for surgical management are shown in Table 2.¹

Table 2. Indications for the surgical management of endometriosis¹

- Severe incapacitating pain symptoms with significant functional impairment
- Severe and advanced disease with significant anatomic impairment (distortion of pelvic organs and/or endometriomas)
- Failure of expectant or medical management
- Noncompliance with or intolerance to medical treatment
- Endometriosis emergencies: Rupture of endometrioma, obstructive uropathy, or bowel obstruction, and tubo-ovarian abscess

Surgical treatment of endometriosis

- Surgical intervention is the initial step in the diagnosis and treatment of endometriosis.

Conservative surgery

- The major goal of conservative surgery is to ablate or excise all visible endometriotic lesions, preserve the uterus and ovarian tissue, and restore normal pelvic anatomy.
- Surgical management for ovarian endometriomas greater than 3 cm in diameter has been shown to improve fertility outcome.
- Cochrane review: Excision of the cyst wall is better than drainage and cauterization of the cyst wall for relief of dysmenorrhea, dyspareunia, and non-menstrual pelvic pain.⁷
- Fertility related outcomes can improve after the excision of endometriomas, concerns that excessive resection of ovarian tissue can compromise fertility still exist.
- Laparotomy is useful for advanced disease with extensive adhesions or involvement of uterine arteries, ureter, bladder, and bowel.
- Laparoscopy is as effective as laparotomy in the treatment of ovarian endometriomas with the added benefit of a shorter hospital stay and quicker recovery time.

Pain outcome of the surgical treatment

Operative laparoscopy is an effective treatment for alleviating pain symptoms in women in all stages of endometriosis.

Surgical treatment options for endometriosis

- Surgical treatment is recommended for mild to moderate endometriosis to alleviate pelvic pain and increase postoperative conception in infertile patients.¹⁵
- Hysterectomy, bilateral salpingo-oophorectomy with the removal of all visible endometriosis should be the last resort for treatment of endometriosis especially in women with advanced disease who have completed childbearing or in women with intractable pain unresponsive to more conservative treatments.

Surgical intervention is the initial step in the diagnosis and treatment of endometriosis.

Laparotomy is useful for advanced disease with extensive adhesions or involvement of uterine arteries, ureter, bladder, and bowel.

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Operative laparoscopy is an effective treatment for alleviating pain symptoms in women in all stages of endometriosis.

Hormone therapy should be discussed with the patient when the ovaries are removed.

Surgery has good impact on painful complaints and postoperative conception in patients with deep endometriosis infiltrating the colon and the rectum.

Clinicians should consider conservative surgery in young and infertile women.

- The clinician should decide whether the surgery is indicated for pain relief, or for infertility or for both.³
 - » Exclude pelvic etiologies like primary dysmenorrhoea, interstitial cystitis, and irritable bowel syndrome (IBS) before planning for surgery.
 - » In women with known or suspected endometriosis laparoscopic surgery is preferable over laparotomy for the diagnosis and treatment of endometriosis associated pelvic pain and infertility. [Evidence level A]
 - » Consider both ablation and excision of the lesion to reduce endometriosis associated pelvic pain and infertility. (Excision provides sample for HPE) [Evidence level C]
- Removal of both ovaries may be necessary in perimenopausal patients or when the ovaries are extensively damaged by the disease.
- Hormone therapy should be discussed with the patient when the ovaries are removed.
- The possible beneficial effect of progestins should be balanced against the risk of breast cancer and the risk of recurrent disease.¹
- Cyst excision allows for better postoperative pregnancy rates when compared to ablation using bipolar current, as well as for lower recurrences rates when compared to ablation using bipolar current.
- Surgery has good impact on painful complaints and postoperative conception in patients with deep endometriosis infiltrating the colon and the rectum.
- Multidisciplinary approach should be considered in patients with deep infiltrating endometriosis (DIE).
- In advanced stages, pain is predominantly caused by organ damage, fibrosis, and adhesions, thus constituting a clear indication for surgical intervention.
- Early laparoscopy can prevent any delays in the diagnosis of disease or symptom progression.¹⁶
- Clinicians should consider conservative surgery in young and infertile women.

Hysterectomy

Hysterectomy with ovarian conservation

- In endometriosis, which is largely an ovarian disease, ovarian preservation should be of prime importance.

- If hysterectomy is indicated (woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriosis lesions at the time of the hysterectomy.²⁴

Hysterectomy with removal of ovaries

- The definitive surgery is hysterectomy with removal of the ovaries and all visible endometriotic lesions in women who have completed their family and failed to respond to conservative treatment.²
- Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.
- Inform the patient that recurrence rate is high if ovarian conservation is done along with hysterectomy.
- Counsel patient regarding risks and benefits of oophorectomy.
- Despite pharmacological treatment the size of endometrioma should be monitored.

Adjunct surgical intervention

- Presacral neurectomy have some benefit in young patient with severe endometriosis.
- Laparoscopic uterosacral nerve ablation (LUNA) for management of dysmenorrhea is not recommended.

Combination of medical and surgical approach

- After laparoscopic excision or ablation of endometriosis, consider hormonal treatment to prolong the benefit of surgery, manage symptoms and delay recurrence [options are Dienogest, Progesterone, Levonorgestrel-releasing intrauterine (LNG-IUS), Combined oral contraceptives (COCs), and Gonadotropin releasing hormone (GnRH) analogues]
- If hysterectomy is indicated (for example, if the woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriotic lesions at the time of the hysterectomy.

Treatment of endometrioma

- The endometrioma size, location, and transvaginal access for retrieval may all have a factor in determining whether patients require surgery.

If hysterectomy is indicated (woman has adenomyosis or heavy menstrual bleeding that has not responded to other treatments), excise all visible endometriosis lesions at the time of the hysterectomy.

Counsel patient regarding risks and benefits of oophorectomy.

LUNA for management of dysmenorrhea is not recommended.

After laparoscopic excision or ablation of endometriosis, consider hormonal treatment to prolong the benefit of surgery, manage symptoms, and delay recurrence (options are dienogest, progesterone, LNG-IUS, COCs, and GnRH analogues).

The age of the patient, endometrioma size and location are factors in determining whether patients require surgery.

Treating 'asymptomatic' endometrioma

- Surgery may be considered in 'asymptomatic' large and abdominally palpable endometriomas, due to a risk of rupture and emergency situation.
- The age of the patient, endometrioma size and location are factors in determining whether patients require surgery.

Treatment of endometrioma recommendations

- Appropriate consent has to be obtained before surgery.
- She should be fully informed of all possible risks associated with the surgical procedure, including general risks of laparoscopic surgery, a potentially reduced ovarian reserve, and the (albeit small) risk of loss of ovary and its consequences.
- The option of preoperative freezing of oocytes, should also be discussed especially in case of a bilateral disease.
- Consider adhesion prevention measures to reduce post-op adhesion formation.
- Using anti-adhesion materials e.g: oxidized regenerated cellulose, polytetrafluoroethylene (PTFE) surgical membrane, and hyaluronic acid (HA) products, as these may be beneficial in reducing postoperative adhesion formation.
- Surgery for endometriosis associated infertility can improve pregnancy rates
- Excision of cyst lining is preferred over drainage + under vision treatment of lesions in the cyst wall.

Post-surgical medical therapy for the prevention of recurrences

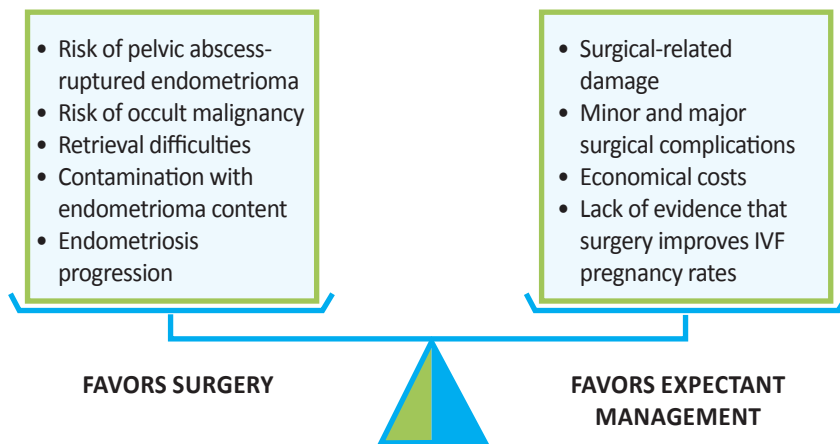
- Recurrence rates can be reduced by achieving pregnancy or post-operative hormonal treatment.
- Various options are Dienogest, Progesterone, LNG-IUS, COCs, and GnRH analogues.

- Although current RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially deep endometriotic lesions.
- Laparoscopic surgery for endometriosis should always be undertaken in preference to laparotomy, where possible.
- The addition of LUNA to laparoscopic removal of endometriosis does not improve pain relief.
- Although PSN (Presacral Neurectomy) might benefit a small number of women, the benefits are likely to be outweighed by the potential for harmful effects.
- Specialized surgical expertise is required by surgeons who undertake surgery for deep endometriosis, and it should be undertaken only at centres of expertise.
- The following IS the recommendation for managing the recurrence of endometriosis:

» Recurrence of the lesion is lower when cystectomy is done.

Recommendations for the surgical management of endometriosis¹¹

Figure 1. Surgery prior to IVF/ICSI cycles



IVF: In vitro fertilization ; ICSI: Intracytoplasmic sperm injection, Human Reproduction Update, Vol.12, No.1 pp. 57–64, 2006

The major benefit of surgery is achieved within 6–12 months of surgery.

Benefit of surgical treatment of stage I–II endometriosis and pregnancy rates³⁵

- In infertile women with endometriosis stage I/II operative laparoscopy (excision or ablation of endometriosis lesions) including adhesiolysis should be performed rather than a diagnostic laparoscopy only, since there is a positive effect in regards to live birth and ongoing pregnancy at 20 weeks of amenorrhea.³⁶
- According to ESHRE guidelines, in management of women with stage I–II of endometriosis, CO₂ laser vaporization of endometriosis should be considered instead of monopolar electro-coagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates.³⁷
- There is a positive effect in regards to live birth and ongoing pregnancy (20 weeks or more)

Benefit of surgical treatment of stage III–IV endometriosis and pregnancy rates³⁵

- Postoperative pregnancy rate vary from a of 30%–67%.³⁸
- 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.
- There is 50% reduction in pregnancy rates after re-operative surgery compared with first line surgery (22% for repetitive surgery versus 40% after primary surgery).³⁹
- 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.³⁸
- The major benefit of surgery is achieved within 6–12 months of surgery.

Surgery for endometriomas prior to IVF

- The benefit of surgery for endometriomas prior to IVF/ICSI:⁴⁰
 1. Inability to access follicles at oocyte retrieval for endometriomas which are >4–5 cms in mean diameter
 2. Concern that oocytes may be exposed to endometrioma fluid, which may damage oocytes
 3. The presumption that endometrioma resection would improve IVF outcome

Although there are a number of concerns, available evidence appears to indicate that:

- There is no reduced ovarian responsiveness with controlled ovarian hyperstimulation (COH) in women with endometriosis.³⁸
- There is no risk of growth or rupture of endometriomas with COH.³⁸
- Clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of abscess is low.
- Ovarian surgery seems to reduce the number of oocytes retrieved, to reduce the peak estradiol levels and to increase total FSH requirement. The ovarian surgery can lead to ovarian failure in 13% of the cases.³⁶
- In infertile women, resection of endometriomas larger than 3 cm does not seem to improve pregnancy rates,³⁶ thus the guideline development group (GDG) according to ESHRE guidelines recommended to consider cystectomy before ART to improve endometriosis-associated pain or the accessibility of follicles.
- The decision to proceed with surgery should be considered carefully if women have had previous ovarian surgery.
- Concerning deep endometriosis, there is no evidence to recommend performing surgical excision of deep nodular lesions prior to ART, to improve reproductive outcomes. However, these women often suffer from pain, requesting surgical treatment.³⁶
- ART treatments do not seem to increase the recurrence rate of endometriotic lesions or symptoms.³⁶
- Surgical treatment of endometriomas prior to IVF is widely practised, although debatable on its effect and need.⁴¹
- Women with a surgically-treated endometrioma have a lower antral follicle count and required higher doses of gonadotrophins for ovarian stimulation.⁴²

The decision to proceed with surgery should be considered carefully in women with previous ovarian surgery.

ART is more effective than repeat surgery in patients who failed to conceive spontaneously after surgery.

- Interestingly, women who had undergone surgical management for a unilateral endometrioma have reduced in the ovarian reserve following surgical intervention. The potential physiological compensation by the normal ovary for the compromised ovary, in conjunction with the higher follicle stimulating hormone doses required for ovarian stimulation, may account for the similar IVF outcomes noted in women who have undergone surgical treatments for their endometriomas.⁴³
- In women with minimal and mild endometriosis, surgical excision or ablation is recommended as 1st line with doubling the pregnancy rate.⁴⁴
- Skilled surgical management for symptomatic large DIE nodules infiltrating the rectum in young women is followed by a high pregnancy rate up to 4 years after surgery.⁴⁵
- ART is more effective than repeat surgery in patients who failed to conceive spontaneously after surgery.⁴⁴
- Management of ovarian endometriomas with Cystectomy vs. drainage and coagulations, is associated with an overall lower recurrence risk and higher spontaneous postoperative pregnancy rate, particularly if the cyst is 3 cm or more in diameter.⁴⁶

Controversies

- There is no reduced ovarian responsiveness with COH in endometriosis
- There is no risk of growth or rupture of endometriomas with COH.
- To date, there are no studies that proved an increased risk of abscess formation following oocyte retrieval in women with endometriomas
- Clinicians may use antibiotic prophylaxis at the time of oocyte retrieval, although the risk of abscess is low.

Women with endometriosis, and the presence of endometrioma, may require ART to achieve a pregnancy. Researchers observed that as compared to women with no surgical treatment, women who had their endometrioma surgically treated before IVF/ICSI had a similar live birth rate and a similar mean number of oocytes retrieved.⁴⁷

- Women with endometrioma undergoing IVF/ICSI have similar reproductive outcomes as compared with those without the disease, although their cycle cancellation rate are significantly higher.
- Reduced ovarian reserve is attributed to the presence of endometrioma per se, and the potential detrimental impact from surgical intervention, individualization of care for women with endometrioma prior to IVF/ICSI may help optimize their IVF/ICSI results.

In a meta-analysis including 10 studies that compared surgical treatment to no treatment reported that surgery for endometrioma had favorable effect on live birth rate per cycle (statistically not significant). However, no significant differences were noted in clinical pregnancy rate between women who underwent surgery for endometrioma and those who did not per cycle 1.08 [7 studies, OR 1.08 (95% CI: 0.80–1.45)]. Also, there were no significant differences in pregnancy rate per cycle among these women.⁴⁰

- No statistical difference in the number of oocytes retrieved and the total number of embryos created per cycle was observed
- No difference in between gonadotrophin ampoules used per cycle and the total gonadotrophin dose per cycle was observed
- No difference in the estradiol peak was noted in the two groups
- No difference between the pregnancy rate per cycle and clinical pregnancy rate per cycle between women who underwent surgery for endometrioma and those who had aspiration of endometrioma was observed
- Endometriosis-related infertility have similar cycle outcomes to other patients going through ART
- The risks of surgical intervention on ovarian reserve prior to initiating therapy should be assessed

Endometriosis-related infertility have similar cycle outcomes to other patients going through ART

The risks of surgical intervention on ovarian reserve prior to initiating therapy should be assessed

Case presentation

A 15-year old girl with a history of two prior laparoscopies for pain and ovarian cyst, and had undergone removal of a mucinous cystadenoma, presented to a gynecologist with chronic pelvic pain.

Treatment and management

The patient underwent a third laparoscopy and was found to have superficial peritoneal endometriosis and filmy adhesions due to prior ovarian surgery. Endometriosis was surgically destroyed with the use of cautery and filmy adhesions were lysed.

Few months later she had a return of pain and was advised a fourth laparoscopy with radical excision by an 'excisionalist' gynecologist. She was found to have superficial peritoneal disease with American Society for Reproductive Medicine (ASRM) defined Stage I endometriosis and underwent radical excision of the peritoneum of the anterior cul de sac, Pouch of Douglas (PoD) and both pelvic sidewalls. She was informed that she had been cured and was not treated with post-op hormonal suppression.

Pain worsened after the radical excisional surgery. She self-referred for care. She was given menstrual suppression with continuous COC therapy for medical treatment of endometriosis but after 6 months she was still having severe pain without bleeding.

Eight months after the radical excisional surgery she elected to have a fifth laparoscopy to address potential adhesions. At that time she was found to have extensive pelvic adhesions with uterus adherent to anterior cul de sac, and adhesions in POD. Both ovaries were involved with adhesions and adherent to the pelvic sidewalls. She was found to have clear and red lesions of superficial peritoneal endometriosis. She underwent a lysis of adhesions and excision of lesions and destruction of endometriosis.

Her pain improved post operatively; menstrual suppression was continued and she has remained with a continued excellent quality of life with over 2 years of follow up.

Case summary and conclusion

- For this patient, radical excisional surgery resulted in increased pain and extensive adhesion formation. It was not curative as endometriosis was documented on follow up surgery.

- Previous publications on long-term follow-up of adolescents with recurrent pain 2-10 years after destruction of superficial peritoneal disease, it was found that there were no increased adhesions and no trend towards disease progression.
- Excisional gynecologists who perform this procedure should not suggest that radical excisional surgery is helpful and without increased risk, until studies have demonstrated long-term benefit in the surgical management of superficial peritoneal endometriosis.

Discussion

- Adolescent endometriosis typically presents as Stage I with superficial peritoneal disease and less commonly as Stage III or IV with deeply infiltrative disease [DIE]
- Endometriosis lesions can be treated by radical excision with removal of the lesion and surrounding tissue or destruction (cautery or laser)
- It has been shown to be beneficial to excise DIE to improve pain
- Radical excision has been promoted by a subset of surgeons and involves removal of large areas of peritoneum with the promise/proposal of a cure and suggestion of no need for medical suppression of endometriosis.
- The best technique to manage superficial peritoneal disease has not yet been defined.

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ENDOMETRIOSIS ASSOCIATED WITH INFERTILITY AND FERTILITY PRESERVATION

- FOGSI President : Dr. Nandita Palshetkar
- Moderators : Dr. Nandita Palshetkar, Dr. Ameet Patki
- Panelists : Dr. Rakhi Singh, Dr. Tushar Kar, Dr. Sachin Dalal, Dr. Parikshit Tank, Dr. Kanthi Bansal, Dr. Monica Singh, Dr. Venugopal M, Dr. Fessy Louis
- Clinical Reporter : Dr. Rohan Palshetkar



From left to right: Dr. Monica Singh, Dr. Rakhi Singh, Dr. Fessy Louis, Dr. Venugopal M, Dr. Sachin Dalal, Dr. Nandita Palshetkar, Dr. Parikshit Tank, Dr. Tushar Kar, Dr. Ameet Patki, Dr. Kanthi Bansal, Dr. Ameya Purandare

ENDOMETRIOSIS ASSOCIATED WITH INFERTILITY AND FERTILITY PRESERVATION

Pathophysiology of endometriosis associated infertility

Pathophysiology¹

- Anatomical distortion
- Adhesions
- Immunology
- Inflammation
- Angiogenesis
- Epigenetic changes
- HOX 10, 11 gene disrupts implantation
- Oocyte quality is affected and ovarian reserve is decreased

Mechanical obstruction caused by pelvic adhesions

- Pelvic adhesion involving ovaries and tubes impair oocyte release from the ovary, inhibit tubal ovum pick up or ovum transport, and/or block sperm transfer into the fallopian tube in patients with moderate to severe endometriosis.²

Impaired embryo receptivity and implantation

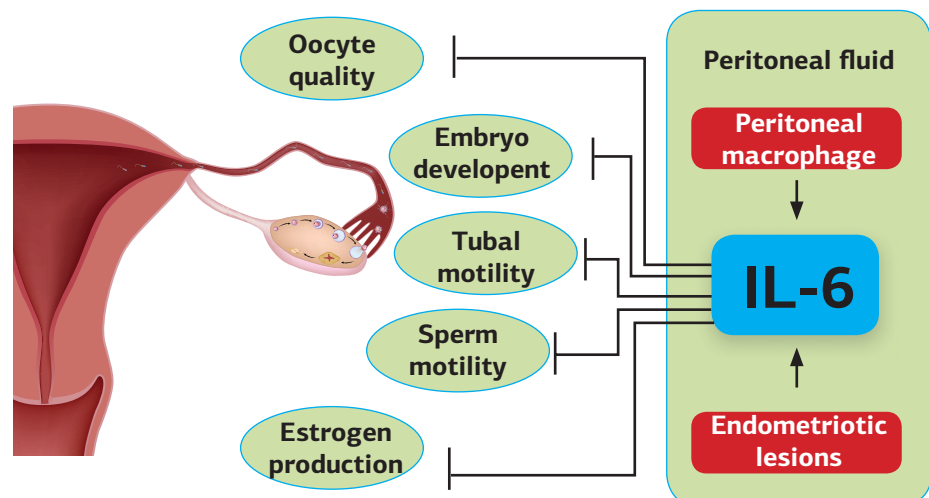
- A receptive endometrium, a functional embryo at the blastocyst developmental stage, and a synchronized dialogue between maternal and embryonic tissues is required for the successful implantation.³
- Endometrial development resulting in endometrial receptivity during the window of implantation requires the subtle collaboration of an extremely large number of different factors.⁴
- The following may affect implantation and endometrial receptivity:⁵
 - » The abnormality of decreased expression of integrin- $\alpha\beta 3$ in the endometrium of the patients with endometriosis.
 - » Increased immunoglobulin A and G, and lymphocytes in the endometrium as a result of peritoneal inflammation.

- » Abnormal production of estradiol by local inflammation
- » Progesterone resistance
- » Increased expression of cyclooxygenase-2 (COX-2) in the eutopic endometrium as well as ovarian endometriotic tissue, which causes abnormal prostaglandin production, and abnormal activation of the inflammation loop by cytokines, which results in local production of estradiol, and increases peristalsis of the myometrium.

Local and systemic inflammatory state with increased concentration of cytokines in peritoneal fluid

- In infertile women with endometriosis, the volume of peritoneal fluid (PF) is significantly elevated compared to those without endometriosis.²
- The PF in women with endometriosis has harmful action on ciliary in the human fallopian tube, sperm binding to the zona pellucida, and sperm acrosome reaction.²
- The endometriotic implants secrete estradiol and progesterone, which attract macrophages, vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8). Various local products, such as growth factors, and inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF- α), and angiogenic cytokines, such as IL-8 and VEGF are also secreted by the increased number of activated macrophages in the PF of patients with endometriosis.²
- Inflammatory state that is created reduces sperm motility and affects the metaphase-II oocyte spindle by impairing the microtubule and chromosomal structure, thereby contributing to infertility.²

Figure 1. Association of Interleukin (IL)-6 and infertility¹



Low ovarian reserve

- Superficial endometriosis and ovarian endometriomas have an adverse effect on the ovulation rates, markers of ovarian reserve, and response to ovarian stimulation.⁶

Endocrine and ovulatory abnormalities

- Decrease of ovarian function caused by repeated surgery from the endometrioma, or by the endometrioma itself may result in ovulatory problems associated with endometriosis.
- Endocrinologic ovulatory disorders occur due to ovulation of immature oocytes that induce an impaired luteal phase and abnormal folliculogenesis and abnormal follicular maturation in endometriosis patients.⁴
- There is an altered expression of estrogen and progesterone receptors in granulosa cells in advanced stage endometriosis.⁷

Abnormal follicle development and ovulatory dysfunctions in endometriosis is due to:

- Reduced number of preovulatory follicles, follicular growth, dominant follicle size, and follicular estradiol concentrations are reduced.²
- Decreased aromatase gene expression as well as estrogen production via the MAPK signal pathway in human granulosa cells in the peritoneal fluid of these women.²
- Higher incidence of apoptotic cells in the granulosa cells of women with endometriosis, indicating poor oocyte quality.²

Assessment⁸

- Age
- Duration of infertility
- Severity of symptoms
- Staging
- Previous surgery or treatment
- Assess ovarian reserve [anti-mullerian hormone (AMH) and antral follicle count (AFC)]

Superficial endometriosis and ovarian endometriomas have an adverse effect on the ovulation rates, markers of ovarian reserve, and response to ovarian stimulation.

There is an altered expression of estrogen and progesterone receptors in granulosa cells in advanced stage endometriosis.

Management of endometriosis associated infertility

For a woman with suspected endometriosis and infertility, the options for becoming pregnant are:⁹

Stage 1 and 2

1. Expectant management
2. *Timed intercourse for 6 months with age no other addition factors*
3. Controlled ovarian hyperstimulation (COH) + intrauterine insemination (IUI)
4. Assisted reproduction (ART)

Stage 3 and 4

5. COH + IUI (if tubo-ovarian relationship is restored)
6. ART

The clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF are listed in Table 1.¹⁰

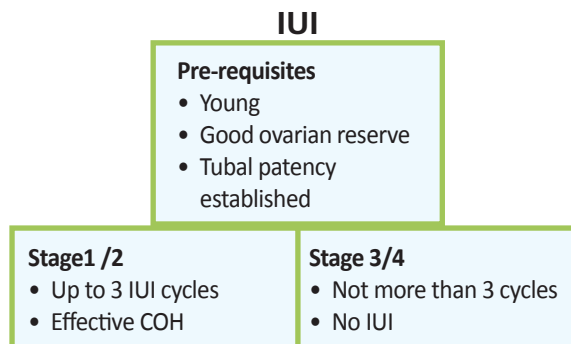
Table 1: Surgical decision for the endometriomas before IVF treatment¹⁰

	Favors surgery	Favors expectant management
Previous interventions for endometriosis	None	≥1
Ovarian reserve	Intact	Damaged
Pain symptoms	Present	Absent
Location	Unilateral disease	Bilateral disease
Sonographic feature of malignancy	Present	Absent
Growth	Rapid growth	Stable

- Women desirous of pregnancy should be recommended for fertility treatment after primary surgery ¹¹

Women desirous of pregnancy should be recommended for fertility treatment after primary surgery.

ART in women with endometriosis²



- IUI should be accompanied by COH using Gonadotropins.

Superovulation and Intrauterine Insemination (SO+IUI)

- IUI with partner or donor sperm is a simple procedure for optimal treatment of couples with minimal/mild endometriosis and normal semen quality.¹²
- Ovulation induction and superovulation (SO) with and without IUI increases fertility rates in patients without distorted anatomy.¹
- COH–IUI is better than expectant management in infertile women with endometriosis.²
- **As per the European Society of Human Reproduction and Embryology (ESHRE), IUI is only recommended in subfertile women with minimal-to-mild endometriosis, and IUI with controlled ovarian stimulation should be considered within 6 months following surgery in the treatment of infertile women with AFS/ASRM stage I/II endometriosis.**¹³
- IUI should be accompanied by COH using Gonadotropins
- In surgically diagnosed endometriosis patients randomized to human menopausal gonadotropin (HMG) with IUI and no treatment for four cycles demonstrated a cumulative live birth rate over 4 cycles of 11% versus 2% (p=0.002, OR 5.6 CI 1.8 to 17.4).¹⁴
- COH may improve pregnancy rates. The odds ratio was 5.6 (95% confidence interval 1.8 to 17.4) in favour of superovulation and IUI.¹⁴
- **SO/IUI is a reasonable early fertility treatment option for women with endometriosis who desire a short potentially more cost-effective treatment options prior to pursuing an IVF cycle and those for whom IVF is not a feasible or desirable option.**¹⁵

IUI with partner or donor sperm is a simple procedure for optimal treatment of couples with minimal/mild endometriosis and normal semen quality.

As per the European Society of Human Reproduction and Embryology (ESHRE), IUI is only recommended in subfertile women with minimal-to-mild endometriosis, and IUI with controlled ovarian stimulation should be considered within 6 months following surgery in the treatment of infertile women with AFS/ASRM stage I/II endometriosis.

IUI should be accompanied by COH using Gonadotropins.

Gonadotropins are most effective for superovulation in women with endometriosis who desire a short treatment option before IVF cycle.

Surgery has no effect on reproductive outcomes in women with endometriomas prior to undergoing IVF.

There is no significant differences in pregnancy rate per cycle, clinical pregnancy rate, and live birth rate between women who underwent surgery for endometrioma and those who do not.

- Gonadotropins are most effective for superovulation in women with endometriosis who desire a short treatment option before IVF cycle.¹⁵

IUI after surgery for endometriosis

- The COH-IUI intervention significantly increases the likelihood of pregnancy over one-year
- Surgery followed by COH-IUI is more effective than surgery alone.¹⁶

IVF and embryo transfer

- IVF is a viable option that can overcome the influence of distorted pelvic anatomy in infertile women with endometriosis.²
- IVF is preferred for infertile couples with male factor and tubal factor issues, or repetitively failed to conceive.³
- Women with endometriosis-related infertility have similar cycle outcomes to other patients going through IVF/ICSI. It is therefore essential for clinicians to assess the risks of surgical intervention on ovarian reserve prior to initiating therapy.¹⁸
- Surgery has no effect on reproductive outcomes in women with endometriomas prior to undergoing IVF.¹⁷
- There is no significant differences in pregnancy rate per cycle, clinical pregnancy rate, and live birth rate between women who underwent surgery for endometrioma and those who do not.¹⁸
- A study by Barri et al showed that the combined strategy of endoscopic surgery and subsequent IVF led to a total of 318 pregnancies, which represents a combined clinical pregnancy rate of 65.8%. This percentage is significantly higher than that obtained with surgery alone ($p < 0.0001$), with 173 patients who were not operated on and who went to IVF as the primary option ($p < 0.0001$) and with 169 patients who had no treatment and achieved 20 spontaneous pregnancies ($p < 0.0001$).¹⁹

Fertility preservation techniques for patients with endometriosis

Embryo/egg freezing

- Oocyte retrieval, IVF, COH, and embryo cryopreservation are the most established fertility preservation techniques (FPT).²⁰

- Cryopreserving oocytes instead of embryos, since it is a less invasive than other FPT, can be considered a good choice in patients affected by endometriosis.²⁰
- Cryopreserving oocytes has no effect on future ovarian reserve, and is a more realistic option for young women without a partner.²⁰
- The risk of pelvic infection or ovarian abscess formation during oocyte retrieval in the presence of ovarian endometrioma should be discussed during family physician consultation.²⁰
- If possible patients with endometriosis are encouraged to freeze oocytes at a younger age and consultation should address to the yield of age-related gamete freezing.²⁰

Ovarian tissue cryopreservation

- Ovarian tissue cryopreservation (OTCP) is currently used worldwide to preserve fertility in young women facing chemotherapy or radiotherapy who are at high risk of losing ovarian function.²⁰
- Healthy fragments of ovarian cortex can be isolated and cryopreserved during surgical removal of endometrioma.²⁰
- Ovarian tissue storing should be individualized according to patients' age, ovarian reserve status, presence of bilateral ovarian lesions, and repeated surgery for those patients with endometriosis undergoing surgery.²⁰

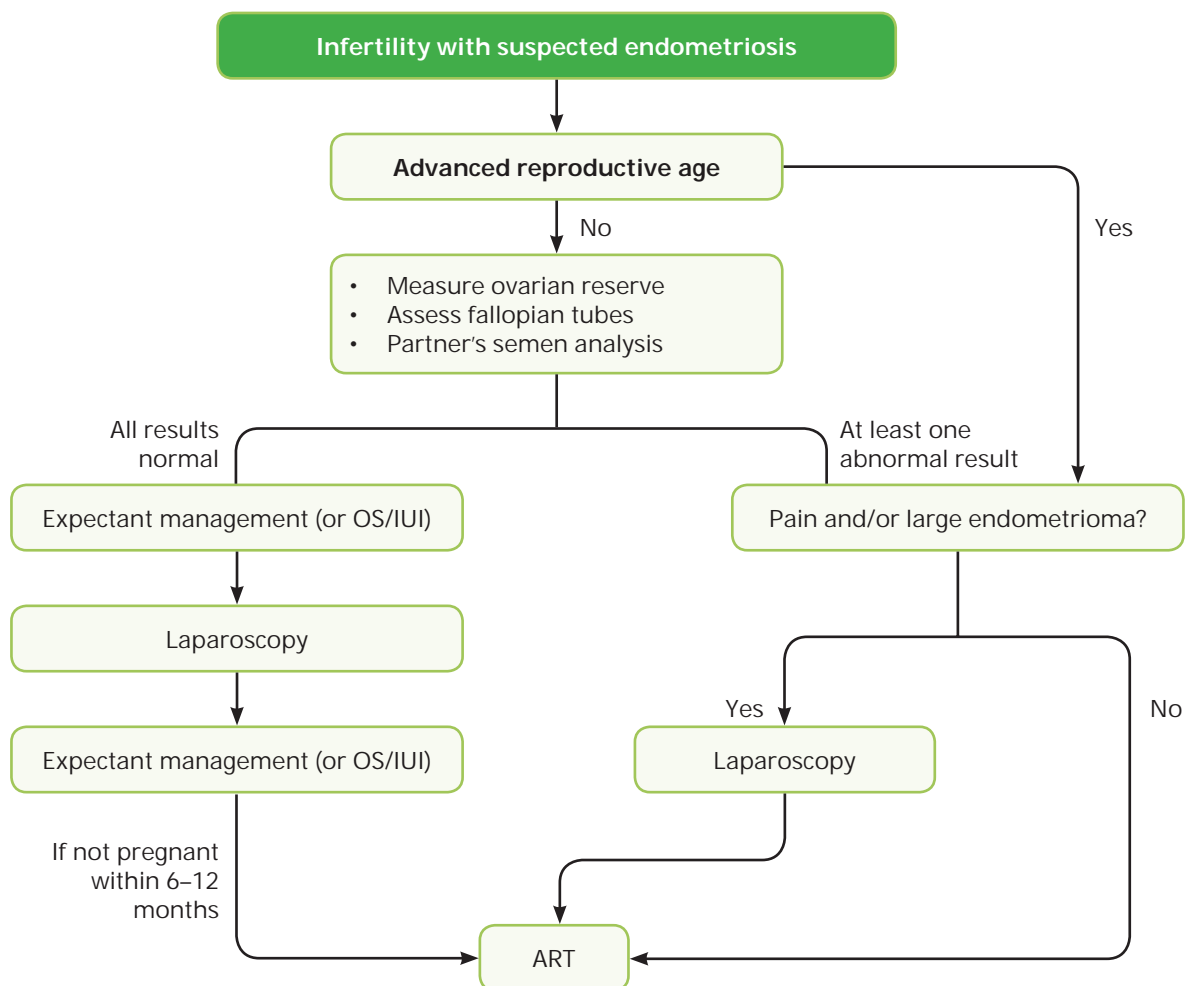
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Ovarian tissue storing should be individualized according to patients' age, ovarian reserve status, presence of bilateral ovarian lesions, and repeated surgery for those patients with endometriosis undergoing surgery.

Table. Fertility preservation techniques for patients with endometriosis: Pros and cons²⁰

EMBRYO/OOCYTE CRYOPRESERVATION	
Pros	Cons
Documented results especially when embryos are frozen	Risk of infections related to oocyte retrieval and abscess formation
No risk of procedure-related ovarian reserve depletion	Poor quality oocytes, embryos (controversial data)
The pick-up may avoid contact of the oocyte with the detrimental effect of the peritoneal fluid	Need of ovarian stimulation that might cause the progression of the disease (controversial data)
Patients suffering from endometriosis are frequent costumers of ART procedures	Need of repeated IVF cycles in order to collect an adequate number of oocytes that can be stored
OVARIAN TISSUE CRYOPRESERVATION	
Pro	Cons
Highly effective technique for fertility preservation	Laparoscopic procedure in these patients may be more difficult and risky
Easily performed during the surgical intervention for the disease	Storing tissue surrounding cyst or pseudocapsule—number and quality of follicles are questionable
No need of ovarian stimulation	Storing healthy tissue remote from cyst may result in ovarian damage and reduced ovarian reserve
Frozen tissue is spared from potential destruction in cases of disease recurrence	No results, so far, have been shown in this class of patients

Algorithm for the management of endometriosis-associated infertility²¹



SO/IUI: Controlled ovarian stimulation/intrauterine insemination.

Case presentation

A 36-year-old woman presented to the infertility clinic along with her partner. She reported that her menstruation progressively became heavier and more painful over the past 3 years. Recently, she had started having pain at the time of ovulation and with deep penetration during intercourse – especially immediately prior to menstruation. Radiographic evaluation indicated presence of endometrioma (Figure below). The couple had been married since past 5 years and had been having regular unprotected intercourse throughout this time, but were unable to conceive. The husband's sperm parameters were normal and evaluation of her post-coital cervical mucus was normal. Furthermore, in spite of five attempts at IUI, with use of clomiphene citrate for the first two cycles and gonadotropins for ovarian stimulation for the next three, the couple had been unsuccessful in achieving a pregnancy.



Figure. An endometrioma of the left ovary

Past medical history

The woman was diagnosed for 'unexplained infertility.' The diagnosis had been based on the findings of laparoscopy and hysteroscopy performed 4 years prior, which had revealed no evidence of uterine or pelvic pathology. Moreover, her menstrual history, home ovulation testing, basal body temperature charting, ultrasounds performed around the time of the luteinizing hormone (LH) surge (based on home ovulation testing), as well as mid-luteal phase plasma progesterone levels, ultrasound evaluation of her uterine lining, and endometrial biopsy, had collectively excluded organic pelvic disease and dysfunction ovulation.

Diagnosis

- Endometriosis associated with infertility.

Intervention

- The patient underwent laparoscopic surgery for the excision of ovarian endometriomas.
- IVF was planned 6 months post-surgery. GnRH analog (Ultra-long protocol of 3 to 6 months) was administered in the period prior to the IVF.
- .

Follow-up

- The patient experienced normalization of menstruation and regression of pelvic pain post-surgery. Uterine vascularization was also observed to normalize before the start of IVF protocol.
- The patient conceived after the IVF treatment.

Points of discussion

- Endometriosis associated infertility
- The better option in infertile women with endometriosis: IVF or IUI?

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