

FERTILITY FOCUS



NEWSLETTER

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An insight on latest development in the field of
assisted reproduction

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I N D E X

A R T I C L E	Page No.
● Adenomyosis and ART	01
● Challenges in infertility management in endometriosis	08
● Recent Advances in Medical Management of Endometriosis	19
● Surgery for early endometriosis -A stepwise approach	20
● Surgical Management of Severe and Deep-Seated Endometriosis	21

PRESIDENTIAL MESSAGE



Dear Friends,

Wish you all a very happy new year and a warm welcome to all in this emerging era from COVID pandemic. We suffered a lot during COVID pandemic in terms of loss of lives, economic, researches, and delay in treatment. But IFS has kept academics always at a great height. To overcome the darkness of COVID pandemic, let's start this New Year with hopes in the eyes to begin with new spirit to research in the field of ART.

It gives me great pleasure to write a short foreword for these new and exciting articles.

Endometriosis is a chronic inflammatory disease affecting 5-10 % of women in reproductive age group. Prevalence of endometriosis age 25-50 % in infertile women and 30-50 % of women with endometriosis presents with infertility. Laparoscopy and visualization is gold standard for the patient and treatment requires a holistic approach which results in multiple surgery for patient. These articles contain all the updated information needed for practicing gynecologist and indeed reproductive medicine specialist for infertile women with endometriosis. This Fertility Focus covers all aspects of treatment strategy for infertile women suffering with endometriosis and adenomyosis.

I hope the readers will get as much pleasure and new knowledge as I did.

I would like to place on record, my sincere thanks to Dr.K. D. Nayar, Dr. Nutain Jain, Dr. Rooma Sinha, Dr. Kuldeep Jain, Dr. Roya Rozati , Dr. Neeti Tiwari and Dr. Richa Khalia

Dr. Sudha Prasad
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Message from Secretary General, IFS



It gives me pleasure to forward "Fertility Focus" from the special interest group (SIG) on Endometriosis. Upholding the academic commitments of the society, Fertility Focus is yet another publication that covers each area in depth covering from basics to recent advances on the subject. Besides webinars and workshops, Fertility Focus is yet another effort of continued sharing of knowledge by the SIG.

Of the fifteen SIG, each one shall be deliberating through this publication, involving stalwarts to extensively review literature and deliberate it through the articles in each FOCUS. This issue contributes to the upcoming developments on the subject of Endometriosis unfolding many dilemmas and controversies on the subject. Hope our readers will find this issue resolving some of the controversies and dilemmas.

Congratulations to the sustained team efforts of the SIG on Endometriosis, including Dr. Roya Rozati and Dr. Neeti Tiwari, the convenor and co-convenor and the contributors of this issue of FERTILITY FOCUS.

Good wishes

Prof. Neena Malhotra
Secretary General, IFS

Adenomyosis and ART



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Adenomyosis is an emerging enigmatic disease for the clinicians, particularly the ART consultants. It is associated with dilemmas and grey areas in almost all aspects - be it epidemiology, diagnosis or treatment. Initially it was diagnosed only in parous women with the definitive diagnosis made on specimens obtained after hysterectomy on histology. Currently with better imaging techniques, it is being diagnosed with increasing frequency at earlier age and in patients with subfertility in infertility clinics. The dilemmas for clinicians begin with determining the accuracy of diagnostic tests to help screen adenomyosis early and setting gold standards of universal acceptability. ANOTHER AREA is to study the impact on infertility and the need for treatment of adenomyosis. Also the efficacy of medical vs surgical fertility sparing treatment needs further elucidation as also the reproductive and obstetric outcome in adenomyosis with or without treatment.

Epidemiology

Initially considered a disease of parous women over 40 yrs it is now being diagnosed with increasing frequency in infertility clinics at younger nulliparous women in infertility clinics. But a casual association between adenomyosis and subfertility is not fully established as of date with some advocating that adenomyosis is infrequent in subfertile women, while others incriminating adenomyosis in subfertility¹

Affects 30% of young women

More common in Asians and Africans

coexist with other co morbidities like fibroids, endometriosis

Pathogenesis-

Adenomyosis is characterised by disruption of the normal boundary between the endometrial basal layer and the myometrium with consequent benign invasion of endometrial glands into the myometrium. This ectopic adenomyotic foci should be at least 2.5 cm away from junctional zone to differentiate it from minimally invaginated basal endometrium. This innate endometrium gives rise to ectopic intramyometrial glands that cause reactive hypertrophy and hyperplasia of adjacent myometrium [2]. Postulated hypothesis is endometrium invaginating in the myometrium with facilitation by hyperestrogenism and mechanical forces causing dysperistalsis. Functional eutopic endometrium with its innate properties compounded by altered smooth muscles of myometrium are speculated to be incriminated. Evidence pointing causal association to endometrial invagination along intra-myometrium lymphatics is weak as it can explain only stromal myosis but fails to explain presence of functioning glands. Some proponents speculate influence of steroids in the pathogenesis. They point to local rather than systemic hyperestrogenism. There is a higher E₂ in menstrual but not peripheral blood via aromatase on androgen precursors conversion of estrone-3-sulp to estrone by estronesulphatase. In secretory phase there is increased conversion of E₂ to estrone because of altered 17- β hydrosteroid dehydrogenase type-2. Also in adenomyosis stromal and endometrial cells have a distinct proteomic profile. Also some endometrial cells have some features of smooth muscles resembling fibroblasts in proliferative phase and immature cells in secretory phase. This suggests some plasticity in endometrial-myometrial interphase. Some suggest altered angiogenesis as evidenced by polymorphism of two angiogenic factors, fibroblasts growth factor 1&2

Diagnosis:

Reference standard for adenomyosis is histopathology. On histopathology in adenomyosis there is the presence of ectopic endometrium in the myometrium. However different definitions vary in terms of the distance of eutopic endometrial foci from the endometrial-myometrial junction. Some define this minimum distance as one low power field [x10] others define it as one medium [x100] or high power field and in some it is 2.5 mm as a minimal distance in the diagnostic criteria of adenomyosis. This threshold distance needs to be defined to differentiate it from minimal invagination of basal endometrium which is a physiological variant. USG parameters used to define adenomyosis are- heterogeneous myometrial area, globular asymmetric enlarged uterus with asymmetrical anterior or posterior wall, nonhomogeneous myometrial echoes, irregular cystic spaces, myometrial linear striations, poor definition of endometrial-myometrial junction FIG 1,2,3. But there is no consensus on the no. of parameters required for diagnosis. Vercellini et al., 1998 used only one parameter [3], while some recommend the presence of all parameters for diagnosis [4] (Sun et al., 2010).

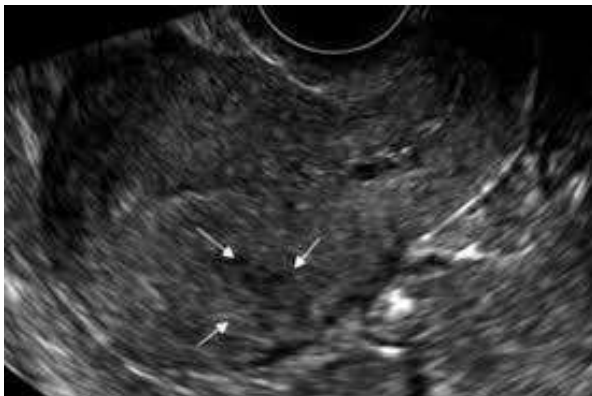


Figure 1

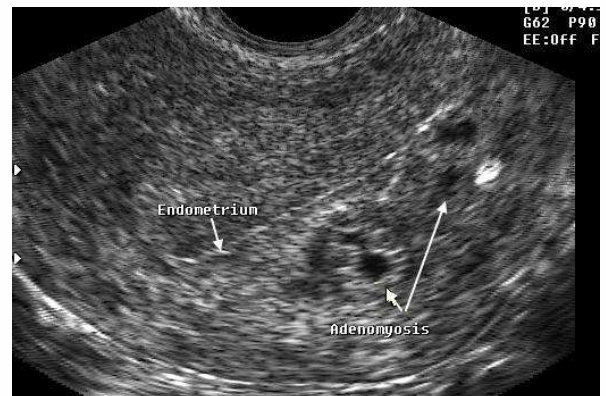


Figure 2

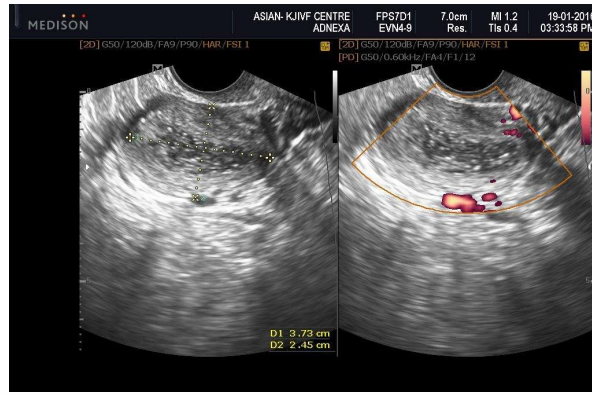


Figure 3

MRI is considered as the gold standard among non-invasive diagnostic tools. But there is a need to define threshold criteria and have internationally agreed definitions with defined cut off thresholds for thickness of junction zone, the prime diagnostic criteria [Kunz et al. 2005]. Some use expansion of anterior and posterior junctional zone (without mentioning any specific thickness), on the other hand some use a junctional zone thickness of >9 mm [Kissler et al. (2008) 16], some set this thickness threshold to 12 mm. Other features of adenomyosis on MRI are a large, asymmetric uterus without leiomyomas, ill defined junctional zone, low signal intensity myometrium in contrast to well circumscribed mass in fibroid, punctuate high intensity myometrial foci.

Effect of adenomyosis on infertility

-Better imaging techniques enabled earlier detection of adenomyosis on USG and MRI in nulliparous females attending infertility clinics. So this change in the trend towards detecting adenomyosis at an earlier age in nulliparous infertile females from the earlier trend which labels adenomyosis as a disease prevalent in the fourth or fifth decade leads to the speculation whether adenomyosis is the cause of infertility. This question becomes more imperative in unexplained infertility when there is no cause seen. So emerged the dilemma for the clinicians whether adenomyosis is associated with infertility and if so is treatment required. On literature search no study was found which aimed to see the effect of adenomyosis on fertility in natural cycles. Main impedance in pregnancy was speculated to be implantation failure esp in ART cycles [6,7, Martínez-Conejero et al., 2011] also document increased miscarriage rate /implantation failure in adenomyosis [8]. But on the other hand two conflicting studies show no effect of adenomyosis [9,10]

Tremellen and Russell 2011 [8] presented case series of 4 FEMALES with multiple IVF failure – RIF in which down regulation with ultralong protocol improved pregnancy rate. In contrast Mijatovic 2010 in an RCT of 74 women with adenomyosis associated with endometriosis showed no difference in outcome compared with 151 patients with only endometriosis in ultralong protocol [9].

Medical management :

In adenomyosis the role of medical treatment is palliative only. The therapeutic gain is symptomatic relief and not the resorption of lesion as there is no cytoreduction. The pathology persists despite treatment with any pharmaceutical drug, irrespective of any length of treatment or any dose and the disease presents again on discontinuation.

The main challenge is in the field of infertility as the treatment is achieved by suppressing hypothalamic pituitary gonadal axis, by suppressing ovulation, abolition of menstruation, inducing a stable steroid hormonal milieu, reducing endogenous estrogen or inducing endometrial differentiation. So gonadotropic agonists, OCP, progestin's, SERM, SPRM, aromatase inhibitors are used.

A hypoestrogenic environment [GnRH agonists, AI, hyperandrogenic [danazol] or hyperprogestogenic [OCP, progestin] is induced on treatment rendering the ectopic endometrium non-functional and suppressing endometrial cell proliferation.

GnRH agonist therapy:

Spontaneous pregnancies are documented within 2 yrs of cessation of long-term use of GnRHa.¹¹ The combination therapy of conservative surgery with a GnRH agonist also has been recommended. The therapeutic advantages / preferences of GnRH agonists over conservative surgery or over GnRH agonists combined with conservative surgery are debatable and recommendations and guidelines are required in this aspect.

Combination of conservative surgery with GnRH agonist/danazol

A meta analysis identified eight studies [4 – case series, 4 case reports] evaluating conservative surgery with or without GnRH agonist. The pooled live birth rate after this mode of treatment was 88.2% (15 of 17). In six studies GnRH AGONISTS WERE USED AND IN TWO Danazol was used. There was a considerable heterogeneity in the type of GnRH agonist, the duration and timing of use as well as the mode of diagnosis of adenomyosis before treatment was offered.¹² A retrospective study comparing conservative surgery with GnRH agonist versus GnRH agonist alone showed live birth rates following conservative surgery versus GnRH agonist alone were 32.14 versus 8%, respectively.¹³

Other conservative treatments include high intensity focused USG, uterine artery embolization. The use of a danazol-loaded intrauterine device) or a vaginal ring in infertility patients with adenomyosis was evaluated by Igarashi et al and they achieved a combined pregnancy rate of 41% (16 of 39) after insertion and removal of these devices.¹⁴

Scant data is available on Uterine artery embolization and high intensity focused USG to cause thermocoagulation are other conservative alternatives of indeterminate significance in treating infertility.

Kim et al. 2005¹⁵ published a study evaluating the effectiveness of uterine artery embolization in the management of adenomyosis and reported a live birth rate of 83.3% (five of six patients). Rabinovici et al., 2006¹⁶ published first successful live birth following USG thermocoagulation in a patient with adenomyosis.

The definitive treatment of adenomyosis is radical surgical treatment hysterectomy which is curative. This is done when multiparous female presents with dysmenorrhoea, menorrhagia in the fourth or fifth decade. But when infertility is the concern, role of fertility sparing conservative surgery for adenomyosis is debatable as it is not possible to isolate and hence excise the adenomatous tissue adequately. The reason for it is that the pathology is diffuse with indistinct boundaries with the normal tissue. Avoiding entering the uterine cavity requires skill and in 30% of cases is entered inadvertently and requires repair. Tensile strength of scar is compromised because of contained adenomyotic foci.

So fertility sparing surgery is done keeping this limitation in mind with the aim to improve reproductive outcome. No detrimental effect has been observed till date because of conservative fertility enhancing surgery.

Role of conservative uterine conserving surgery compared with GnRH agonists is not clear. There are no clear indications of which and when patient should undergo fertility conserving surgery and not GnRH agonist.

It is to be noted that when the size of uterus exceeds 12 cm [>12 weeks], bulk reduction surgery should be advised. Followed by GnRH agonist and ART. If it fails other alternative is hysterectomy with surrogacy and it should be done /advised.

In focal adenomyosis / diffuse adenomyosis, surgery can be done by laparoscopy /or laparotomy or lap with laparotomy. FIG 4. Laparotomy offers an advantage as palpation helps discern pathological tissue from normal. Takeuchi et al., 2006 17 reported live birth and Strizhakov and Davydov, 1995 18 reported pregnancy after conservative surgery involving excision of the adenomyotic tissue followed by hysteroplasty either laparoscopically or via laparotomy.

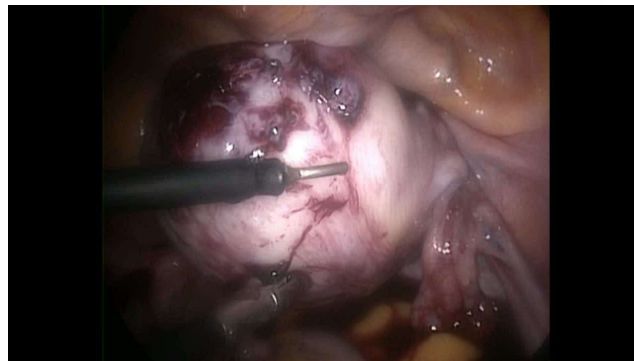


Figure 4

An overall live birth rate of 36.2% (21 of 58) was achieved following the conservative surgery. Fujishita et al., 2004 28 in a retrospective study compared the classical method of adenomyomectomy with a new modified reduction surgery [transverse H incision technique]. The classical technique involved a uterine incision followed by step-wise resection of adenomyotic tissue and closure. The newer technique modified the incision to the shape of an H and this was followed by raising serosal flaps and excision of the adenomyomatous tissue. The new technique was associated with a 50% pregnancy rate, compared with no pregnancy with the older classical method. The odd of having a live birth with the old classical method compared with the newer technique was 0.14 (95% CI, 0.00 and 4.47).19

The time to pregnancy was 4 and 6 months. The classical surgery involves V-shaped uterine incision followed by step-wise wedge resection of adenomyotic tissue followed by closure. Here adenomyotic tissue remains on both sides of the incision. The created wound is sutured but in the modified technique an H shaped incision followed by raising serosal flaps and excision of the adenomyomatous tissue is done.

Another technique involves wedge shaped removal of adenomyotic tissue with a thin margin after an incision. Another adenomyotic skill involves complete excision with a triple flap method. Asymmetric dissection of uterus longitudinally, dissecting myometrium diagonally, opening uterine cavity transversally adenomyotic tissue excised >5mm of inner myometrium, then >5mm of serosal myometrium and then suturing the cavity and removal of adenomyoma by morcellator. Literature is scant when fertility preserving surgery is making it difficult to draw conclusions.

Conclusion:

Adenomyosis presents a challenge as there has been changes in concepts involving this disease. Now it is detected in earlier age group in nulliparous infertile women in contrast to the previous belief that it is a disease of parous women.

Equally debatable is whether it is the cause of infertility especially unexplained infertility when there is no cause apparent for infertility. However there is enough evidence to suggest that implantation rates, pregnancy rate and live birth rates are significantly less in adenomyosis and high risk of miscarriage rates are reported. Ideal approach for these patients is GnRH followed by ART or a combination of GnRHa along with bulk reduction surgery followed by ART to give best outcome.

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Challenges in infertility management in endometriosis : A case based scenario

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Endometriosis is a chronic inflammatory disease affecting 5-10% of the women of reproductive age. In infertile women the prevalence of endometriosis as high as 25-50% while 30 -50% of women with endometriosis present with infertility. ⁱBiological mechanisms that link endometriosis and infertility are following ⁱⁱ

- ✓Distorted pelvic anatomy
- ✓Altered peritoneal function
- ✓Altered hormonal & cell-mediated function
- ✓Endocrine and ovulatory abnormalities
- ✓Impaired implantation
- ✓Effect on oocyte and embryo quality
- ✓Abnormal utero-tubal transport

Endometriosis being a chronic inflammatory condition is associated with low ovarian reserve, poor oocyte quality and impaired implantation which poses unique challenges in management of infertility in these patients. Following are few real cases of infertile women with endometriosis who posed challenges in their management with their final outcome.

Case 1

A 28 years old lady presented with inability to conceive for 3 years. She has regular menstrual cycles. Her investigations shows that S. AMH is 3.1 ng/ml, bilateral tubes are patent and husband semen analysis is normal. She has already taken clomiphene for 4 cycles with timed intercourse over a period of one year.

Will you consider laparoscopy in her?

Laparoscopy was shown to be cost-effective in initial management of young women with unexplained infertility. ⁱⁱⁱ Laparoscopy completes the evaluation and also gives an opportunity to 'see and treat' in unexplained infertility in young women. However, a recent review published showed that the role of laparoscopy in diagnosis of unexplained infertility is limited and if planned should be combined with therapeutic interventions if required. ^{iv}

In this patient after counseling patient was taken up for laparoscopy and the findings were

- * Endometriotic spots seen on post surface of uterus, uterosacral ligaments and ovarian fossa which were fulgurated
- * Bilateral tubes and ovaries healthy with normal tubo-ovarian relationship
- * On chromopertubation- Bilateral spill present

What is the role of surgery in minimal/mild endometriosis ?

Objective of laparoscopy in minimal and mild endometriosis is to destroy or remove all or most of the endometriotic implants . Cochrane review published in 2014 that removal or destruction of minimal and mild endometriosis improves fertility . It improves clinical pregnancy rate by a risk ratio of 1.44 (95% CI:1.24-1.68) and odds of live birth by 1.94(CI:1.20-3.16).^v

How will you proceed in this patient after laparoscopy ?

According to ESHRE Guidelines 2014 in infertile women with stage I/II endometriosis , clinicians may consider ovarian stimulation and IUI within 6 months after surgical treatment and pregnancy rates are similar to those achieved with unexplained infertility.^{vi}

Which drug to be used for ovarian stimulation for IUI in such patients ? Clomiphene, Letrozole or gonadotropins ?

Gonadotropins are not cost effective and at the doses which may give better pregnancy rates than oral drugs the risk of multiple pregnancy increases. Clomiphene and letrozole has been associated with similar live birth rates in unexplained infertility.

Outcome:

Patient conceived in second IUI cycle with gonadotropins and had a healthy live birth at term.

Case 2

A 32 years old lady presents with primary infertility for 3 years. Her ultrasound pelvis reveals 3 cm endometrioma in left ovary. Her S. AMH – 2.6 ng/ml and husband semen analysis normal. No tubal evaluation has been done so far.

How will you proceed ?

According to ESHRE guidelines (2014) in patients with stage III/ IV endometriosis operative laparoscopy can be considered instead of expectant management to improve spontaneous pregnancy rates.

Case 2 (operative notes)

- * Uterus normal in size and shape
- * Left ovary enlarged and adherent to the ovarian fossa. During adhesiolysis an endometriotic cyst (3 cm) drained , cystectomy done

- * Right ovary had endometriotic spots on the surface which were fulgurated.
- * Fimbrial end of left tube was adherent to ovary which was freed
- * Right tube and tubo-ovarian relationship normal.
- * On CPT – B/L free spill

What next after surgery?

Role of IUI after surgery:

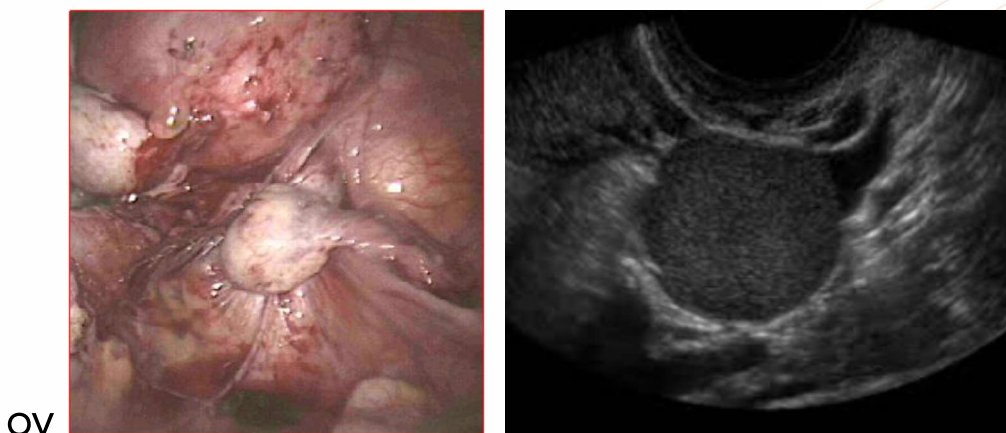
Both ASRM (2012) and ESHRE (2014) recommend that OS+IUI in settings of minimal and mild (stage I/II) endometriosis. But in moderate and severe cases also if tubal patency is established and good tubo-ovarian relationship restored after surgery, OS with Gn and IUI can be offered for 3-6 cycles before proceeding to IVF. [Mavrelou D, Saridogan E, The Journal of Obstetrics and Gynaecology of India. 2015;65(1):11-16.] A systematic review and meta-analysis of 19 observational studies (11 retrospective, 6 prospective) concluded that IUI could be a reasonable option over expectant management in moderate –severe endometriosis. Whether it should be structurally offered before IVF needs to be investigated by RCTs in terms of time-to pregnancy, safety and cost effectiveness.^{viii}

Outcome

The couple was counseled about the options and they chose to try naturally for 3 months and then try OS and IUI. She conceived in the second month after surgery which ended in a healthy live birth.

CASE 3

Mrs. J, 30 years old presented with primary infertility for 2 years. She underwent laparoscopy where she was diagnosed with severe endometriosis and was advised IVF after surgery. Her husband's semen parameters are normal. Her AMH was 2.3 ng/ml and AFC : 5 in each



Patient failed to follow up and came to us after 2 years. Now her pelvic ultrasound showed a 4 cm endometriotic cyst in right ovary and left ovary stuck behind the uterus and Serum AMH is now 1.4 ng/ml.

* Would you consider a repeat laparoscopy?

According to ESHRE Guidelines (2014) in infertile women with endometrioma greater than 3 cm, there is no evidence that cystectomy prior to IVF improves pregnancy rates. Infact the clinicians should counsel the women with endometrioma about the risk of loss of ovarian function after surgery hence decision for a repeat surgery should be considered carefully.

Indications of Repeat laparoscopy in endometriosis with infertility:

- * Rapid growth in the size of endometriotic cyst
- * Suspicious features seen on ultrasound / MRI
- * Inability to access the follicles in normal ovarian tissue
- * Excessive pain that can be attributed to the cyst
- * Risk of spontaneous rupture of cyst

Which protocol will you use in IVF for this patient?

Following considerations should be kept in mind while deciding protocol :

- 1.Age of the patient and duration of infertility
- 2.Ovarian reserve markers (AMH and AFC)
- 3.Stage of endometriosis
- 4.Presence of other confounding factors

Prolonged downregulation : Different mechanisms by which it works in endometriosis:

- * Suppression of ovulation by GnRH agonists reduces exposure of endometriotic implants to growth factors present in follicular fluid which is involved in proliferation of endometriotic implants.
- * There is a direct inhibition of proliferation of endometriotic implants by regulation of angiogenic and apoptotic factors.
- * Inhibition of menstruation reduces exposure to thrombin and its protease activated receptor; factor which leads to cell inflammation
- * Inhibition of uterine contractions also blocks mechanical stress

Pitfalls of Ultra-long protocol

- * Time-consuming
- * Dampens the ovarian response
- * Higher cycle cancellation rates
- * Side effects like vasomotor instability and bone loss

According to Cochrane review (2019) it is uncertain that long term GnRH agonist therapy pre-IVF in patients with endometriosis impacts clinical pregnancy rates , miscarriage rates or live birth rates.^{ix}GnRH antagonist protocol is suitable for both extremes of ovarian reserve in endometriosis. It is a good choice for poor responders, patient with poor ovarian reserve and endometrioma or after its surgical excision .

What problems do you anticipate during OCR?

- * Difficult to access the follicles beyond the cyst
- * Inadvertant puncture of the cyst with risk of spill and infection
- * Contamination of follicular fluid with endometriotic fluid
- * Ovaries stuck behind the uterus

Do you practice segmentation of IVF in severe endometriosis?

In order to limit the risk of disease flaring and optimize the results some authors propose GnRH antagonist protocol, agonist trigger and freeze all in endometriosis.[De Ziegler D, Pirtea P, Carbonell M et al. Assisted reproduction and endometriosis. Best Practice Res Clin Endocrinol Metab. 2019;33(1):47-59.] According to another study, GnRH antagonist protocol, freeze all and then frozen transfer after prolonged down-regulation has shown excellent outcomes in endometriosis.[Surrey ES et al. RBM Online. 2017]

Case 4

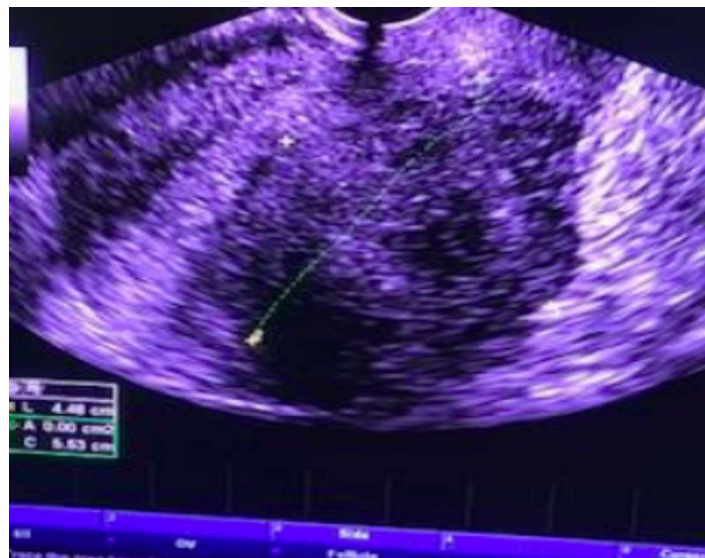
Mrs K, 36 years old complained of infertility for 5 years. Though her cycles are regular she has been experiencing heavy flow and severe dysmenorrhea for last 3 years. She gives history of laparoscopy done 3 years back where bilateral endometriotic cysts were excised, adhesiolysis done and uterus was found to be adenomyotic.

She has undergone two IVF cycles in past:

-1st June 2018, Antagonist cycle, FSH 225 +LH 75 from day7, OCR-6, 2 day 2 embryos transferred in fresh cycle -missed abortion

-2nd May 2019, Antagonist protocol, FSH 300+LH 75 from day 2, OCR -3, 1 day 5 frozen transferred - failed

Her pelvic ultrasound is suggestive of 2 cm endometrioma in left ovary and uterus has 5x4 cm diffuse adenomyotic area. Left tube shows 3x1.5 cm hydrosalpinx. Her S.AMH is 0.9 ng/ml and husband semen parameters are within normal limits



What are your concerns with adenomyosis and how do you counsel the couple ?

According to a recent meta-analysis (2017) adenomyosis adversely affects the clinical pregnancy rates, miscarriage rates and live birth rates in women undergoing IVF. [Younes G, Tulandi T. Effect of adenomyosis in in vitro fertilization treatment outcomes: a meta-analysis. FertilSteril .2017;108(3):483-490.] The authors also concluded that prognosis of diffuse adenomyosis is worse than focal adenomyoma and removal of adenomyoma may improve outcome.

Detrimental effect of adenomyosis on implantation:

- * Impaired endometrial –myometrial interface and vascular growth
- * Altered uterine peristaltic activity
- * Increased levels of prostaglandins in ectopic endometrium
- * Higher expression of P450 in eutopic endometrium
- * Decreased pro-implantation integrins and HOXA-10 gene expression.

How will you proceed for IVF in this couple ? Will you consider any pre-treatment ? Medical vs. surgical?

Pre-IVF management of adenomyosis

- * Diffuse adenomyosis has worse prognosis than focal adenomyoma
- * Surgical treatment is more feasible for focal adenomyoma (>5 cm) as it can be easily excised .
- * Prolonged down regulation with GnRH agonist appears to be beneficial
- * In order to avoid the detrimental effect of prolonged downregulation on ovarian stimulation, its use before frozen transfer could be more cost-effective.

Will you consider mock transfer in her ?

Performing a mock transfer is desirable in women with adenomyosis as the clinician can assess uterine cavity length and direction , pre-decide the type of catheter and know if there is any difficulty in transfer and be prepared.^{xiii}

Outcome :

Patient was taken up for antagonist cycle where FSH 300 +LH 75 was given from day 2. Five oocytes were retrieved and 3 day 6 embryos were frozen in 3 straws. Before frozen transfer, three doses of GnRH agonist depot were given 4 weeks apart. Ultrasound guided sclerotherapy of left hydrosalpinx was done .

How many embryos will you consider transferring ?

Adenomyosis is associated with second trimester miscarriage, pre-term birth and pre-eclampsia. Hence multiple pregnancy should be avoided and single embryo transfer preferred.

Do you consider Atosiban therapy during embryo transfer to improve her chances?

Women with adenomyosis are known to have abnormal uterine contractility. A recent RCT concluded that Atosiban treatment before embryo transfer in endometriosis is effective in priming the uterus making it suitable for implantation.^{xiv} More studies are required to validate this.

Outcome:

Single day 6 embryo was transferred. Patient conceived, had few episodes of APH in antenatal period due to placenta previa. Developed Pre-eclampsia at 34 weeks. LSCS done at 36+5 weeks, 2.4 kg healthy female baby born.

CASE 5

Mrs A, 31 years old presented with primary infertility for 5 years. She is a known case of Grade IV endometriosis, diagnosed on laparoscopy done in March 2019.

She gives history of 2 failed IVF cycles in past.

1st Sept 2019 – long protocol, OCR -5, ET- 3 day 3 fresh (quality no known)

2nd Nov 2019- Antagonist, FSH 225 + LH 75, OCR - 8, ICSI - 4 2pn, no embryos

Her serum AMH is 1.7 ng/ml. Husband semen analysis normal.

Whether ICSI should be done for all cases of endometriosis?

In a prospective randomized study on laparoscopically diagnosed moderate /severe endometriosis and normozoospermic males including 786 oocytes, it was found that sibling oocytes achieved higher fertilization rates with ICSI as compared to IVF (73.3% vs. 54.7%). According to this study, ICSI should be preferred over conventional IVF in endometriosis.^{xv} More evidence is required.

What abnormalities are encountered in oocytes in endometriosis? How is the fertilization rate in patients with endometriosis?

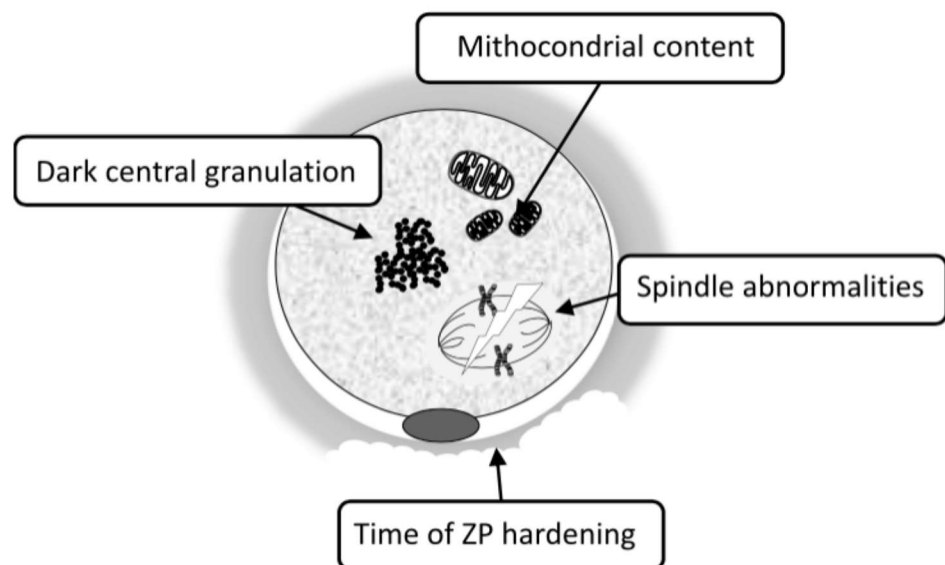


Fig. 1 Representative morphological changes in oocytes from women affected by endometriosis

Endometriosis and biological markers of oocyte quality

Ultrasonographic and histological data have shown that ovarian follicles in patients with endometriosis are decreased in number and are more atretic. The intrafollicular environment is also affected due to reduced P450 aromatase expression and increased reactive oxygen species. According to a systematic review, oocytes retrieved in women affected with endometriosis are more likely to fail in vitro maturation and show altered morphology and lower cytoplasmic mitochondrial content as compared to those with other causes of infertility. There is a definitely a reduction in number of mature oocytes obtained in these patients but its impact on fertilisation rate needs more scientific evidence

*** How will you proceed for her next cycle ?**

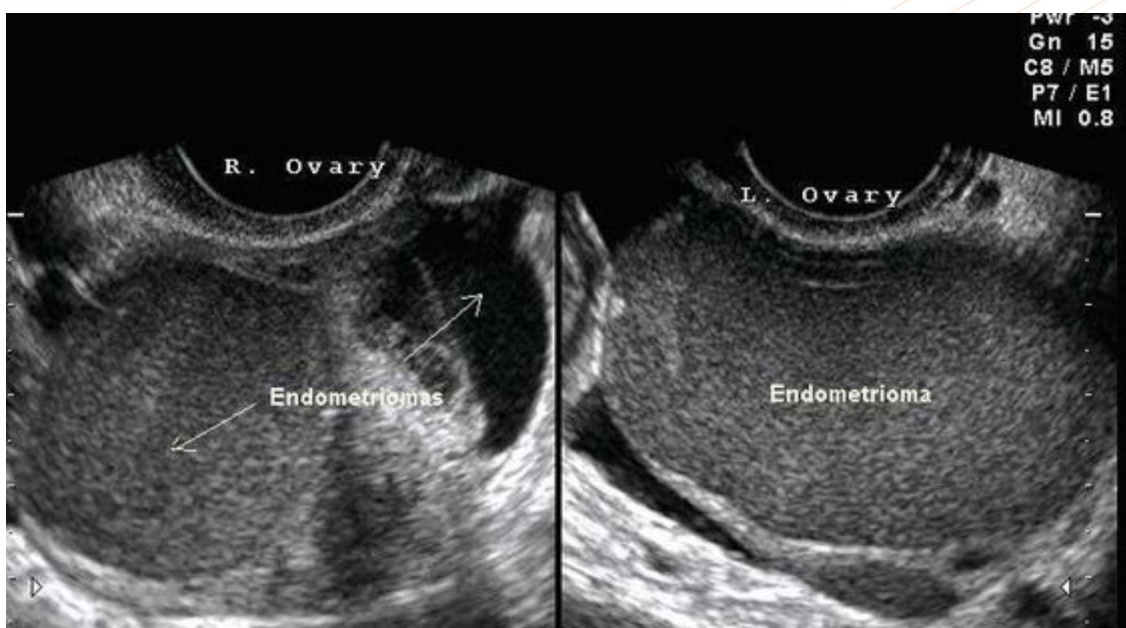
Case 5 (third ivf cycle)

The couple were counseled regarding their guarded prognosis in view of previous 2 cycles. She was given two doses of GnRH agonist depots 4 weeks apart. From 2nd day of cycle Inj FSH 225 and Inj LH 75 were started. Her final E2 was 1417 and 9 oocytes were retrieved out of which there were only 3 M II which were injected. Both OCC and Oocytes were poor quality. 2 Day 2 embryos (1-3C, 1-4C) were transferred which failed.

Now the couple has been offered donor oocytes.

Case 6

A 26 years old unmarried lady presented in casualty with complain of severe dysmenorrhea not relieved with analgesics. 3 years back she was operated for similar complaints where on laparoscopy bilateral endometriotic cystectomy and adhesiolysis was done. After surgery she received GnRH agonist depot injections for 3 months followed by combined oral contraceptive pills off and on but she left all medicines 1 year back. Her ultrasound pelvis revealed bilateral endometriotic cysts rt ovary 6x5 cm and left ovary 8x6 cm and S.AMH is 1.4 ng/ml.



Will you consider a repeat laparoscopy in her? What measures will you take during laparoscopy to preserve her ovarian reserve?

Since she has come with acute symptoms with large bilateral endometriotic cysts she will require repeat laparoscopy. Pre-operative counseling regarding the risk of lowering of ovarian reserve should be explained. Meanwhile during surgery care should be taken to preserve ovarian function.

Fertility preservation during surgery for endometriosis

- * Delay first surgery
- * First surgery by an experienced surgeon to delay recurrence
- * The plane between endometriotic cyst wall and ovarian cortex should be clearly delineated.
- * Care must be taken while doing dissection near hilum
- * Use dilute vasopressin to reduce bleeding
- * Avoid use of electrocautery, instead use suturing or hemostatic sealants

Fertility preservation in Endometriosis

Will you offer oocyte cryopreservation to her?

The following table summarises the fertility preservation in endometriosis:^{xvi}

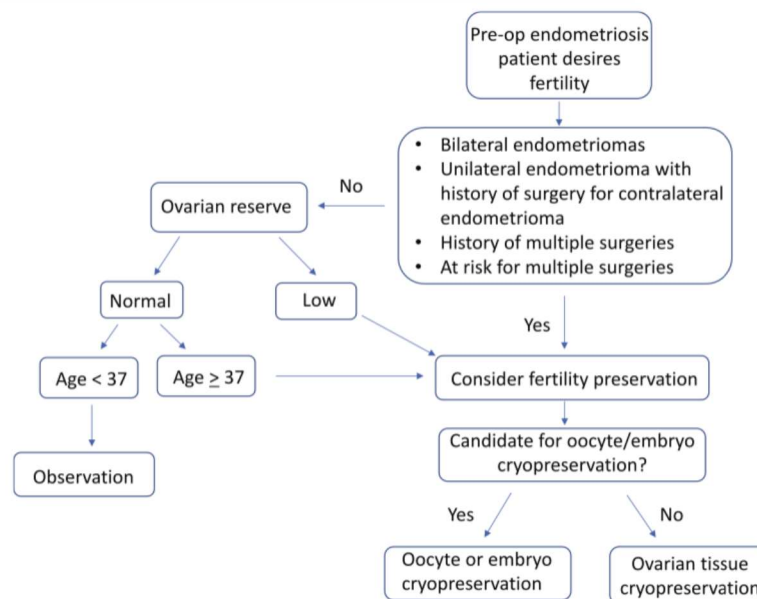


Figure 1. Practical approach to fertility preservation in presurgical endometriosis patients.

Follow-up :

The girl agreed to get oocyte cryopreservation done but she has concern regarding increased recurrence of endometriosis after COH. How will you counsel her ?

Recurrence of endometriosis after IVF

A Systematic review of 16 studies concluded^{xvii} :

- * Endometriosis related pain is not worsened by IVF
- * IVF does not increase the risk of recurrence of endometriosis
- * A mild increase, if at all may occur in the size of endometrioma (low-quality evidence)
- * Deep endometriosis may get worsened by IVF (very low quality evidence)

TO CONCLUDE ...

- * Low ovarian reserve is often a challenge in endometriosis due to disease per se and the surgical treatment
- * Prolonged down regulation may be beneficial in severe endometriosis but can further blunt the ovarian response.
- * Emerging interest is seen in segmentation of IVF in endometriosis, freeze all and frozen embryo transfer after prolonged down regulation.

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Recent Advances in Medical Management of Endometriosis



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ABSTRACT:

Endometriosis is an enigmatic disease which is supported by various theories. The main sequelae of endometriosis are represented by infertility and chronic pelvic pain. In the last decades, manifold pharmacological agents have been tested for the treatment of endometriosis. Till date, the first line treatment of endometriosis associated pain is still represented by continuous use of oral contraceptives. Progestins are considered as an acceptable alternative. The current treatments are either surgical or hormonal, however having limitations like the risk of recurrence, side effects, contraceptive effect for women desiring pregnancy and cost. Various new classes of drugs like Aromatase inhibitors, Selective estrogen receptor modulators, Selective progesterone receptor modulators, are being used apart from Gonadotropin Releasing Hormone analogues, progestins, dienogest and danazol. The progesterone resistance is counteracted by various progestins (medroxyprogesterone acetate, dienogest, danazol, levonorgestrel) or by selective progesterone receptor modulators. The future studies should define new drugs to use for prolonged durations with poor side effects by considering that endometriosis is a chronic disease.

Keywords: Endometriosis | Dienogest | Aromatase Inhibitors

Surgery for early endometriosis -A stepwise approach



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ABSTRACT:

Endometriosis is a chronic inflammatory condition which is difficult to diagnose. Treatment requires a holistic approach which may result in multiple surgeries for the patients. It's a lifelong disability for the patient and one needs to be aware of the patient's symptoms and desire at that point in her life to be able to counsel an institute an appropriate treatment. As we do not have any biochemical tests to confirm endometriosis, hearing to patients symptoms and digital pelvic exam are still relevant in diagnosing endometriosis. Laparoscopy and visual lesion is the gold standard in diagnosis. Pain and infertility are the two main issues for which a surgical intervention is often sought. Rarely a suspicion of lurking malignancy may warrant a surgery. The first surgery has the best outcome and gives the patient the best shot to a long-term solution. Hence it is recommended that surgery for endometriosis should be done both by an experienced surgeon as well as at a centre where all infrastructure is available. Being an adhesive disease, it is common knowledge that adhesions can be difficult to manage during laparoscopic surgery. However, there is no doubt that minimal access surgery either laparoscopy or with robot assistance gives an excellent surgical outcome and should be offered to patients. The surgical options in endometriosis are either a conservative approach or complete ablative surgery removing the uterus along with both the ovaries. The two technical issues with the surgery are the possibility of loss of ovarian reserve and recurrence. Ovarian tissue loss results from damage to the healthy cortex and the follicles, and prolonged use of electrosurgery especially at the hilum. Recurrence after surgery is dependent on the disease volume at the time of the surgery. Patients with advanced stages of the disease, bilaterality and large cysts have higher chance of recurrence. The surgical techniques that are used which depend on the skill of the surgeon is one of the most important factors that determines the outcomes in terms of ovarian reserve and recurrence.

Surgical Management of Severe and Deep-Seated Endometriosis



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INTRODUCTION:

It is impossible to manage infertility without addressing endometriosis adequately, with its incidence in this group being almost 50%(1). Symptomatic infertile patients or where IVF efforts have failed, definitely deserve surgery, but decision in rest of the cases is more ambiguous (2). Once surgery is decided, it becomes our responsibility as caretakers to either evolve or delegate for optimum surgical benefit, since deep infiltrating & severe endometriosis still remains a management challenge. It is the most commonly under treated or abandoned surgery.

Endometriosis famously distorts the anatomical planes, obliterates POD, causes adhesions around the uterus, ovaries and tubes. The extra genital manifestation and deep infiltration which is around 5mm deep is named deep infiltrating endometriosis (DIE). It affects rectosigmoid & rectovaginal septum (70-86%)(3), appendix(15%), caecum, retroperitoneum, ureters, bladder, lungs, vagina and even scar tissue. "What the mind doesn't know the eyes doesn't see." Being aware of these possibilities helps us diagnose them. Preoperative assessment can't be stressed enough and is the mainstay of triage and management of these patients.

PREOPERATIVE ASSESSMENT

History taking is vital. While infertility is our main concern, adjunctive symptoms like cyclical- pelvic pain, dysmenorrhoea, deep dyspareunia, bowel and bladder symptoms (like cyclical dyschezia, diarrhoea, constipation, dysuria) should be patiently elicited. Patients may need prompting, since they may believe that one has nothing to do with another. Examination should be meticulous including speculum examination for vaginal nodule, PV/PR/bimanual examination for any induration in rectovaginal septum which may indicate DIE(4). Here it is important to look for involvement of rectal mucosa, its extent in terms of lateral/ post wall, distance from anal verge, diameter of the lesion etc. Induration of uterosacrals and nodularity of POD may indicate a challenging surgery.

Ultrasound(TAS + TVS+ TRUS) forms the mainstay of its assessment and is a modality that most infertility specialists are very comfortable with. Endometriomas, adhesions, relative immobility aren't usually missed. POD obliteration, hydroureter/ hydronephrosis/ non-functioning kidney, rectovaginal nodules, adhesions to the pelvic sidewall should be looked for, as these cases require additional preparations like ureteral catheterization, multidisciplinary involvement. TVS is very effective in skilled hands & can diagnose and exclude DIE in RV septum effectively(5). It is a good practise to approach TVS systematically and compare your findings intraoperatively to develop pattern-recognition skills. MRI, cystoscopy, barium enema can be other adjuncts in a disease affecting these non genital regions. Around 200 Bio markers, including Ca-125 have been evaluated for prediction of disease and severity and were found ineffective.

SURGICAL MANAGEMENT

Surgery for endometriosis is for the brave hearted, but this bravery should be judicious and backed with experience. Laparoscopy is the modality of choice being minimally invasive, but also because it affords better visualisation, magnification of the surgical area & pneumoperitoneum assists in retroperitoneal dissection. Therapeutic surgery should be combined with the diagnostic procedure instead of scheduling two different ones. Benefits of surgery on infertility become more with increasing severity. Research has shown salutary effects of surgery on both cumulative and spontaneous pregnancy rates (51 to 81%)(6). Prerequisites to operate on severe endometriosis and DIE are understanding of avascular spaces of pelvis, neurovascular bundles, energy sources, availability of multidisciplinary care & expertise with retroperitoneal dissection.

Preoperative preparations

A detailed consent with the patient about the planned & possible surgery, complications, expectations, future planned fertility procedure, effect on ovarian reserve, possibility of bowel, bladder, ureteric resection in high risk cases is must.

Optimization of any comorbidities, cessation of aspirin, or combined hormonal pills prior to surgery to avoid bleeding and thromboembolism respectively becomes even more important here because of the higher use of these drugs in these patients. Liquid diet 2 days prior to the surgery and preparing the bowel the preceding evening with peganol, helps with better visualisation and limiting spillage in inadvertent injury.

Intraoperative preparations

EUA preoperatively may yield new information. WHO pre op check-up helps in bringing the whole team to same wavelength and discourages any errors due to complacency and miscommunication. Some methods of dissection are

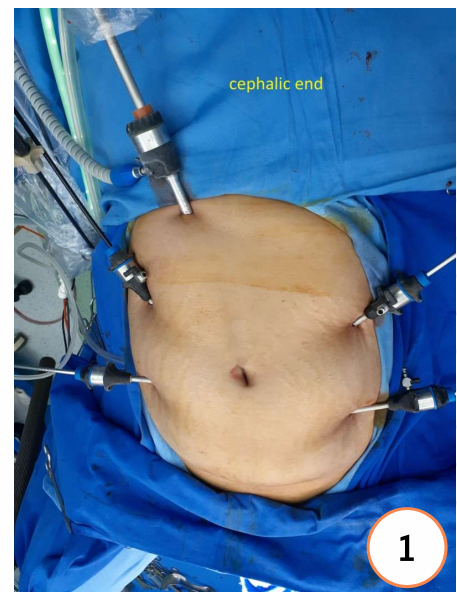
1. Blunt hook scissors with/without mini-bipolar cautery
2. Harmonic shears
3. CO2 laser/ any of low energy devices
4. Aqua-dissection

Amongst one of the emerging methods is CO2 laser with hydrodissection. Use of hydrodissection with infiltrating ringer lactate over ureter or rectum, lifts the scar tissue away from them and has been increasing used in combination with CO2 laser (its penetration is stopped by the water underneath). It is alright to be guided by personal experience and familiarity in your choice.

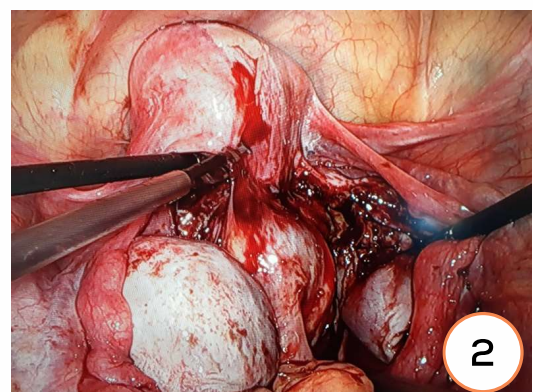
Port placement should be optimised for difficult dissection with ports placed a little higher than usual (Fig. 1). Anaesthetist should avoid nitrous oxide to avoid insufflation of gut. Deep trendelenburg with dorsal lithotomy is the position of choice (after inspecting upper abdomen, gut and diaphragm for disease). Finding the perfect planes for dissection require traction and countertraction. Strong uterine manipulator (eg. Rumi), a rectal probe and a sponge holder with a swab to delineate the vaginal fornix (Fig. 2) can make surgery much easier. Appendix and caecum are always examined, being the second commonest location of DIE at around 15%.

FIGURES:

1. Optimum placement of ports for a difficult case; notice the camera and working ports are placed more cranial



2. Post Rectal adhesions with ovarian endometriomas



Principle of surgery

Basic tenets of this surgery are -

1. Excision of all visible disease
(Excision of infiltrated part of rectum, bladder and ureter may be a part of this excision)
2. Restoration of normal anatomy
3. Prevent or delay recurrence

Need to go more radical with more morbidity and complications, has to be balanced against risk of leaving disease and an infinitely more difficult surgery later. This is where the experience counts most, to know when to be bold and when to not meddle and refer.

Steps of surgery – Ovarian endometriosis

All endometriomas larger than 3cm are recommended for a cystectomy instead of drainage & fulgurating the base. However, the surgery can cause a decrease in postoperative AMH and AFC(7)& should be done meticulously and gently in a good plane of cleavage. Incision should be at most bulging part of the endometrioma or opposite to the meso-ovarium to avoid damaging the blood supply and consequently the ovarian reserve. It is worth spending some extra time to find the correct plain. Avoid using traumatic grasper on the ovarian side, minimize use of cautery esp. on the mesenteric end. In patients with poor ovarian reserve or prior ovarian surgery, there is merit in considering a trial of assisted reproductive techniques, before subjecting them to a surgery that may further deteriorate ovarian reserve. Adhesiolysis should be done, tubo-ovarian relationship restored. Dissection of ovary from the pelvic side-walls can be perilous, & if required should be assisted by retroperitoneal dissection and ureterolysis. Case reports of ureteric injury & non-functioning kidneys are not uncommon. ICG and ureteric catheterization are essential adjuncts for surgeons taking these cases heads-on.

Steps of surgery – dense adhesions

Intestine, omentum, adnexa, POD and uterus may be adhered to each other, making dissection very hazardous. Using painstaking patience and meticulous technique, dissection to be started from the area of thinnest, transparent adhesions. Another approach is to start at the pelvic brim to trace the ureters, next ovaries are dissected and moved anteriorly along with the tube and may also be temporarily suspended anteriorly to ease approach to POD by using a T-lift.

Steps– DIE/ obliterated POD

Some experts consider DIE to be a separate entity & may appear independently or in conjunction with other phenotypes. It may be completely retroperitoneal and not readily appreciated requiring closer inspection of POD. Rectal tenting reliably predicts involvement of rectovaginal septum. Opening B/L pararectal spaces & tracing ureters till the uterosacral helps

in difficult Rectovaginal dissection. Uterus is stoutly anteverted with uterine manipulator and rectum made prominent using a rectal probe and then an ant rectal wall shaved off the post cervix and allowed to fall back till the rectovaginal space (a clear cotton candy space) is seen caudally. RV nodules can be held with forceps and shaved from the rectum posteriorly(8). Any affected vaginal or cervical region is excised with 1 cm clear margin and repaired, excision on the rectal side is more conservative with margin with fibrosis instead of clear margin deemed acceptable.

There are times when the disease infiltrates into deeper layers of muscularis or mucosa. In such patients involved part of rectum needs to be excised to prevent a worse disease in the future or a stricture. This can be in the form of disc excision where a disc shaped area of full thickness of rectum is removed and re-sutured using disc staplers transrectally. Generally, infiltrating lesions less than 3 cm diameter, involving less than 50% of rectal margin, 8- 10 cm from the anal verge can be tackled by this method making a more risky and complicated resection anastomosis unnecessary(9).

Any lesion beyond above parameters or where it has not been possible to do a disc resection are dealt with rectal resection anastomosis(10). It goes without saying that both these procedures need liaison with a competent GI surgeon & are not uncommon in specialised endometriosis centres. While technically challenging, these are very rewarding as recurrence of rectovaginal disease is very low.

Steps – other non-genital sites

Attempts to exercise any symptomatic infiltrating growth in bladder, diaphragm and GI should be made. Ureter may also be involved, any intrinsic involvement may need excision of the affected part uretero-neo-cystotomy with a psoas hitch. This may be a 2 staged procedure especially if B/L ureters are involved.

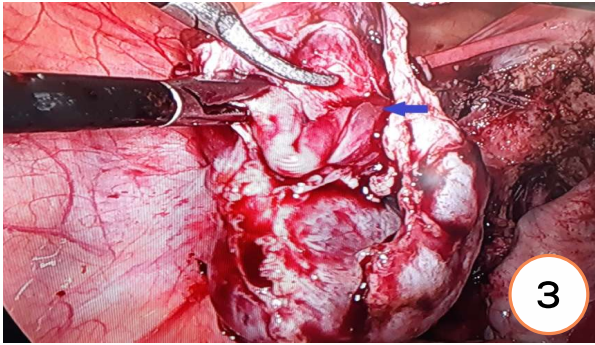
Assessment for bladder & rectal injury is essential. Adhesion prevention forms an important part of the surgery, with iso-dextrin, ringer-lactate, barriers are all used without a conclusive winner.

RESPONSE AND RECURRENCE

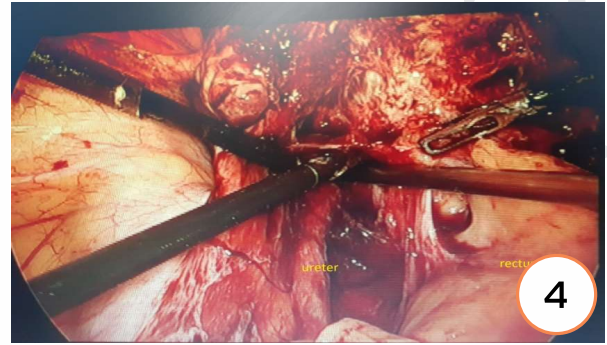
The recurrence of the rectovaginal disease is much less when compared to other forms of endometriosis, many studies finding it less than 5% compared to 20 – 40% in other forms of endometriosis(9). Thus, while surgery for DIE is challenging, it is also fruitful. Relief in pain scores are unequivocal with about 85% women becoming free of pain(9). Most importantly spontaneous and cumulative pregnancy scores have been found to be around 59% and 81% in these patients(13).

CONCLUSION

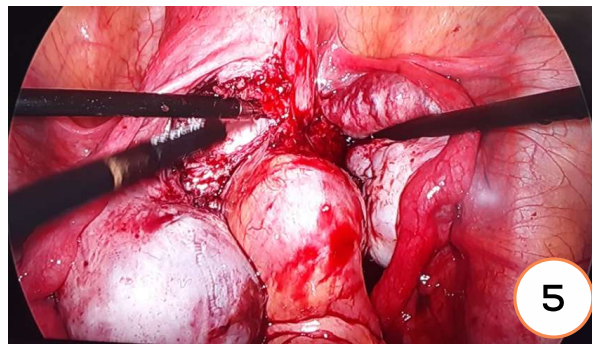
Endometriosis as a disease affects the patients beyond just infertility, hence surgery is also an opportunity to address others symptoms. Systematic history taking, examination and intraoperative evaluation is imperative to diagnose and address its various manifestations correctly. This surgery is an ultimate test for a gynae-endoscopic surgeon requiring technical precision & skills, patience, appropriate set-up and multidisciplinary inputs. The results are frequently rewarding enough to make it all worthwhile.



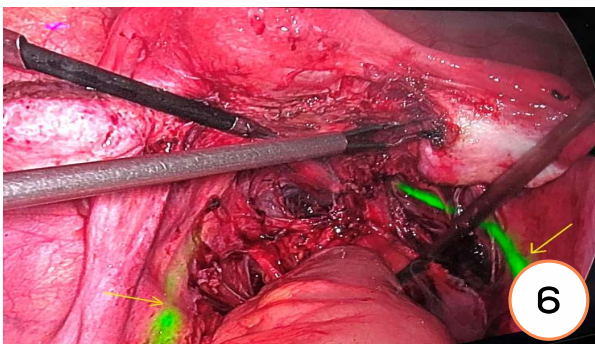
3. Correct plain of dissection in an ovarian endometrioma.



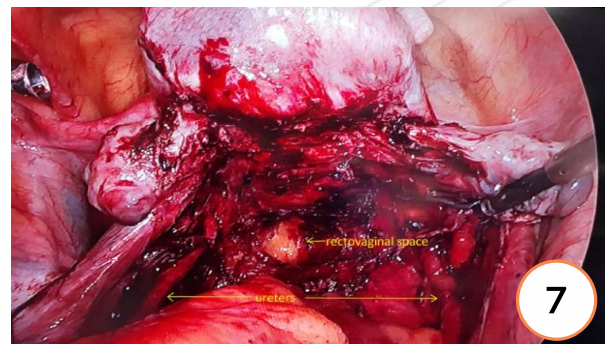
4. Medial para-rectal clearing.



5. Dissection of rectum from the uterus anteriorly; the whitish rectovaginal fascia depicting the correct plane.



6. Indocyanine Green under infrared frequencies clearly demarcating ureters.



7. Complete dissection of DIE- Both ureters traced till uter-sacrals with rectum completely dissected away from the cervix; fibro-fatty layer of recto-vaginal septum visible.

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