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The Mumbai Obstetric & Gynecological Society

MOGS MEDIA

Vol 4 | Endometriosis



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President's Message



Dear Colleagues,

It gives me great pleasure to bring to you the fourth edition of '**MOGS MEDIA**'. This is a series of focussed newsletters where we bring to you an important subject discussed in detail with all the latest updates which are relevant to you in your daily practise. This issue is on the important and common problem of Endometriosis. The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you the latest information on the subject and we are thankful to them.

I am sure you enjoyed the unique '**Youngistan**' conference -By the young for the young at heart conference and the many focussed webinars we did in the month of July-August 2020. I hope the '**Pearls of wisdom**' videos which you are receiving regularly are adding to your knowledge. Our digital PG training programme-The **NA Purandare** practical training event which has hundreds of young doctors tuning in, is helping young doctors get ready for exams and clinical practise. Our outreach programmes are being well received.

On 30th August we host the **Conflict to Clarity** conference on the digital platform with many outstanding international and national speakers. Do register for this wonderful event on controversial gynaecological problems and their solutions.

MOGS **V Care & Share** programme was started by us to support our frontline workers and the women whose health we look after. PPE, N95 masks, face shields, fetal dopplers, thermal scanners etc have been donated by us to all major and many peripheral municipal and government hospitals.

We lent our support to breast feeding mothers in breast feeding week, by giving hundreds of new mothers in municipal hospitals protein supplements, masks, sanitizers etc. We are now supporting resident doctors all over Mumbai by giving immunity boosters etc. We need your help and support for this ongoing programme . You can donate by online payment on our website or by bank transfer.

We have many different academic and fun activities planned this year Do visit our website for updates. **www.mogsonline.org**

Thank you once again for all your support over the years and we look forward to a wonderful year at MOGS.

Stay safe, stay healthy.

*"Never underestimate the difference YOU can make in the lives of others.
Step forward, reach out and help. This week reach to someone that might need a lift" – Pablo*

Best Wishes

Dr Rishma Dhillon Pai

President MOGS.

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Editors' message

Dear MOGS members,

The MOGS Media series of news letters have been one of the highlights of the MOGS year so far. The newsletter is the med on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous three issues on **Preterm Birth, Anaemia and Nutrition in Pregnancy** and **Optimising IUI Results** were well received and widely appreciated by readers throughout the country.

It is with great pride that we bring you the fourth issue on **“Endometriosis”** which aims to be a compendium aimed at practice algorithms and treatment options for the practicing gynaecologist. It is a single stop reference with recent publications, updated evidence and key practice points on this subject. While previous publications have offered discussions on either medical management or surgical treatment alone, this volume aims to bring you the best of both worlds in a single publication.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative. We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

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ADOLESCENT ENDOMETRIOSIS

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MOGS Yuva Lead 2020 - 21

Introduction

Dysmenorrhea is the most common menstrual symptom in adolescent girls and young women while endometriosis is the most common cause of secondary dysmenorrhea.¹ Endometriosis is a common benign and chronic gynaecological disorder related to the presence of endometrial glands and stroma outside of their normal location and causing inflammation.²

The true prevalence of endometriosis in adolescents is unknown, however, two thirds of adolescent girls with dysmenorrhea unresponsive to medical therapies have endometriosis at the time of diagnostic laparoscopy.¹ In a study, 12% of adolescent girls lost days of school or work each month because of dysmenorrhea and almost one in four respondents self-administered pain medication monthly without having seen a physician to evaluate the cause of their pain.³

Evaluation

Adolescents are susceptible to delays in accessing medical care. However, a delay in presentation, diagnosis and treatment is common for patients of all ages with dysmenorrhea.¹ The time to diagnosis of pelvic pain in adolescents is approximately 5.4 years as compared to 1.9 years if they present in adulthood.⁴

The initial evaluation for all patients presenting with dysmenorrhea includes a medical, gynaecological, menstrual, family and psychosocial history to determine whether the patient has primary dysmenorrhea or secondary dysmenorrhea. Clinicians should suspect secondary dysmenorrhea if the patient reports severe dysmenorrhea immediately after menarche or progressively worsening dysmenorrhea, abnormal uterine bleeding, mid-cycle or acyclic pain, lack of response to empirical medical treatment, family history of endometriosis, a renal anomaly, other congenital anomalies (spine, cardiac, or gastrointestinal) or dyspareunia.¹

In a 2015 study of adolescent girls (mean age 17.2) with laparoscopically diagnosed endometriosis, many presented with acyclic non-menstrual pain, with 56% reporting a preoperative complaint of at least one gastrointestinal symptom, and 52% reporting at least one genitourinary symptom.⁵

Patient should be encouraged to maintain a pain diary to keep track of the frequency and character of pain which will also help to determine if the pain is cyclic and related to bowel or bladder function. Complaints of difficulty participating in normal activities, missing school, or avoiding extracurricular activities secondary to pain suggest that medical intervention is required.

A physical examination is important, but it may not be possible to perform a complete examination for all adolescents. The goal of the physical examination should be to try to determine the aetiology of the pain and to rule out an ovarian tumour or anomaly of the reproductive tract. For an adolescent who is not sexually active, a per rectal examination may be preferred over a per vaginal examination. A Q-tip can be inserted into the vagina to document a patent vagina. A common finding in the setting of endometriosis includes cul-de-sac tenderness.⁶

Laboratory investigations

Laboratory studies should include a pregnancy test. A CBC (complete blood count) and ESR will help to rule out an acute or chronic inflammatory process. Urinalysis will help identify a urinary tract source of pain.⁶

The biochemical markers of this disease have been known for years, and new developments may permit a noninvasive and timely diagnosis of endometriosis. CA 125, Ca 19.9, ICAM-1, and IL-6 together with follistatin and urocortin have proven to be the most reliable markers for endometriosis diagnosis. Their role is limited in clinical practice due to low specificity.⁷ In patients with a known diagnosis of endometriosis, CA-125 is useful to follow the progress of disease, but has no place as a screening test due to its high rate of false positives.⁶

Radiology and imaging studies

Imaging in endometriosis has its own drawbacks and limitations. Ultrasound evaluation of the pelvis is the most helpful radiological study in patients with pelvic pain. Though transvaginal ultrasonography has the highest sensitivity to diagnose or exclude ovarian endometrioma and endometriosis, its utility in the adolescent age group may be limited. Ultrasound can identify and exclude other causes of pelvic pain such as ovarian cysts, torsion, tumours, genital tract anomalies and appendicitis.⁶

Where appropriate consent has been obtained, in women with symptoms and signs of endometriosis, transvaginal sonography is also useful for identifying rectal endometriosis and probe tenderness can be elicited.⁸ CT scan with contrast may help rule out appendicitis in cases of acute pain, but is otherwise not helpful. MRI is an excellent but expensive modality for evaluation of genital tract anomalies.⁶

Ideally, the gold standard for diagnosis of endometriosis is the demonstration of endometrial glands and stroma in the biopsy specimen from a location outside of the endometrial cavity.¹

Laparoscopy

Laparoscopy in adolescent endometriosis is now preferred only if the patient does not respond to medical line of therapy, presence of endometriomas or deep infiltrating endometriosis. The appearance of endometriosis may be different in an adolescent than in an adult woman. In adolescents, endometriotic lesions are typically clear or red and therefore difficult to diagnose

early.¹ Techniques described to enhance visualisation of the lesions include moving the laparoscope close to the peritoneum (magnification technique) and filling the pelvis with saline and “diving in” with the laparoscope.

Lesions suspicious of endometriosis should be sampled and biopsied and visible lesions should be fulgurated, ablated or excised at the time of initial laparoscopy. Occasionally, biopsy of a suspicious lesion may not confirm endometriosis and visual diagnosis may suffice so that treatment can be initiated.⁹

At laparoscopy, most adolescents are diagnosed with early stage endometriosis (American Society of Reproductive Medicine stage 1 or 2), although there are a number of recent reports of young women presenting with more advanced disease^{10,11,12,13}

It is important to counsel the patient and their family that the location and stage of endometriosis is not related to the severity of symptoms and its relapse of disease. Although typically diagnosed with earlier stage disease, adolescents may still experience substantial pain because the clear and red lesions are more metabolically active and are associated with greater prostaglandin production than the “powder burn” lesions seen in adult women.¹⁴

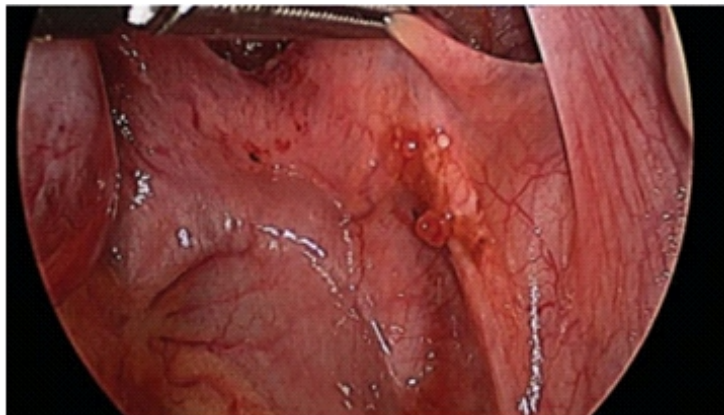


Fig 1 Clear/polypoid and vesicular lesions of endometriosis in adolescents

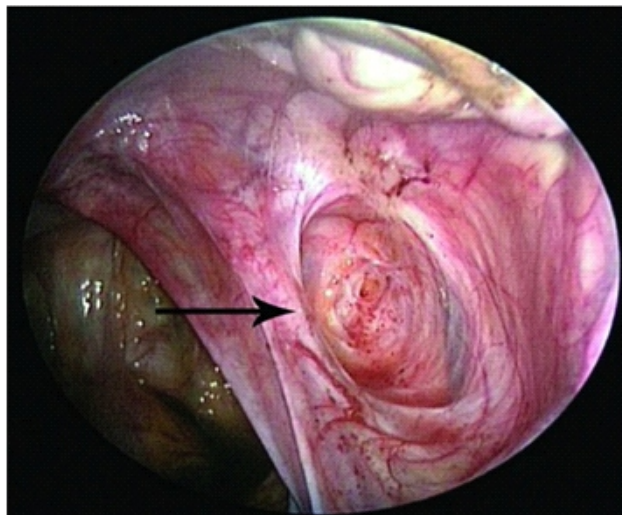


Fig 2 Peritoneal defect (arrow) with red punctate lesions in the centre of the defect in the right ovarian fossa in a 16-year-old patient with stage II endometriosis

Management

The goals of therapy include

1. Symptom relief
2. Suppression of disease progression
3. Protection of future fertility.

There is no cure for endometriosis, nor a single best treatment option. Therapy must be individualised.¹⁵ However, medical therapy is now preferred as the first line of treatment in young women.

NSAIDs

When the evaluation of pain suggests endometriosis, or adhesions, a trial of NSAIDs is recommended. The patient should be counselled to begin the medication before the expected onset of severe pain.

Combination estrogen and progestin therapy

A low-dose oral contraceptive may also improve symptoms of dysmenorrhea by suppressing hormonal stimulation associated with ovulation and decreasing menstrual flow.⁶ Continuous low-dose combination oestrogen/progestin therapy diminishes pain from endometriosis by creating a hormonal "pseudopregnancy" state in which endometrial implants are relatively inactive. This has traditionally been used in the past few decades when better options were unavailable.

Progestins

Progestins are recommended as a first-line hormonal therapy for the treatment of endometriosis-related pain. Progestational agents include norethindrone acetate (15 mg daily orally), medroxyprogesterone acetate (30–50 mg daily orally) and depot medroxyprogesterone acetate (150 mg intramuscularly every 1-3 months), Dienogest 2mg daily for 3 - 6 month seach of which will improve symptoms in approximately 80% to 100% of patients with endometriosis.¹⁶


With the availability of Dienogest, the treatment modalities in young endometriosis have undergone a sea change. Dienogest 2mg daily has proven its safety and can be used continuously for upto 5yrs.¹⁷ Continuous administration of Dienogest leads to decidualisation and atrophy of the endometrial lesions. It also has anti-inflammatory, antiangiogenic and antiproliferative effects. In a dose of 2 or 4 mg/day, dienogest has been shown to have a favourable profile for safety and efficacy, patients reported improvement in the endometriosis related symptoms and an overall improvement in quality of life.¹⁸

At therapeutic doses, progestins may be associated with side effects such as weight gain, bloating, depression, and irregular bleeding. However, many patients tolerate this therapy very well. The patient is started on empirical medical therapy and a provisional diagnosis of endometriosis can be made if the patient responds well to the medical treatment. In cases where disabling pain persists, laparoscopy to diagnose and treat endometriosis and rule out other issues becomes essential.³

Surgical management

The benefits of laparoscopy not only include confirmation of the presence or absence of endometriosis but also other causes of chronic pain such as adhesive disease. Laparoscopy also works as a therapeutic measure to treat endometriosis with coagulation, ablation, or resection of visible implants and adhesive disease with lysis of adhesions. After shared decision making, some patients may opt for medical treatment of suspected endometriosis without having a confirmed pathologic diagnosis to avoid laparoscopy.¹

Endometriotic implants have variable morphology, which has been described in the revised American Society of Reproductive Medicine (ASRM) Classification of Endometriosis and should be staged as per the revised ASRM Classification in order to facilitate follow-up and comparison if future surgery is performed.



**AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS**

Patient's name _____ Date _____
 Stage I (Minimal) - 1-5 Laparoscopy _____ Laparotomy _____ Photography _____
 Stage II (Mild) - 6-15 Recommended treatment _____
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40 Prognosis _____

ENDOMETRIOSIS		<1 cm	1-3 cm	>3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CULDESAC OBLITERATION			Partial 4	Complete 40
Ovary	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
Tube	Dense	4	8	16
	R Filmy	1	2	4
	Dense	4*	8*	16
	R Filmy	1	2	4
	Dense	4*	8*	16

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

Fig 3 Revised American Society for Reproductive Medicine (rASRM) Staging of endometriosis

Surgery alone is not adequate for endometriosis as there can be microscopic residual disease that needs suppression with medical therapy. Patients with endometriosis who have pain even after surgical therapy and suppressive hormonal therapy often benefit from GnRH agonist therapy with add-back medicine to prevent bone loss and early menopause for a period of 3 - 6 months.^{3, 19}

GnRH agonist therapy for treatment of endometriosis for young women under the age of 18 years is however, not recommended owing to detrimental effects on bone mineral density.^{3, 20}

Conclusions

Adolescents with endometriosis often benefit from ongoing education and support and integration of other multidisciplinary services such as biofeedback, pain management teams and support groups. There is an absence of longitudinal data on fertility rates in adolescents with endometriosis and early diagnosis and treatment may protect this population's future fertility.

References

1. Dysmenorrhea and endometriosis in the adolescent. ACOG Committee Opinion No. 760. American College of Obstetricians and Gynecologists. *ObstetGynecol* 2018;132:e249–58.
2. A.Y.Black and M. A. Jamieson, "Adolescent endometriosis," *Current Opinion in Obstetrics and Gynecology*, vol. 14, no. 5, pp. 467–474, 2002.
3. Zannoni L, Giorgi M, Spagnolo E, Montanari G, Villa G, Seracchioli R. Dysmenorrhea, absenteeism from school, and symptoms suspicious for endometriosis in adolescents. *J Pediatr Adolesc Gynecol* 2014;27:258–65.
4. Greene R, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. *FertilSteril* 2009;91:32–9.
5. Dun EC, Kho KA, Morozov VV, Kearney S, Zurawin JL, Nezhat CH. Endometriosis in adolescents. *JSL* 2015;19(2):e2015.00019.
6. Laufer, M. R., Sanfilippo, J., & Rose, G. (2003). Adolescent Endometriosis. *Journal of Pediatric and Adolescent Gynecology*, 16(3), S3–S11. doi:10.1016/s1083-3188(03)00066-4
7. R. Socolov, S. Butureanu, S. Angioni et al., "The value of serological markers in the diagnosis and prognosis of endometriosis: a prospective case-control study," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 154, no. 2, pp. 215–217, 2011.
8. Good clinical practice recommendations on endometriosis FOGSI 2017
9. Laufer MR. Helping "adult gynecologists" diagnose and treat adolescent endometriosis: reflections on my 20 years of personal experience. *J Pediatr Adolesc Gynecol* 2011;24(5 suppl):s13–7
10. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *FertilSteril* 1997;67:817–21.
11. Dun EC, Kho KA, Morozov VV, Kearney S, Zurawin JL, Nezhat CH. Endometriosis in adolescents. *JSL* 2015;19(2):e2015.00019.
12. Seo J, Lee D, Yoon B, Choi D. The efficacy of postoperative cyclic oral contraceptives after gonadotropin-releasing hormone agonist therapy to prevent endometrioma recurrence in adolescents. *J Pediatr Adolesc Gynecol* 2017;30:223–7.
13. Audebert A, Lecointre L, Afors K, Koch A, Wattiez A, Akladios C. Adolescent endometriosis: report of a series of 55 cases with a focus on clinical presentation and long-term issues. *J Minim Invasive Gynecol* 2015;22:834–40.
14. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. *Expert Opin Pharmacother* 2012;13:2157–70.
15. Yoost J, LaJoie AS, Hertweck P, Loveless M. Use of the levonorgestrel intrauterine system in adolescents with endometriosis. *J Pediatr Adolesc Gynecol* 2013;26:120–4.
16. Luciano AA, Turksoy RN, Carleo J: Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. *ObstetGynecol* 1988;72:323
17. Neil P. Johnson, Lone Hummelshoj, for the World Endometriosis Society Montpellier Consortium. *Human Reproduction*, Vol.28, No.6 pp. 1552–1568, 2013
18. Kohler G, Faustmann TA, Gerlinger C, et al. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. *Int J Gynaecol Obstet*. 2010;108: 21–25.
19. Sadler Gallagher J, Feldman HA, Stokes NA, Laufer MR, Hornstein MD, Gordon CM, et al. The effects of gonadotropin-releasing hormone agonist combined with add-back therapy on quality of life for adolescents with endometriosis: a randomized controlled trial. *J Pediatr Adolesc Gynecol* 2017;30:215–22
20. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014 Mar;29(3):400-12. doi:10.1093/humrep/det457.

FERTILITY ENHANCING ENDOMETRIOSIS SURGERY



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Introduction

Endometriosis has been a curse for women in their reproductive age and laparoscopy has proven to be a boon for sufferers. Endometriosis is defined as a chronic gynaecologic disease characterised by endometrial like tissue outside of the uterus and is associated with pelvic pain and infertility.¹ It can occur anywhere in the body but the most common sites are ovaries, cul-de-sac, uterosacral and broad ligaments, fallopian tubes, sigmoid colon and appendix.

Classification

The three main types of endometriosis are **superficial peritoneal, deep infiltrating and ovarian endometrioma**. The classification of endometriosis used in clinical practice is:

Stage I : Minimal endometriosis – isolated superficial disease on the peritoneal surface with no significant associated adhesions.

Stage II : Mild Endometriosis – scattered superficial disease on the peritoneal surface and ovaries, totalling less than 5cm in aggregate, with no significant associated adhesions.

Stage III : Moderate endometriosis - multifocal disease, both superficial and invasive (including endometriomas >1 cm), that may be associated with adhesions involving fallopian tubes and/or the ovaries.

Stage IV : Severe endometriosis- multifocal disease, both superficial and invasive, including large ovarian endometriomas, usually associated with adhesions, both flimsy and dense, involving the fallopian tubes, ovaries, and cul-de-sac.

Ovarian endometrioma

For women with endometriomas, literature is clear; the cumulative pregnancy rate 1-3 years after surgical treatment is approximately 50% for women with endometriomas. Endometriomas usually appears as smooth, dark cysts, typically associated with adhesion and containing the dense brown chocolate-like fluid (hemosiderin from ovarian/endometriotic haemorrhage).

Sign and symptoms

The mean age of diagnosis is 25 to 35 years. The disease exhibits a broad spectrum of clinical signs and symptoms but most important is infertility and pain, affecting the quality of life. Pain symptoms can range from dyspareunia, chronic pelvic pain, deep pelvic pain, dysmenorrhoea, dyschesia (rectal involvement), bowel and bladder symptoms (usually cyclic). The pain is mediated

by actions of inflammatory cytokines in the peritoneal cavity and irritation or direct infiltration of the nerves in the pelvis.

Infertility and endometriosis are strongly associated, as approximately 30-50% of women with endometriosis have infertility. The mechanisms responsible for infertility in endometriosis include distorted pelvic anatomy, inflammation, aberrant endometrial gene expression and premature depletion of the ovarian follicular pool. The severity of endometriosis may not correlate with the number and severity of symptoms.

Diagnosis

Clinical diagnosis and physical findings in women with endometriomas vary widely. Masses felt on pelvic examination can be confirmed by transvaginal ultrasonography (TVS). Endometriomas can be unilocular or multilocular cysts and mostly adherent to the posterior surface of the uterus or in the pouch of Douglas. The haemorrhagic fluid inside the cystic cavity gives homogenous, low level echogenicity (ground glass appearance) on TVS. Bilateral endometriomas adherent to each other gives a “kissing ovaries” appearance. Magnetic resonance imaging can be done to differentiate endometriomas from other cystic masses of ovary. Laparoscopy with histological examination of excised cyst wall is the gold standard for diagnosis.²

Ovarian cystectomy

The objectives of surgical treatment for endometriosis are to restore normal anatomical relationships, remove all visible and deep endometriosis to the extent possible and prevent adhesions. Laparoscopic techniques improve the operative outcomes as it gives magnification, minimum tissue trauma and meticulous haemostasis compared to laparotomy.

Indications for ovarian cystectomy

1. Endometriomas are responsible for severe dysmenorrhoea, dyspareunia, deep pelvic pain
2. Large endometriomas with possibility of rupture
3. Patients with Infertility

Timing of surgery

Surgery should be planned in the post menstrual phase, when vascularity is lower and possibility of bleeding intraoperatively is lesser. The procedure should be scheduled close to the assisted reproduction treatment if patient is infertile and desirous of pregnancy.

Pre-requisites for laparoscopic ovarian cystectomy

1. Consent –the patient should be thoroughly explained about the procedure like chances of reduction of ovarian reserve and its consequences, risk of recurrence and rare possibility of oophorectomy.
2. Evaluation of the ovarian reserve –the patient should undergo evaluation for ovarian function beforehand. Various methods for ovarian reserve determination are the s anti-Mullerian hormone (AMH) levels, antral follicle count (AFC), peak systolic velocity (PSV) on ovarian Doppler and the ovarian volume measurement on ultrasound.

Surgical steps

Various techniques described for the treatment of ovarian endometrioma are simple drainage, ablation and excision of endometriotic cyst. Excision is favoured due to the low risk of recurrence, relief of pain and enhanced subsequent spontaneous pregnancy rates.

For endometriotic cyst excision, standard port placement of laparoscopy should be considered but may vary depending upon the previous surgery and surgeon's preference.

Pneumoperitoneum is gained by Veress needle or direct trocar entry method.

After the entry into the abdominal cavity, one should inspect the peritoneum, adhesions and spread of endometriosis to other abdominal organ, pelvic organs, especially contralateral ovary should be visualised vigilantly. One should examine the endometriotic cyst for its size, extent and adhesions.

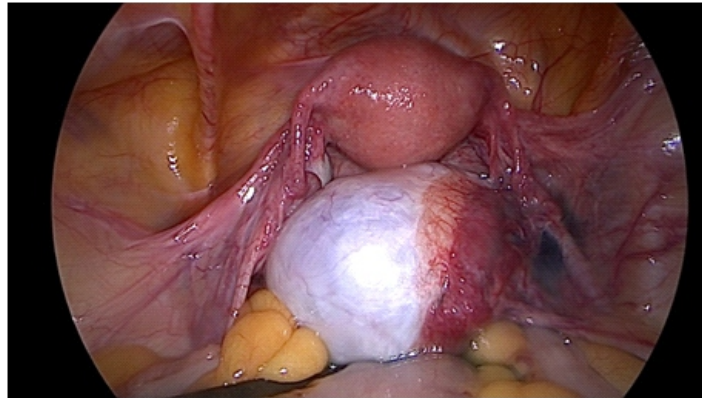


Fig 1 Right Ovarian Endometriotic Cyst

The procedure starts with separating the ovarian cyst from surrounding adhesions. In the process, cyst may get ruptured at its weakest point; if not, it may be punctured and the chocolate material may be aspirated followed by a peritoneal wash with normal saline. The ovary should be freed from all the adhesions by fine dissection.

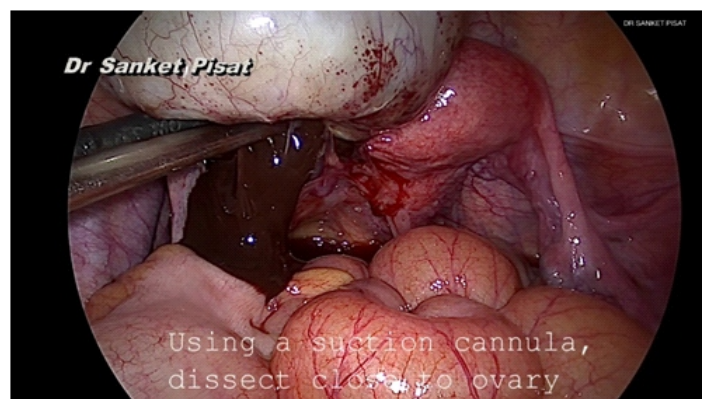


Fig 2 Endometrioma Drainage

Enlarge the incision into the cyst followed by Inj. Vasopressin (20 IU in 200 ml) which is injected, preferably with the help of a VVIN (Visual vasopressor injection needle) to avoid inadvertent intravascular injection. This will distinguish cyst wall from ovarian cortex developing the plane of separation. It also helps in minimising blood loss that drastically decreases the use of cauterisation after removing cyst wall.

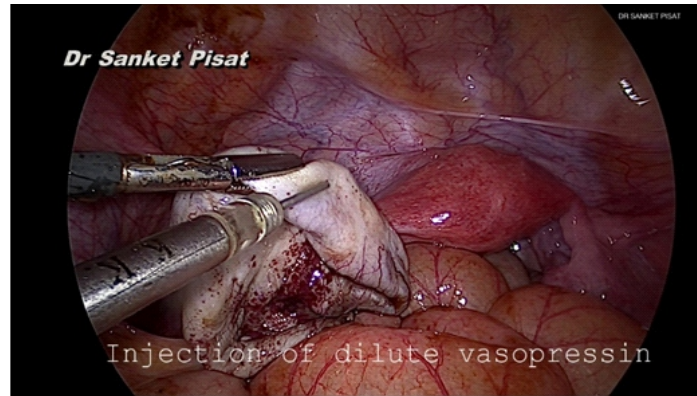


Fig 3 Injection of Dilute Vasopressin

Following the plane of separation, cyst wall and ovarian cortex are held with grasper and gently separated from each other by traction and counter traction. The procedure is continued till the hilum is reached. As this is a highly vascular point, the cyst can be cauterised, cut and separated away from ovary.

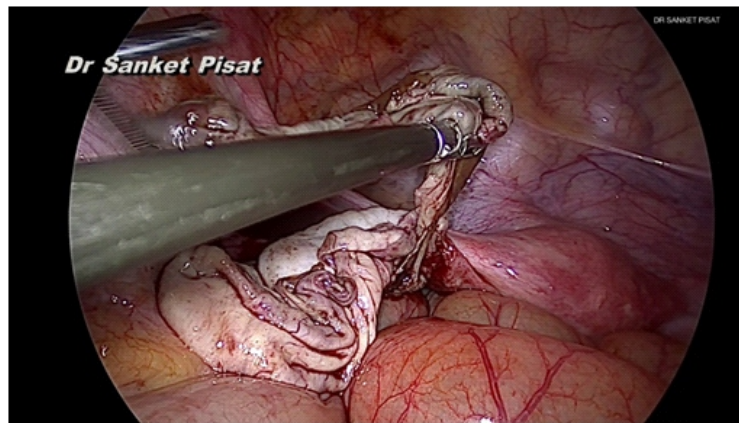


Fig 4 Removal of The Cyst Wall

The cyst wall can be removed with the help of an endo-bag or by rail-roading through 10mm port. The ovarian cortex area is inspected for active bleeding points and should be cauterised only if required.

Confirm the haemostasis and reconstruct the ovary by approximating sutures so that raw areas of the ovarian cortex stick to each other, preventing adhesion of the ovary to other organs. Furthermore, adhesions can be prevented by anchoring the ovary to the round ligament, or placing Interceed as an adhesion barrier.

Minimal use of electro surgery is the key point to preserve ovarian reserve as there is loss of follicles to some extent because of thermal spread leading to collateral damage.

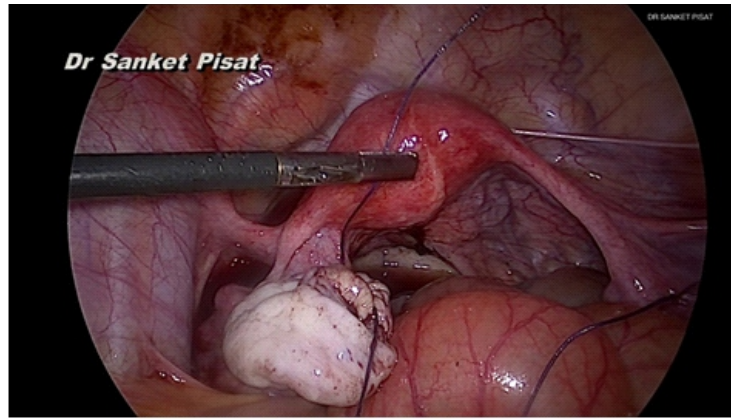


Fig 5 Suturing of the ovarian stroma

Adhesiolysis in superficial endometriosis

In the late 20th century, transition from laparotomy to laparoscopy took place and laparoscopic adhesiolysis remains the mainstay in managing pelvic pain related to endometrial adhesion. Laparoscopy provides better visualisation, also the microsurgical principles of laparoscopy help effectively in preventing adhesions when compared to laparotomy.

Adhesion formation in endometriosis is mainly due to the inflammatory component and can cause infertility (distorted anatomy), small bowel obstruction and chronic pain. Surgical difficulty at the time of operation can be addressed by thorough knowledge of pelvic anatomy. Laparoscopic adhesiolysis was found to reduce pain in approximately 70% of patients immediately after the procedure as per a systemic review.

The decision to proceed with surgical intervention requires careful analysis of risk and benefit. Superficial implants cannot be localised well by clinical examination and are not visible on any imaging modality. Contrast placed in rectum or vagina can help to know the extent of invasion into the layers of colon (serosa, muscularis, and mucosa) in deep infiltrating endometriosis. MRI can detect bladder endometriosis. Patients not responding to medical therapy should be consider for surgical intervention. Laparoscopy is the diagnostic as well as therapeutic (see and treat) modality for the adhesions related to endometriosis.

Surgical steps

When performing adhesiolysis, optimal results depend upon the use of microsurgical technique, gentle tissue handling and meticulous haemostasis with minimal tissue fulguration. Adhesiolysis can be performed by number of techniques including blunt and sharp dissection, electro-dissection, aqua-dissection and laser dissection.

The primary trocar is placed at the umbilicus most of the time. In patients with vertical scar and umbilical hernia, trocar can be placed at Palmer's point (it is located on left side below the lowest rib in the mid-clavicular line). This will allow examination of adhesions of bowel to umbilicus and help in excising it so that trocar can be placed at umbilicus for further surgery. Other trocars should be placed as widely apart as possible to facilitate the instrument handling.

Blunt dissection is most basic form of adhesiolysis. This technique is usually used in treating thin, avascular adhesions that separate along the natural planes by mechanical force.

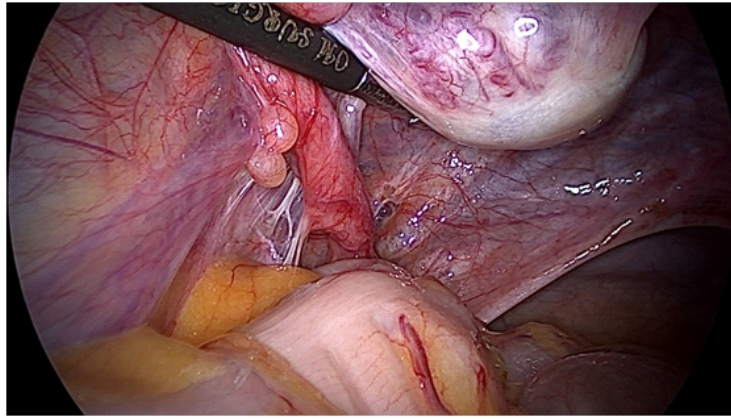


Fig 6 Thin flimsy adhesions of endometriosis

Virtually any type of laparoscopic instrument can be used to place traction on an adhesion to cause separation. If bleeding or significant resistance is encountered, this technique should be abandoned. A good bipolar energy source must be kept handy to manage unexpected bleeding.

Sharp dissection is the preferred method for dealing with all adhesions, especially thick avascular adhesions. The advantage of sharp dissection over electrodissection is the decreased risk of inadvertent risk of electrodissection. The adhesion is held on tension with an atraumatic grasper, and scissors are used for the lysis of adhesive band. It is important to turn the tip of scissors toward the optical viewing angle to avoid vascular or bowel injury.

Aqua dissection is used to free adhesions from the pelvic sidewall to avoid injury to the ureter or the great vessels. It is also a useful technique in removing endometriotic nodules. With this technique, the peritoneum is grasped and an incision is made large enough to place the tip of powered suction-irrigation device. Irrigation is used to force fluid under the peritoneum, causing it to balloon out from deeper tissues. The adhesion or peritoneum can be dissected free.

Monopolar or bipolar energy is frequently used to lyse thicker vascular adhesions. When using electrodissection, care must be taken to avoid injury to bowel. It is always best to start from the normal area to the diseased area. As known areas are freed from adhesion, unknown areas become recognisable. Newer bipolar energy instruments that seal and cut simultaneously, or the harmonic scalpel that uses ultrasonic energy to seal vessels can be used.

Laser dissection has been used in laparoscopy with great success as a result of minimal lateral thermal spread compared with most forms of electrodissection. However, it should be noted that this form of energy is indeed still an energy source and achieves haemostasis through lateral thermal spread. The small spot size of laser makes this useful tool for precision adhesiolysis. The CO₂ laser has depth of penetration of 0.1 mm is excellent for cutting.

The harmonic scalpel is used with a technique similar to both bipolar dissection (laparoscopic coagulating shears and Harmonic ACE) and monopolar dissection (scalpel tip), depending on which tip is used. This technique does not use electrodissection. These have the advantage of limited lateral thermal spread, similar to the newer bipolar electrodissectional instruments.

	Blunt dissection	Sharp dissection	Monopolar/ Bipolar energy	CO2 laser dissection	Harmonic
Tissue to be dissected	Thin and avascular adhesion bands	Thick avascular adhesion bands	More thick and vascular bands, adherent to bowel, ureter	Adhesiolysis that requires precision	Preferred when distorted anatomy due to adhesions
Instrument	Any blunt instrument	Laparoscopic scissors	Bipolar scissors, vessel sealers	CO2 Laser	Harmonic scalpel
Advantages	Used for flimsy adhesion	No lateral thermal spread, Inexpensive, no smoke	Haemostasis and separation of tissues can be achieved (espvascular adhesions)	Highly precise	Minimal lateral spread, less smoke, tissue contact feedback
Disadvantages	Not recommended due to chances of bleeding	As haemostasis cannot be achieved cannot used for vascular adhesions	Lateral thermal spread, produces smoke	Expensive, tedious to handle, produces smoke	Expensive, coagulation is slow

Table 1 Methods of adhesiolysis, their advantages and disadvantages

Commonly encountered sites

Uterosacral ligament The majority of adhesions lie between the rectosigmoid and uterus at or below the level of cervix and uterosacral ligaments. Nodularity of the uterosacral ligament can cause the ureter to be adherent to the inferior margin of the ovary. If a lesion overlies the ureter, it can be mobilised with blunt dissection along its pelvic course, pushing and spreading just adjacent to the ureter rather than directly on it. This will prevent ureteric injury. Fulguration of superficial endometriotic spot and excision of obvious lesion on uterosacral ligament is recommended.

Rectal endometriosis Endometriosis of the rectum ranges from simply adhesions between rectum and cervix to nodular disease involving the outer serosa of the rectum, to disease involving the rectal mucosa. In such cases one should avoid starting dissection at the most dense adhesion area and instead, should mobilise the surrounding avascular space first as this will clarify the correct plane to sharply cut and divide two adherent structures.

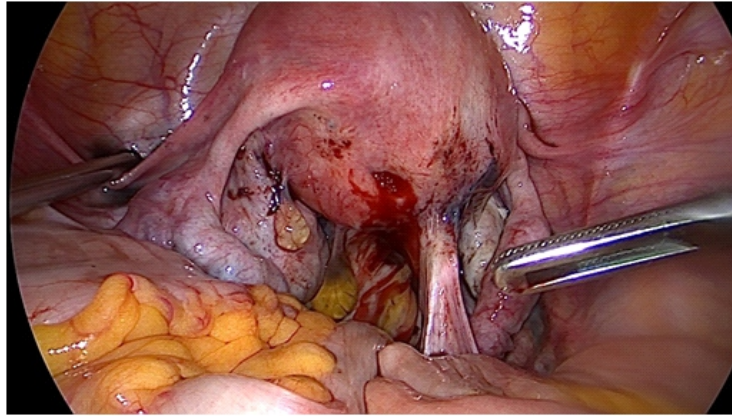


Fig 7 Deep infiltrating endometriosis of the posterior compartment

Bladder endometriosis Endometriosis can form implants on the bladder surface or create adhesions between uterus and bladder, sometimes even as high as the fundus of the uterus. Lesions on the bladder are excised by first making a small incision in the overlying bladder peritoneum and then gently pushing bladder downward away from the endometriotic lesion. This will significantly reduce the bladder injuries.

Appendiceal endometriosis In superficial endometriosis, the appendiceal tip can be adherent to the adnexa while in deep infiltrating stages it can reach near uterosacral ligaments or caecum and may cause obstruction leading to ilio-caecotomy. Also, in the future there are chances of involvement of appendix in endometriosis. Appendicectomy is recommended during elective surgery for endometriosis.

Excision vs ablation of superficial endometriosis : a dilemma

The two most common methods, ablation of endometriotic lesion with electrosurgery or complete excision present their own peculiar issues. Excision allows complete treatment of endometriosis regardless of depth and severity of disease that result in higher level of pain relief and dyspareunia. A randomised control trial by Kristin R et al stated that excision and ablation shows similar effectiveness for the treatment of pain associated with superficial endometriosis, with ablation showing more significant individual response in immediate postoperative period.⁴

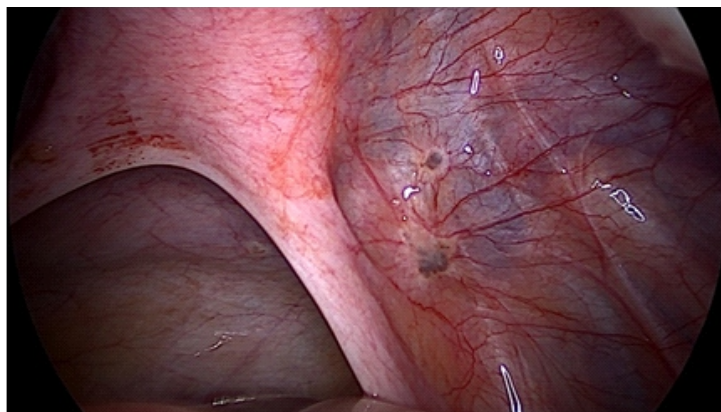


Fig 9 Superficially visible endometriotic implants over the course of the ureter

The debate between excision and ablation stems from the concept that the endometriotic lesions seen at diagnostic laparoscopy are only the tip of the iceberg, with a larger dissemination retroperitoneally. In these cases, mere ablation of the visible part of the lesion may not result in complete cure. This dilemma can be addressed by stating that excision and ablation are not mutually exclusive. It seems logical to use excision for deep disease; where the use of an energy form would result in either damage to an underlying structure such as ureter or incomplete treatment. However, for superficial disease not located over vital anatomical structures like the ovaries, ablation may be sufficient.

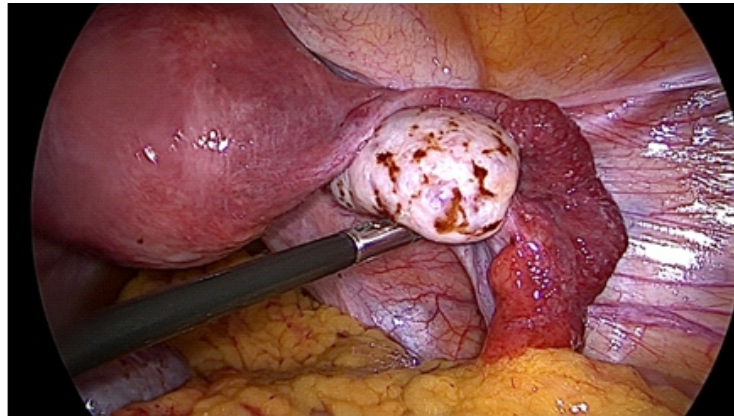


Fig 10 Superficial endometriotic implants over the surface of the ovary without visible cysts

Pundir J et al in an updated systematic review concluded that laparoscopic excision significantly improves the major symptoms of endometriosis like dysmenorrhoea, dyschezia and chronic pelvic pain than laparoscopic ablation.

	Excision	Ablation
Type of endometriosis	For Deep endometriosis	For superficial endometriosis
Tissue for histological diagnosis	Yes- hence can rule out malignancy	No- risk of missing malignancy
Chances of recurrence	Minimal (2008 Cochrane review)	High
Treatment	Adequate	Inadequate for deep endometriosis
Ovarian Reserve	Well preserved	Compromised

References

1. Speroff's Clinical Gynecologic Endocrinology and Infertility, Ninth edition, Wolters Kluwer Publishers, Chapter 32, page 3211.
2. Te Linde's Operative Gynecology, Eleventh edition, Lippincott Williams & Wilkins Publishers, Chapter 37, Page 1066.
3. Pisat S, van Herendal B. Pisat's Visual vasopressor injection needle; an innovative tool for increasing patient safety in laparoscopic myomectomy. *SurgTechnol Int*2017;9;30.
4. Riley KA, Benton AS, Deimling TA, Kunselman AR, Harkins GJ. Surgical Excision Versus Ablation for Superficial Endometriosis-Associated Pain: A Randomized Controlled Trial. *J Minim Invasive Gynecol.*2019;26(1):71-77.doi:10/1016/j.jmig.2018.03.023.
5. Pundir J, Omanwa K, Kovoor E, Pundir V, Lancaster G, Barton Smith P, Laparoscopic excision versus ablation for endometriosis-associated pain – Updated systematic review and meta-analysis. *The Journal of Minimally Invasive Gynecology* (2017), doi: 10.1016/j.jmig.2017.04.008



MEDICAL MANAGEMENT : OPTIONS AND PATHWAYS

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Background

Endometriosis is a chronic, inflammatory, hormonal, immune, systemic and heterogeneous disease with three different phenotypes (superficial, ovarian endometrioma and deep infiltrating endometriosis), which is associated with adenomyosis in 30% of patients.

Diagnosis of endometriosis and adenomyosis should be based on history, examination and imaging; a diagnosis of endometriosis should no longer be considered synonymous with immediate surgery. Modern management of endometriosis should be patient focused rather than focused on the endometriotic lesions; medical treatment can be administered without histological confirmation.¹

Focal issues in management

Approximately one third of women suffering from endometriosis are clinically asymptomatic. However, when symptomatic the most common presenting symptom is pelvic pain. Therefore, the two primary goals for medical management of endometriosis are pain control and suppression of estrogen production.²

Endometriosis associated pelvic pain (EAPP)

Endometriosis management should be individualised according to the patient's intentions and priorities; management strategies can vary from country to country as pain perception and health-care systems differ around the world.

Pain symptoms should be treated without delay to avoid central sensitisation, as this can become autonomous, occurring independently of the peripheral stimulus, and can explain coexisting chronic pain syndromes.

Medical management should be the first therapeutic option for patients with pelvic pain who have no immediate desire for pregnancy; assisted reproductive technologies can be performed without previous surgery for selected patients with infertility.¹ In adolescents, post-surgery and to prevent recurrence, medical management forms the mainstay.

Empirical management

Ideally, known causes of pelvic pain should be ruled out.^{3,4} Especially in the adolescent age group, it is of paramount importance to be aware of the paradigm shift in the approach in recent years. While traditionally laparoscopy with targeted biopsy and histopathological confirmation has been the gold standard, in recent years this has been replaced by empirical medical management in the adolescent population where one would like to avoid endoscopic surgery at a young age.⁵

The therapeutic armamentarium consists of NSAIDs (mefenamic acid), low dose combined oral contraceptive pills, transdermal patch and GnRH agonists like leuprolide and goserelin. The new option we have available is dienogest, a progestin which has been used for upto 5 years to prevent recurrence and has prevented the need for surgery during that period.⁶

NSAIDs

NSAIDs block the cyclooxygenase (COX) enzymes which are essential for the production of the inflammatory mediators. Selective COX₂ inhibitors like rofecoxib also inhibit the growth of the endometrial tissue. NSAIDs are the first-line agents in the management of pain and dysmenorrhea due to endometriosis. In women who are desirous of fertility, mefenamic acid is given in EAPP. However, these are ineffective in suppressing the disease process and not useful as longterm therapy.

Oral progestins

Of all oral progestins, dienogest 2 mg/day is the most effective option. Some initial breakthrough bleeding may occur but it settles over time. It can be safely administered for upto 5 years.

Other progestins which may be used include norethisterone and cyproterone acetate, though these are not preferred as a primary choice any more. Their limitations include impairment of fertility, risk of thromboembolism, high rates of recurrence after discontinuation.

Combined oral contraceptives (COCs)

COCs have traditionally been used since many decades and have their own advantages and disadvantages. They provide symptomatic relief but do not suppress the disease process or prevent progression. They offer a cheaper option with a good safety profile.

COCs inhibit ovulation, decrease gonadotropin levels, reduce menstrual flow and cause decidualisation of endometriotic implants. They can be used continuously for prolonged periods but a break of 4-7 days can be given if breakthrough bleeding occurs. After stopping therapy for 6 months, recurrence of symptoms is common.⁷

GnRH agonists

The commonly available GnRH agonists leuprolide, buserelin, naferelin and goserelin are effective in treatment of endometriosis. They act by blocking the ovarian cycle and causing hypoestrogenism with consequent regression of endometriotic implants.

However, they can only be used for short periods of 3-6 months owing to their impact on bone mineral density. They should be used with add back therapy to prevent bone loss. The addition of add back therapy does not modify the success of treatment. Add back is recommended with estrogen only (estradiol 1 mg/day orally or gel).

GnRH agonists are more effective than oral contraceptive pills for treatment of endometriosis. However, owing to their side effect profile, their use is limited to patients more than 16 years of age and for a maximum period of 6 months.

Progestins

Progestins are effective in treating endometriosis by inhibiting its growth, induction of anovulation, inhibition of blood vessel growth, and anti-inflammatory actions. Progestins cause ovarian suppression, endometrial decidualisation, atrophy and alteration in steroid receptor ligand binding. They are also responsible for the local modulation of immune response (suppression of IL-8 production, increase of nitric oxide production, reduction of TNF- α induced nuclear factor- χ - β).

They demonstrate effects on angiogenesis, suppression of transcription of basic fibroblast growth factor (bFGF), suppression of vascular endothelial growth factor (VEGF) and cysteine rich angiogenic inducer (CYR61), progesterone receptor expression and progesterone resistance and a direct effect on nerve fibre intensity.

Levonorgestrel intrauterine system (LNG-IUS)

The levonorgestrel intrauterine system (LNG-IUS) is reported to be an effective, safe and well accepted methodology of treatment for endometriosis.

The LNG-IUS is postulated to have multiple actions including local effect on the ectopic endometrium resulting from depletion of the estrogen and progesterone receptors through the inhibition of synthesis and expression of estrogen and progestin receptors, a direct effect on the eutopic endometrium by inhibition of endometrial production of estrogen-induced growth factors or growth factor-binding protein, resulting in an anti-proliferative effect, glandular atrophy, and decidualisation. Furthermore, there may be a reduction of local vascular angiogenesis, a reduction in pelvic-vessel congestion and an increase in apoptosis, reduction in peritoneal fluid macrophage activity and a modification in the production of cytokines responsible for the maintenance of lesions and pain.

Besides breakthrough bleeding in the initial few weeks, there are few side effects. It has also been used in adolescents in the western world, though this is probably impractical in India. In the treatment of adenomyosis, non-compliant women and for patients who refuse surgery this may be one of the therapies which may be considered.

Depot medroxyprogesterone acetate

This has traditionally been mentioned in textbooks and before the modern era was used in patients who had poor compliance to COCs. The incidence of breakthrough bleeding, weight gain and other issues have gradually reduced the uptake of this option.

Danazol

Owing to its androgenic side effects, this is rarely used in modern medicine and is unavailable in many territories. For patients with deep infiltrating endometriosis, patients awaiting surgery, scar endometriosis or adenomyosis it may have a limited role.

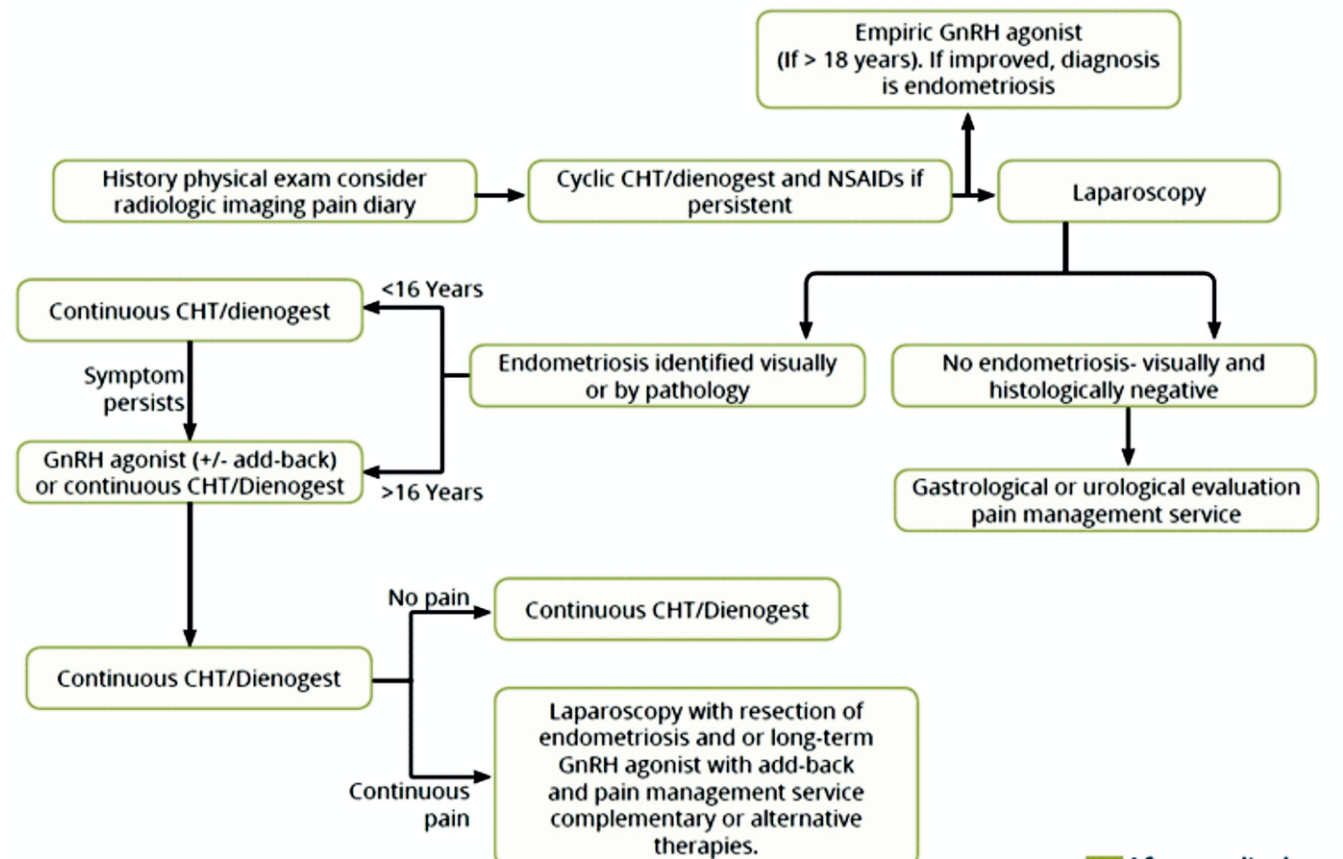


Fig 1 Management algorithm for Adolescent Endometriosis⁷

Dienogest

Dienogest is a 19-nortestosterone derivative associated with high specificity for progesterone receptors and demonstrates less anti-androgenic effects. It also has anti-inflammatory, anti-angiogenic and anti-proliferative effect resulting in desiccation of lesions with continuous administration. In recent years, this molecule has revolutionised the medical treatment of endometriosis.

Optimal dose

A 24-week study conducted to evaluate the efficacy and safety of dienogest at doses of 1, 2, and 4 mg/day orally in the treatment of endometriosis found that the mean revised American Fertility Society scores reduced from 11.4 to 3.6 (n=29; p<0.001) in the 2 mg dienogest group and from 9.7 to 3.9 (n=35; p<0.001) in the 4 mg group. Dienogest at 2 and 4 mg/day was associated with symptom improvements in substantial proportions of women. Both doses were generally well tolerated, with low rates of treatment discontinuation due to adverse events. The 1 mg dose arm was discontinued owing to insufficient bleeding control. Hence, Dienogest at 2 mg once a day is recommended as the optimal dose in the treatment of endometriosis.⁸

Effectiveness and long term treatment

168 women were enrolled in a 65 week longterm study to observe the safety and efficacy of dienogest over a long period of time. The intensity of pain showed significant sustained improvements.

The mean visual analogue scale (VAS) score was statistically significantly reduced by 43.2 (± 21.7) mm over the total treatment period of 65 weeks ($p < 0.001$). Mean VAS decreased from 56.9 mm at baseline of the placebo-controlled study to 34.1 mm at baseline of the long-term study, to 11.5 mm at the end of the 53 additional weeks of treatment. During a 24-week treatment-free period following the long-term study, VAS increased only moderately, suggesting that dienogest induces a beneficial effect that may persist after treatment cessation.⁹

Another study from Japan with 135 patients over 52 weeks showed moderate or marked global improvement measured by change in the severity of five subjective symptoms (lower abdominal pain, lumbago, dyschezia, dyspareunia, and pain on vaginal examination) and two objective findings induration involving pouch of Douglas and uterine mobility in 72.5% of patients after 24 weeks and in 90.6% after 52 weeks of dienogest treatment. Patient satisfaction with dienogest at the end of treatment was high, with 88.9% of women responding that they were 'certainly willing' or 'would prefer' to use dienogest again.¹⁰

A 60-month treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced EAPP and avoided pain recurrence post-surgery. Dienogest was administered in 37 women (age 39 ± 8 years) with laparoscopically diagnosed endometriosis based on the need for longterm treatment to manage severe and/ or recurrent endometriosis, either to prevent lesion recurrence post-laparotomy or to treat women unsuitable or unwilling to undergo surgery. Majority of the patients ($n=30$) were previously treated with COCs.¹¹

The VAS score (median) was 10 mm at 12 and 24 months, and 20 mm at 36, 48 and 60 months of treatment. In the 15 women treated with dienogest with no prior surgery, the median baseline VAS score for EAPP was 80 mm. The VAS score (median) was 20 mm at 12 and 24 months, and 30 mm at 36, 48 and 60 months of dienogest treatment. The patient satisfaction with dienogest providing pain relief was very high. All laboratory parameters remained within the normal range; haemostasis, lipid and liver parameters did not defer from the reference range.

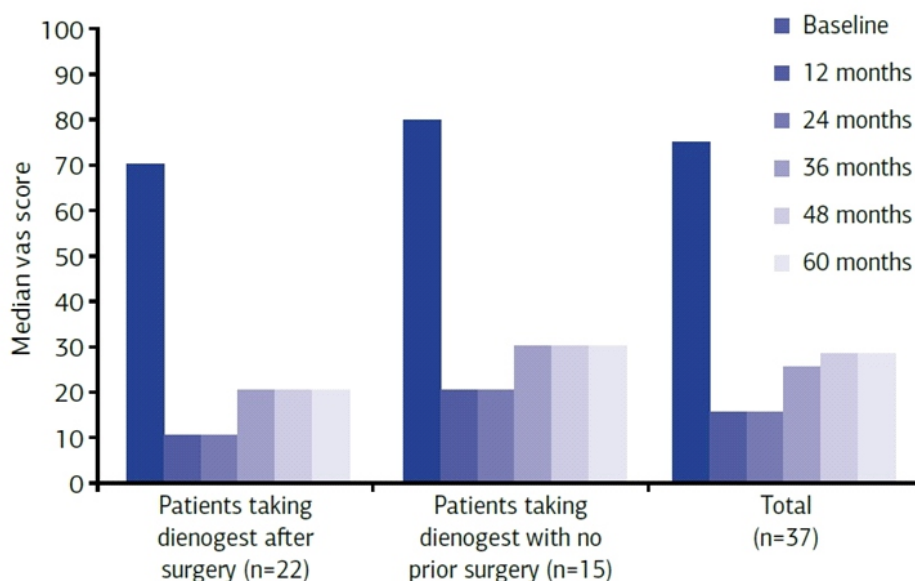


Fig 2 VAS scores after 12, 24, 36, 48 and 60 months of dienogest¹¹

Common adverse drug reactions reported were headache, breast discomfort, depressed mood, and acne, each occurring in <10% of women, and were generally of mild-to-moderate intensity and associated with low discontinuation rates. Women treated with dienogest less frequently experienced events representing other hypoestrogenic symptoms (such as hot flushes, vaginal dryness and decreased libido and sleep disorder) than women treated with leuprolide.

As can be seen from the studies above, treating patients to prevent recurrence, post-surgery and for long term treatment for patients unsuitable for surgery or those who refuse surgery are all ideal usage case scenarios for dienogest.

Prevention of recurrence

As can be seen from the table below, the lowest incidence of recurrence between three commonly used treatments GnRH analogues, COCs and dienogest is the last of the three with only 2.6% recurrence at the end of 5 years while it is highest with GnRH agonists (53.4%) and intermediate with COCs.

Post op treatment options and duration*	Recurrence period after treatment*	No medications ⁵	GnRH ^{2,6,7}	OC ¹		Dienogest ^{3,4}	
		N/A	6 months	< 1 year	>1 year	6 months	5 years
18 months		N/A	10.3%	N/A	N/A	N/A	N/A
2 years		21.5%	N/A	N/A	N/A	4%	N/A
3 years		N/A	12.8%	49%	22%	N/A	N/A
4 years		N/A	N/A	N/A	N/A	21%	N/A
5 years		Up to 50%	53.4%	N/A	N/A	N/A	2.6%

Long term treatment is suggested
Medications after operation reduces recurrences rate
* Indirect comparison. For ease of reference only. 1. Vercellini et al. Am J Obstet Gynecol 2008; 2. Ke et al, 2015; 3. Yanase et al. Gynecol Endocrinol 2015; 4. Ota et al, 2015; 5. Guo et al, 2009; 6. Sesti F et al, 2009 7. Waller KG et al, 1993

Table 1 Incidence of recurrence with various therapies

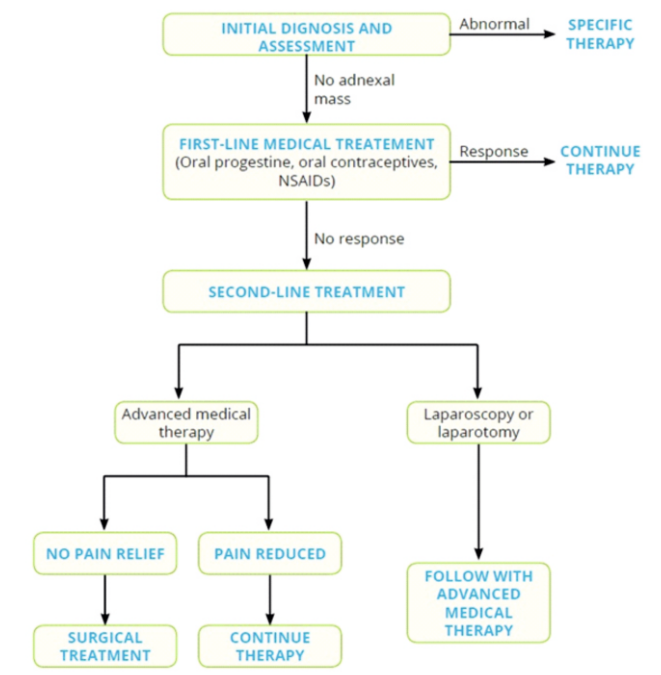


Fig 3 Simplified algorithm for medical management of adult endometriosis⁷

Conclusions

For the medical management of endometriosis, the clinician has always been presented with a plethora of options. However, until now we were limited by safety concerns, acceptability, compliance issues and the fundamental problem that the primary disease process was rarely addressed through medical therapy.

With the availability of dienogest, we have a safe, effective and readily accepted option which can be used at any age during a woman's reproductive career. It has been proven to be effective in long term studies up to five years and prevents recurrence in nearly 98% of patients. For adolescents, patients who refuse surgery, those who are unsuitable for surgery, in cases where we wish to avoid repeat surgery and in those who have been operated in order to prevent recurrence, dienogest represents an ideal option in the modern era.

References

1. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nature Reviews Endocrinology* 2019; 15:666-682. <https://doi.org/10.1038/s41574-019-0245-z>
2. Bedaiwy MA. Evidence-based long-term management of endometriosis: Medical therapy and treatment of infertility. *Middle East Fertility Society Journal*. 2011; 16:236-39.
3. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE Guideline: Management of women with endometriosis. *Hum Reprod*. 2014;29(3):400-412. doi:10.1093/humrep/det457
4. FOGSI. Good Clinical Practice Recommendations on Endometriosis. FOGSI Press 2016.
5. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: A 12-week, randomized, double-blind, placebo-controlled study. *Eur J Obstet Gynecol Reprod Biol*. 2010; 151(2):193-98.
6. Ota Y, Andou M, Yanai S et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. *JEPPD*. 2015; 7(2): 63-67.
7. Endometriosis Vision: Protocols for Practice. A FOGSI Publication 2019.
8. Köhler G, Faustmann TA, Gerlinger C, et al. A dose-ranging study to determine the efficacy and safety of 1,2, and 4mg of dienogest daily for endometriosis. *Int J Gynaecol Obstet*. 2010; 108(1):21-5.
9. Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: Efficacy of long term dienogest treatment. *Arch Gynecol Obstet*. 2012; 285(1):167-73.
10. Momoeda M, Harada T, Terakawa N et al. Long-term use of dienogest for the treatment of endometriosis. *J Obstet Gynaecol Res*. 2009; 35(6):1069-76.



ENDOMETRIOMA AND FERTILITY

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Introduction

Endometriosis is a modern-day gynaecological dilemma which has left many a gynaecologist and fertility specialist perplexed. Though we have learnt a lot about the condition over the years, a lot is yet left to be discovered. In this chapter we explore what we understand presently about endometriomas and their effect on fertility.

Endometrioma

It is a cyst found most commonly in the ovary of women suffering from endometriosis and is made up of endometrial tissue and often has a chocolate like consistency; hence also called chocolate cyst. It is found in 17 to 44% of women suffering from endometriosis.

Pathophysiology

- Endometriomas are benign cysts which originate as endometriosis of the ovary. This ectopic endometrium has the potential to undergo cyclical changes under the action of ovarian hormones similar to the endometrium in the uterus.
- While proliferative changes occur in response to estrogen in this ectopic endometrium, secretory changes often fail to occur due to a deficiency of steroid receptors in this ectopic endometrium.
- Every month with cyclical changes in hormones this ectopic endometrium continues to grow and shed and the shed contents remain trapped and encysted.
- Over time the serum in this trapped blood gets absorbed, leaving behind a chocolate coloured fluid trapped within the cyst
- These cysts can be unilocular or multilocular or they can be unilateral or bilateral.
- This fluid is often rich in inflammatory mediators and blood being a known irritant often causes a dense tissue reaction around the cyst which in turn causes dense adhesions of the cyst to nearby visceral tissue.

Impaired fertility

Endometriosis and endometriomas have been known to interfere with all stages of embryo development and implantation.

Ovary – Endometriomas are associated with

- Fewer follicles and fewer oocytes available due to follicular necrosis and poor recruitment of existing antral follicles

- Altered steroidogenesis by developing follicles
- Poor quality of developing oocytes
- Higher incidence of luteinised unruptured follicle
- Luteal phase defect post ovulation

Fallopian tube

- Anatomical distortion of the tube and disturbance of the tubo-ovarian alignment and interaction
- Higher incidence of tubal blockage
- Poor oocyte quality associated with low fertilisation rates in the fallopian tube
- Reduced sperm motility and poor sperm binding to oocytes due to a variety of reasons including increased cytokine secretion in peritoneal fluid of patients suffering from endometriosis
- Poor embryo quality resulting in developmental arrest of embryo in the tube

Uterus

Endometriomas are associated with lower implantation rates attributable to

- Altered hormone regulation (steroidogenesis) in endometriosis resulting in poor endometrial lining
- Reduced uterine receptivity
- The reduced uterine receptivity is due to an altered immunological response in body. In patients with endometriosis there is an over expression of B cells which produce antibodies which act against the endometrial antigens. In addition, endometriosis is associated with T cell and macrophage dysfunction and nonspecific polyclonal B cell activation

Hypothalamo-pituitary axis

- Altered pituitary ovarian axis
- Altered LH surge

To summarise, endometriomas are associated with poor fertilisation rates, poor implantation rates and high miscarriage rates.

Diagnosis of endometrioma

Has been covered in the previous article on Fertility Enhancing Endometriosis Surgery

Endometrioma and fertility treatment

The main objectives in the treatment of endometriomas are:

- a. Alleviate symptoms and improve the quality of life
- b. Enhance fertility
- c. To restore normal anatomy as far as possible
- d. To remove or reduce ectopic endometrial implants as far as possible
- e. To prevent recurrence

ASRM Guideline

Guidelines issued by the Practice Committee of American Society of Reproductive Medicine 2012 for endometriosis and infertility state that

- The age of the female, pelvic pain, duration of infertility & stage of endometriosis should be considered while formulating a management plan.
- In cases of mild endometriosis, the use of laparoscopic surgery merely to increase the likelihood of pregnancy is not justified.
- While doing laparoscopic surgery for other indications, if endometriotic lesions are discovered, one can safely consider ablating or excising these lesions.
- For women under the age of 35 with Stage 1 or 2 endometriosis associated infertility, expectant management or ovulation induction/ intrauterine insemination can be considered as first line therapy.
- For women above the age of 35 with Stage 1 or 2 endometriosis, a more radical approach like ovulation induction with IUI or IVF should be considered.
- In women with Stage 3 or 4 endometriosis associated infertility, conservative surgical therapy with laparoscopy may be beneficial.
- Surgical management of endometrioma should include resection or ablation, rather than drainage. Resection is the preferred mode of treatment.
- For women with Stage 3 or 4 endometriosis and infertility in whom conservative surgery has failed or who are of an advanced age may directly benefit from IVF/ ICSI and embryo transfer.

Fertility treatment options

In Grade 1 and Grade 2 endometriosis, with no other coexisting factors contributing to infertility and when the patient is relatively young in age, ovulation induction coupled with timed intercourse or IUI can be tried. The results with timed intercourse can range from 5-6 % and IUI from 10-15% depending on case to case scenario.

Ovulation induction can be done with

Clomifene citrate a selective estrogen receptor modulator which has an antiestrogenic effect at the hypothalamopituitary axis level and promotes gonadotropin release. This in turn promotes folliculogenesis.

Letrozole an aromatase inhibitor which reduces peripheral conversion of androgens to estrogens and indirectly promotes gonadotropin release. This has recently been proven to be free of associated congenital malformations and has been approved for use in ovulation induction. Doses range from 2.5-7.5 mg/day from day 2 to 6 of menses.

IVF/ICSI in endometriosis is recommended in cases of

- Tubal blockage
- Severe endometriosis
- Where conservative management has failed

- Associated severe male factor for infertility
- Advanced age
- Multiple factors contributing to infertility

Surgical management of endometriomas for infertility is restricted to the following conditions

- a. Stage 3-4 endometriosis
- b. Pre IVF if the endometrioma is large and prevents OPU
- c. As an adjuvant surgery if laparoscopy is being done for other procedures
- d. Inseverely symptomatic endometriosis

Surgery prior to IVF

Advantages

- Removal of cyst leads to decreased oxidative stress in ovary
- Leads to lesser pressure atrophy of ovary
- Oocyte quality may improve

Disadvantages

- Healthy ovarian tissue is lost leading to decreased AMH
- Any laparoscopic surgery has its own associated risks of surgery and anaesthesia especially in cases with severe adhesions.

Even if an endometrioma is more than 4 cm, and the patient is for IVF, if the follicles can be easily accessed and the patient is asymptomatic, it is better to leave the endometrioma alone.

Conclusion

In the present scenario we can safely conclude that endometriosis can affect all aspects of fertility. Also, management of the condition needs to be individualised as the severity of the symptoms often don't correlate with the grading of the disease. The decision to opt for medical or surgical management would have to take into account the medical severity of the disease in addition to the patient's comfort and preference.



SURGICAL MANAGEMENT OF STAGE III-IV DISEASE

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Introduction

Endometriosis is a benign, estrogen dependant gynaecological disease affecting 5-10% of women of reproductive age and 20-40% of women undergoing ART.¹ It is characterised by the presence of endometrial glands and stroma in ectopic sites in the body the commonest sites being the Pouch of Douglas, ovaries, ovarian fossa and rectosigmoid with lesser incidence of involvement of the urinary tract, other parts of the small and large intestine and very rarely other abdominal and extra-abdominal organs.

The AFS classification/ staging of endometriosis although flawed, seems to be the most widely followed. Whereas mild to minimal disease involves active lesions with little or no distortion of the organs and anatomy, moderate to severe disease involves a mixture of extensive disease and fibrosis with distortion of anatomy, greater degree of ovarian destruction and usually deep infiltration (>5mm by definition of deep infiltrating endometriosis) of organs such as the rectosigmoid and other parts of the bowel and the urogenital systems.

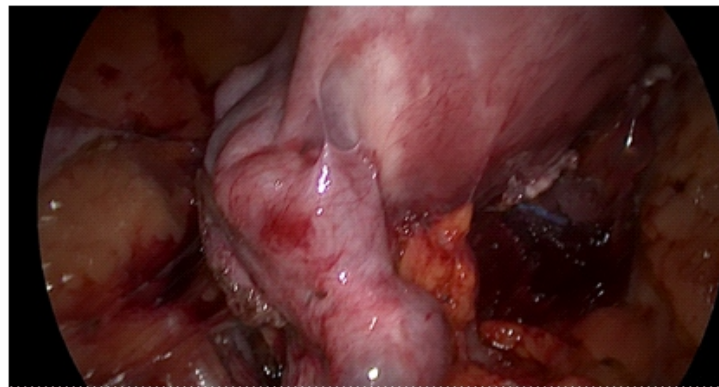


Fig 1 Deep infiltrating endometriosis



Fig 2 Rectovaginal endometriosis

Presentation

Symptomatology of endometriosis varies greatly. Severe dysmenorrhea is usually present due to active disease causing inflammation along with fibrosis entrapping the pelvic nerves and presence of associated adenomyosis, deep infiltrating nodules and ovarian endometriosis. Menorrhagia may be an occasional feature.¹

Rectovaginal endometriosis occurs in 5-12.4% women with endometriosis and is distributed along the rectum (13-55%), sigmoid (18-47%), ileum (2-5%), appendix (3-18%) and occasionally at other sites. Bowel involvement may be asymptomatic or with vague symptoms ranging from diffuse pain, intestinal hurry and constipation. Bowel obstruction and hematochezia are rare symptoms along with the occasional presence of a mass protruding into the bowel lumen.²

Similarly, bladder endometriosis is often an incidental diagnosis on radiological investigation of endometriosis with some patients complaining of repeated urinary, dysuria (21-69%) and catamenial menstruation (0-35%) and is often misdiagnosed as interstitial cystitis. It occurs usually between 20-57 years of age.³

Ureteric endometriosis is the probably the only life threatening form of abdominopelvic endometriosis since it is often asymptomatic (50%) in the early stage and 10% of women may present with silent renal failure. Cyclical haematuria is a rare feature (15%) since the disease is usually extrinsic. The common symptom is colicky flank pain (25%) due to ureteric obstruction.⁴

Indications for treatment

Any symptomatic disease requires therapy. The need for treatment of asymptomatic disease is uncertain but probably justified considering its potential for progression and rarely malignant change. Patients with endometriosis associated infertility often benefit from surgery due to increased spontaneous pregnancy rates, improved access to the ovaries during ART and improved inflammatory and endocrinemilieu. This has to be balanced again the risk of complication, delay in initiation of infertility treatment and possibility of extreme reduction of ovarian reserve.

Preoperative investigations

A transvaginal ultrasound in conjunction with a raised serum CA-125 remains the mainstay of diagnosis of endometriosis with extremely accurate diagnosis of endometriomas and deep infiltrating disease. An HE4 (raised in malignancy but not in endometriosis) and ROMA index may be useful in ruling out malignancy in uncertain situations.⁵

Deep infiltrating endometriosis of the rectovaginal and uterosacral area can be accurately diagnosed by a transvaginal and transrectal ultrasound. This also allows evaluation of the degree of seromuscular infiltration of the rectal nodule and loss of mobility between the ovaries, uterus and vagina and rectosigmoid (sliding sign). However, an MRI is needed to evaluate more extensive disease and lesions in the sigmoid or higher.⁶



Fig 3 MRI in advanced stage endometriosis

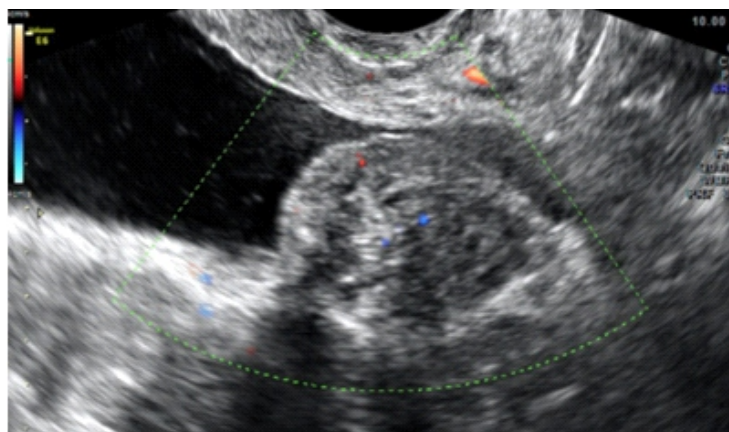


Fig 4 Colour Doppler in bladder endometriosis

Bladder endometriosis is visible as a bladder nodule with moderate to minimal vascularity on Colour Doppler. Cystoscopy reveals bluish submucosal lesions. A biopsy is necessary to rule out malignancy.⁷

Ureteric endometriosis presents as unexplained hydroureter with associated features of endometriosis such as dysmenorrhea (39-79%), pelvic pain (47-64%) and dyspareunia (70%) and a clinically palpable uterosacral nodule or fibrosis. MRI reveals hyperintense deposits of endometriosis surrounding and/or infiltrating the ureter.

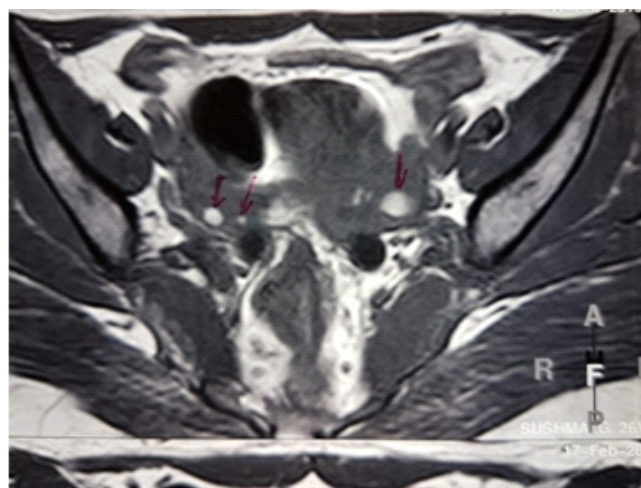


Fig 5 MRI in ureteric endometriosis

Altered renal function is seen in 30% of patients and a renogram will establish whether the kidney can be salvaged (GFR > 10%). Together with an MRI, it helps grade the disease. Ureterscopy may reveal mucosal oedema and infiltration but is of no therapeutic value.⁸

Grade	Pathology
0	Peritoneal endometriosis
1	Retroperitoneal disease surrounding ureter without dilatation
2	Hydroureter / hydronephrosis but normal renal function
3	Symmetrical split clearance & normal total clearance
4	Impaired split & total clearance
5	Silent kidney

Table 1 Grades of ureteric endometriosis

Indications for medical management

Medical therapy is the first line of treatment for symptomatic disease except in ureteric endometriosis since it can worsen ureteric compression due to fibrosis. Medical therapy may be avoided in infertile women who have undergone a complete or near complete excision of disease since it delays initiation of fertility treatment. It is of doubtful value in isolated deep infiltrating nodules. Medical therapy is of benefit in adolescent and recurrent endometriosis and following surgery in women not desirous of fertility.

Trials have shown that the highest cure rates are achieved with combined medical and surgical treatment (60% with recurrence 8-17%) followed by medical (55% with recurrence 22-28%) or surgical (50% with recurrence 20-24%) treatment alone. A trial of 3-6 months may be attempted for bladder endometriosis. Some studies have suggested a 60% response to therapy.⁹

Surgical management

Any patient not responding to a trial of medical therapy is a candidate for surgical management. Ureteric endometriosis does not benefit from medical therapy and needs urgent surgical intervention. Infertility often benefits from surgical therapy followed by IUI or ART. However, repeat surgeries and surgeries for bilateral ovarian disease especially in the presence of low ovarian reserve are best avoided or deferred till after ovum pickup.

Conservative surgical therapy involves removal of endometriotic implants and restoration of pelvic anatomy. In women who have completed child bearing and/ or having extreme symptoms refractory to medical or conservative surgical management are candidates for more radical surgery involving total hysterectomy with bilateral salpingo-oophorectomy with parametrectomy with excision of deep infiltrating disease. Ovarian conservation of part or whole of one or both reasonably healthy ovaries in a young woman undergoing hysterectomy for endometriosis is a matter of debate because of the risk of recurrence of disease (10-15%) and the rare occurrence of endometriosis associated ovarian cancer but should be considered as a viable option given the low incidence of compliance with HRT and risks of early menopause.

When operating in older women with endometriosis and ovarian lesions, the risk of endometrioid and clear cell cancers should be kept in mind and a frozen section employed if necessary. Laparoscopy is the route of choice for any form of surgery for endometriosis with laparotomy being considered in the rarest situations (incidental diagnosis of malignancy or complications not amenable to endoscopic treatment). Robotics has penetrated into the field of endometriosis surgery but whether they represent a step up is a matter of debate considering the costs and lack of tactile sensation which is of utmost importance in pelvic dissection in distorted anatomy.

Surgical principles

Laparoscopic adhesiolysis, adhesion prevention and ovarian endometriosis have been dealt with in a preceding article.

Bowel endometriosis

The surgical therapy for bowel endometriosis (usually rectosigmoid) is determined by the size of the lesions, depth of penetration (serosa 95%, muscularis propria 95%, submucosa 38% and mucosa 6%) and presence of multifocal (62%) and multicentric (28%) lesions.

There are essentially three types of approaches.¹¹ Small (< 50% bowel circumference) and isolated nodules involving the serosa or superficial muscularis are shaved off till healthy tissue is visualised. The rectosigmoid is infiltrated with 150-200 ml methylene blue and any thinned out stained area or obvious enterotomy is closed transversely with interrupted sutures of 2-0 or 3-0 delayed absorbable material.

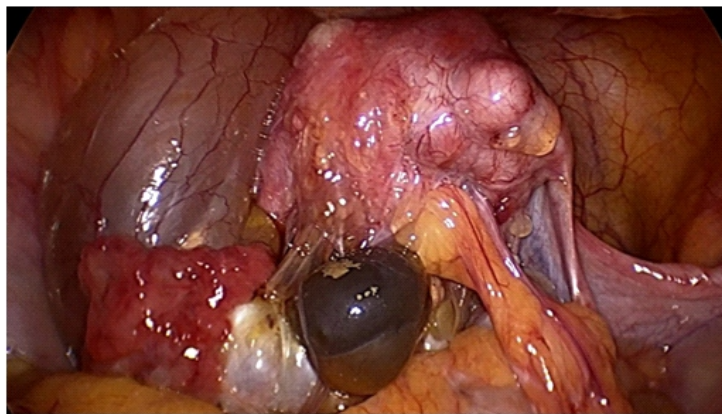


Fig 6 Severe endometriosis with rectovaginal infiltration

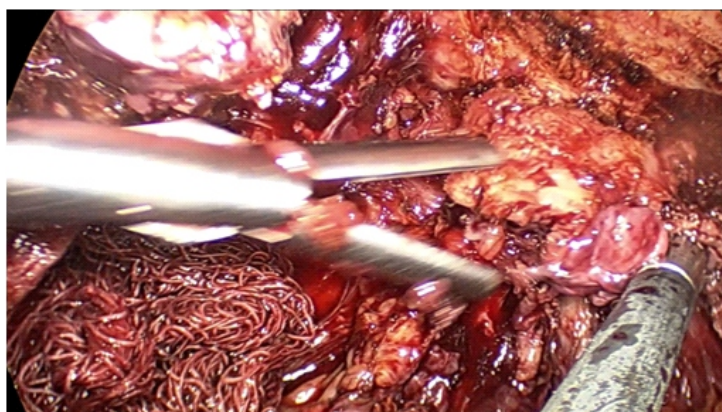
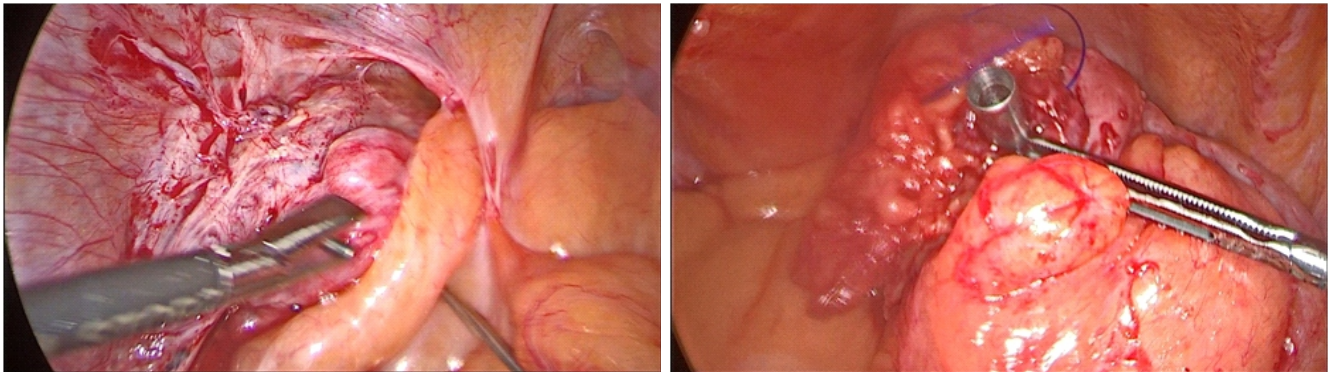


Fig 7 Rectovaginal nodule being excised

Lesions involving mucosa or submucosa require discoid or full thickness excision. A circular stapler may be used. However, excision with scissors or ultrasonic scalpel with feel of tissue is better in order to remove disease with a margin of healthy tissue. The bowel is closed in 2 layers transversely with 2-0 or 3-0 delayed absorbable interrupted sutures. Multiple lesions, recurrent lesions or lesions involving more than 50% of bowel circumference are best treated with a segmental resection anastomosis to avoid recurrence and stricture.

Most lesions are amenable to shaving and discoid resection since the nodule usually involves the anterior aspect of the bowel. Although the risk of recurrence is lower with resection anastomosis (2% versus 5% with discoid excision and 22% with shaving), the incidence of complications is high (3-10% major complications with 10% fistulas, 1.5% anastomotic leak and IBS in 55% of women) along with studies showing 12% without penetration beyond muscularis (unnecessarily aggressive surgery) and 20% positive margins (incomplete surgery).

With regards to fertility, aggressive excision of deep infiltrating disease seems to improve outcomes with ART possibly because of improved inflammatory and endocrine milieu and better access to ovaries for ovum pickup.¹²



Figs 8 and 9 Bowel endometriosis

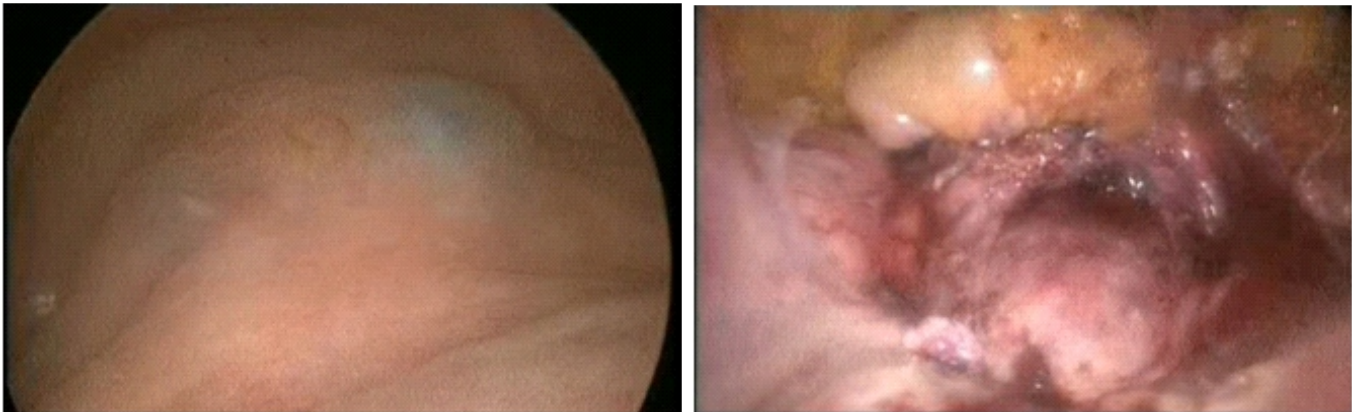
Bladder endometriosis

Bladder endometriosis infiltrates the detrusor muscle and is associated with superficial implants (58.6%), deep infiltrating endometriosis (27.6%) and adhesions (81%). Its association with adenomyosis and previous uterine surgery is uncertain.⁸

Surgery is almost always by laparoscopic route. Cystoscopy is done to evaluate the extent of the disease. It is wiser to stent the ureteric orifices since wide excision of the nodule may bring the orifices close to the line of incision. If the nodule is close to the ureteric orifice, the mucosa is incised encircling the nodule by resectoscope and mobilised away from the orifice before proceeding with laparoscopy. This may obviate the need for a ureteric reimplantation.

The bladder is mobilised anteriorly from the space of Retzius and the paravaginal space. The bladder is divided vertically to approach the nodule. The nodule is excised and the bladder flaps dissected off the uterocervical surface. It has been recommended to excise underlying myometrium to reduce the risk of recurrence but the benefit of this manoeuvre is uncertain. The

bladder is sutured in 1-2 layers with 3-0 delayed absorbable or barbed sutures. If the nodule cannot be mobilised away from the ureteric orifice or is infiltrating the ureter a reimplantation should be considered. Complications following the surgery are extremely rare.



Figs 10 and 11 Bladder endometriosis

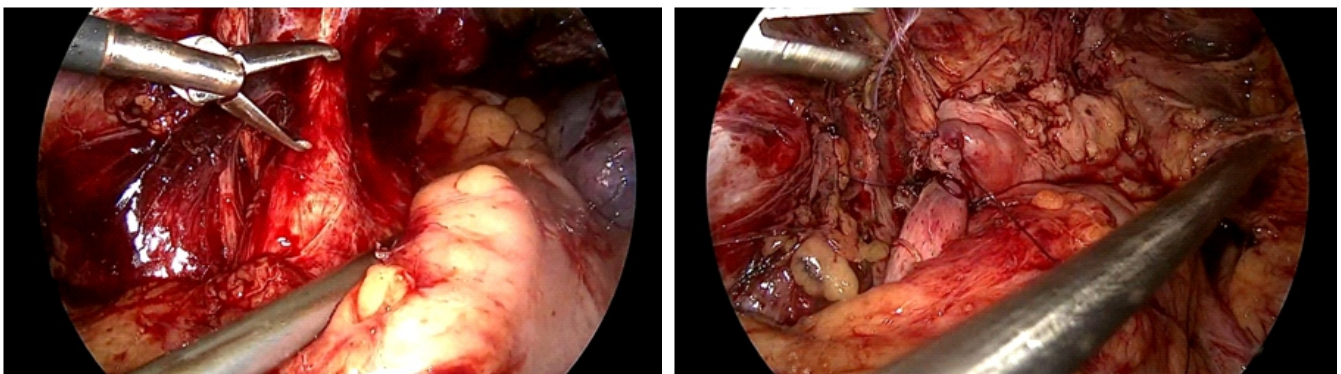
Ureteric endometriosis

Ureteric endometriosis usually is endometriosis of the parametrium encircling the ureter (extrinsic 60%) and rarely infiltrating the muscularis and lumen (intrinsic 40%). Its prevalence is 0.01-1.7% in endometriosis, usually unilateral with predisposition for the left ureter and involving the distal 3-4 cm and a peak incidence of 30-35 years.¹³

Surgical therapy involves ureterolysis from the pelvic brim to the ureterovesical junction. In case of intrinsic disease, recurrent disease and severe stricture not resolving with ureterolysis and excision of the nodules, the diseased part may be excised and the ureter reimplanted into the urinary bladder with or without the need of a Boari flap. The ureteric catheter is removed after 6-8 weeks.

There is virtually no role or uretero-ureteric anastomosis and simple stenting. Nephroureterectomy may be considered in absence of ipsilateral renal function with often coexistent pyoureter. An ipsilateral salpingo-oophorectomy is often recommended although the evidence regarding its benefit is scanty.

Following surgery, resolution of symptoms occurs in 88-95% of cases with recurrence requiring intervention in 6-12% of women. Complications are rare and transient with ureteric injury 0.2-2%, bladder anastomotic leakage 2-8%, VUR 16-30% and transient voiding dysfunction in 25% of women.¹⁴



Figs 12 and 13 Dilated left ureter and reimplantation into bladder

Conclusion

Endometriosis is the epidemic of modern gynaecology and involves much suffering in young women. The field of endometriosis therapy is complex and rapidly evolving in terms of our understanding of disease evolution, technology, surgical techniques and drugs. But a combination of developments on all these fronts have allowed us to offer reasonably effective treatments for the various forms of endometriosis.

References

1. Falcone T, Flyckt R. Clinical Management of Endometriosis. *Obstet Gynecol*, 2018; 131: 557-71
2. Bazot M et al. Accuracy of magnetic resonance imaging and rectal endoscopic sonography for the prediction of location of deep pelvic endometriosis. *Hum Reprod*, 2007; 22: 1457-63
3. Kotodziej A et al. Urinary tract endometriosis review. *Urology Journal*, 2015; 12: 2213-5
4. Raimondo D et al. Severe ureteral endometriosis: frequency and risk factors. *Journal of Obstetrics and Gynaecology*, 2018; 38 (2): 257-60
5. Mallick R. The diagnosis and management of severe endometriosis. *MOJ Surgery*, 2017; 4 (5): 107-12
6. Koninckx PR et al. Deep endometriosis: definition, diagnosis and treatment. *Fertil Steril*, 2012; 98 (3): 564-71
7. Maccagnano C et al. Diagnosis and treatment of bladder endometriosis. *Urol Int*, 2012; 89 (3): 249-58
8. Serrachioli R et al. Conservative laparoscopic management of urinary tract endometriosis (UTE): surgical outcome and long term follow up. *Fertil Steril*, 2010; 94 (3): 856-61
9. Vercellini P, Buggio L, Somigliana E. Role of medical therapy in the management of deep rectovaginal endometriosis. *Fertil Steril*, 2017; 108 (6): 913-30
10. Hayasaka S et al. Risk factors for recurrence and re-recurrence of ovarian endometriomas after laparoscopic excision. *J Obstet Gynecol Res*, 2011; 37 (6): 581-5
11. Milone M et al. Colorectal resection in deep pelvic endometriosis: Surgical technique and post-operative complications. *World Journal of Gastroenterology*, 2015; 21 (47): 13345-51
12. Ceccaroni M et al. Nerve-sparing laparoscopic eradication of deep endometriosis with segmental rectal and parametrial resection: the Negrar method. A single-center, prospective, clinical trial. *Surg Endosc*, 2012; 26 (7): 2029-45
13. Chou MT et al. Prophylactic ureteral catheterization in gynecologic surgery: a 12 year randomized trial in a community hospital. *International Urogynecology Journal*, 2009; 20 (6): 689-93
14. Nezhat C et al. Urinary tract endometriosis treated by laparoscopy. *Fertil Steril*, 1996; 66 (6): 920-4



ADENOMYOSIS

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"Adenomyosis... a significantly neglected and misunderstood uterine disorder..."

Overview

Adenomyosis is a common benign gynaecological condition but its diagnosis and treatment remain a clinical challenge to gynaecologists. The true incidence of adenomyosis is unknown and the prevalence varies widely due to the lack of a standardised definition and diagnostic criteria.

Adenomyosis is usually concurrent in its occurrence with endometriosis. Di Dona et al¹ showed a prevalence of 21.8% in women undergoing surgery for endometriosis. Adenomyosis is best defined by Bird in 1972 as "the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium".²

Pathogenesis

The exact pathogenesis of adenomyosis remains debatable. The diagnosis of adenomyosis is made when ectopic endometrial implants are found within the myometrium of the uterus. The most common and widely accepted theory involves the downward invagination of the endometrialbasalis layer into the myometrium due to either myometrial weakness or altered immunologic activity leading to disruption of the endometrial-myometrial interface, also known as the "junctional zone (JZ)".³

Diagnosis

One accepted criterion is the presence of endometrial tissue more than 2.5 mm below the endomyometrial junction or a Junctional Zone (JZ) thickness of more than 12 mm.⁴ The modification of the uterine structure may range from thickening of the JZ of >12 mm to nodular or diffuse lesions involving the entire uterus which is classified as "focal adenomyoma" where the endometrial deposits are more localised at one site within the uterine wall as a confined lesion or "diffuse adenomyosis" where endometrial deposits are found dispersed within the myometrium.⁴

Presentations

The classic presentation of adenomyosis is heavy, painful menstrual bleeding, typically occurring in multiparous women between 40 and 50 years of age. Heavy menstrual bleeding is present in up to 40–60% of patients, which is attributed to the enlarged endometrial surface area or the increased vascularity of the endometrium. Dysmenorrhea occurs in 15–30% of patients. Both the amount of bleeding and degree of pain were shown to be significantly correlated with the degree

of myometrial invasion. Other presenting features include chronic pelvic pain, dyspareunia, and the finding of an enlarged uterus in an asymptomatic woman. Women with adenomyosis have been shown to have a decreased quality of life.

There is also increasing evidence to show an association between infertility and adenomyosis. Various mechanisms postulated in this aetiology include impairment of sperm transport, abnormal uterine contractility, free radicle metabolism. Adenomyosis is also speculated to be cause of recurrent implantation failure after IVF treatment.

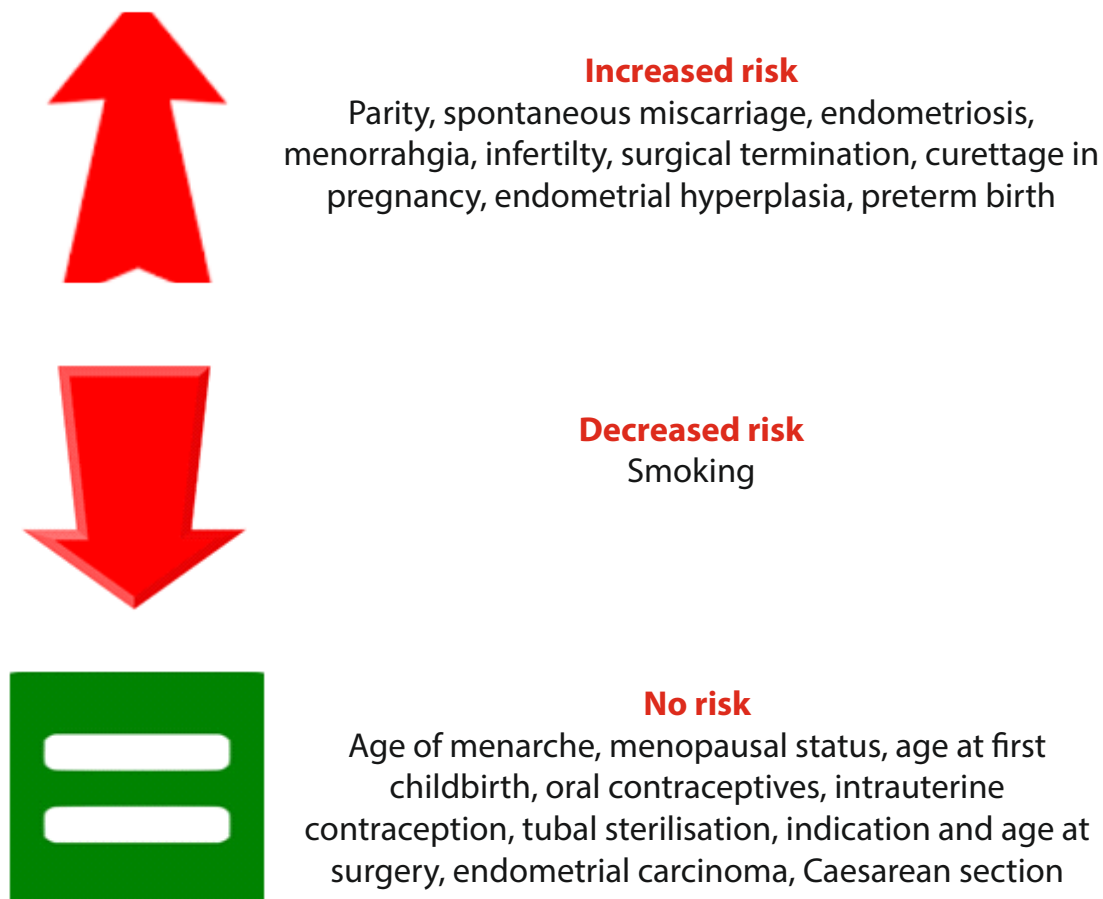


Fig 1 Summary of risk factors and symptoms of adenomyosis⁵

2D ultrasound

Two dimensional (2D) transabdominal USG may reveal uterine enlargement or asymmetric thickening of the anterior and posterior myometrial walls. However, transabdominal USG is often not accurate enough in diagnosing adenomyosis as it fails to provide sufficient image resolution for visualization of the myometrium.

Therefore, 2D transvaginal USG is often the first-line investigation. Transvaginal USG has a sensitivity of 80–86%, specificity of 50–96% and an overall accuracy of 68–86% in diagnosing diffuse adenomyosis.⁶ In suspicious cases, Doppler sonography may be helpful to differentiate from the fibroid as per the vessel pattern.

Uterine enlargement in the absence of leiomyomas
Asymmetric enlargement of the anterior or posteriomyometrial wall
Lack of contour abnormality or mass effects
Heterogeneous, poorly circumscribed areas within the myometrium
Hyperechoic, poorly circumscribed areas within the myometrium
Hyperechoic islands or nodules, finger –like projections or linear striations, indistinct endometrial stripe
Anechoic lacunae or cysts of varying size

3D ultrasound

Three-dimensional (3D) USG improves diagnostic accuracy of adenomyosis as it allows better imaging of the JZ. Upon 3D USG, adenomyosis is characterised by a thickened or irregular JZ.

Magnetic Resonance Imaging (MRI)

MRI is the gold standard imaging modality for assessing the JZ in the evaluation of adenomyosis. The common features of adenomyosis on MRI include thickening of the JZ, JZ thickness ≥ 12 mm, or irregular junctional thickness with a difference of >5 mm between the maximum thickness and the minimum thickness, an ill-defined area of low signal intensity in the myometrium on T2-weighted MR images as islands of ectopic endometrial tissue identified as foci of high signal intensity on T1 weighted image.⁷ Both TVS and MRI show high levels of accuracy for the non-invasive diagnosis of adenomyosis. However, MRI may be particularly useful in the assessment of focal adenomyoma and provides important information on whether surgery should proceed.

Shear wave elastography

Adenomyosis is associated with a significant increase of the myometrial stiffness estimated with shear wave elastography. Further studies are required to verify the clinical usefulness of such an approach.

Hysterosalpingography

An occasional finding of speculations measuring 1–4 mm in length, arising from the endometrium towards the myometrium, or a uterus with the “tuba erecta” finding may be suggestive of adenomyosis.

Hysteroscopy

Though limited data is available various hysteroscopic appearances of adenomyosis have been described like irregular endometrium, endometrial defects, superficial openings, hypervascularisation, strawberry pattern, cystic haemorrhagic lesions.

Management

Medical treatment

Medical treatment for adenomyosis is similar to that given for endometriosis. Apart from providing symptomatic relief, hormonal treatment mainly works by inhibition of ovulation, cessation of menses, improving the hormonal milieu and causing decidualisation of the endometrial deposits.

Analgesics They are usually the first line of treatment for symptomatic pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting the cyclooxygenase (COX-1 and COX-2) and decreasing the production of prostaglandins.

Oral contraceptive pills (OCPs) Combined oral contraceptive pills work by inhibiting ovulation by suppressing the release of gonadotrophins.

Danazol causes a hypogonadic state and thus is widely used for the treatment of endometriosis and abnormal uterine bleeding. However, data on its use in adenomyosis remains limited. This may be due to its unwanted adverse effects after systemic treatment.

Dienogest is a selective synthetic oral progestin with pronounced local effect on endometrial tissue. It has been shown to be effective in the treatment of endometriosis associated pelvic pain. A prospective clinical trial has shown dienogest to be a valuable alternative to depot triptorelin acetate for treatment of premenopausal pelvic pains in women with uterine adenomyosis. 41 patients were allocated to receive oral dienogest (2 mg/day) or triptorelin acetate (3.75 mg/4 weeks) for 16 weeks. Both the treatments were highly effective in relieving dysmenorrhea, dyspareunia and chronic pelvic pain associated with adenomyosis.⁸

Levonorgestrel releasing intrauterine device (LNG-IUD)

LNG-IUD is an intrauterine device which releases 20 micrograms of levonorgestrel per day with proven efficacy for treatment for abnormal uterine bleeding. It acts locally and causes decidualisation of the endometrium and adenomyotic deposits. It alleviates dysmenorrhea by improving uterine contractility and reducing local prostaglandin production within the endometrium.

LNG-IUD appears to be an effective method in relieving dysmenorrhea associated with adenomyosis⁹ and is more effective than the combined OC pill, improved the quality of life and appears to be a promising alternative treatment to hysterectomy. LNG-IUD may be used in conjunction with the other treatment modalities like GnRH analogues or Transcervical resection of endometrium (TCRE).

GnRH agonists

GnRH agonists are effective in alleviating dysmenorrhea and relieving menorrhagia associated with adenomyosis. However, due to the undesirable climacteric side effects and risk of osteoporosis, treatment with GnRH agonists is usually restricted to a short duration of 3 – 6 months

although the duration of use may be extended if add-back estrogen therapy is employed. Discontinuation of treatment usually leads to regrowth of the lesions and recurrence of symptoms.

Selective estrogenreceptor modulator (SERM)

Selective estrogen receptor modulators like tamoxifen or raloxifene have been tried in the treatment of endometriosis. However, their value in the treatment of adenomyoma has not been formally explored.

Aromatase Inhibitors

Adenomyotic deposits are estrogen dependent. A prospective randomised controlled study found that the efficacy of aromatase inhibitors (letrozole 2.5 mg/day) in reducing the volume of adenomyoma as well as improving adenomyosis symptoms was similar to that of GnRH agonists (goserelin 3.6 mg/month).

Ulipristal acetate

Ulipristal acetate (UPA) is a potent selective progesterone receptor modulator. There is good evidence to suggest that it can be used to shrink fibroid and control menorrhagia. It is possible that it may be similarly effective in the treatment of adenomyoma but literature data is lacking.

Antiplatelet therapy

There is new evidence to suggest a role of antiplatelet therapy in treating adenomyosis. Emerging evidence suggests that endometriotic lesions are wounds undergoing repeated tissue injury and repair (ReTIAR) leading ultimately to fibrosis. Adenomyotic lesions are thought to have similar pathogenesis to that of endometriosis

Uterine artery embolisation

Uterine artery embolisation (UAE) has been used to treat symptomatic fibroids since the 1990s. There is increasing evidence to suggest that it is also effective in the treatment of management of adenomyosis.

High intensity focused ultrasound

High intensity focused ultrasound (HIFU) is another nonsurgical treatment for uterine fibroids that focuses high intensity ultrasound in the target lesion causing coagulative necrosis and shrinkage of the lesion. Both MRI and USG can be used for guidance for the procedure. MRI has better real time thermal mapping during the HIFU treatment. Yet, ultrasound guided HIFU is less costly and offers real time anatomical monitoring imaging, an indicator in treatment response. It is effective in both focal and diffuse lesions.

Endomyometrial ablation or resection

There is limited data on laparoscopic or hysteroscopic endometrial ablation in treating adenomyosis. This should probably be performed in a centre of excellence by surgeons competent in such procedures.

Hysterectomy

Hysterectomy is the definitive treatment option for intractable symptomatic adenomyosis when conservative or symptomatic treatment have failed.

Conclusions

- Many treatment modalities are now available for the treatment of adenomyosis.
- The management plan ought to be individualised, depending on the presenting symptom and the desire to achieve a successful pregnancy.
- Recent development in various nonsurgical and surgical options has significantly improved the prospect of a successful treatment in women wishing to conceive again.

References

- 1 N. Di Donato, G. Montanari, A. Benfenati et al., "Prevalence of adenomyosis in women undergoing surgery for endometriosis," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 181, pp. 289–293, 2014.
- 2 C. C. Bird, T. W. McElin, and P. Manalo-Estrella, "The elusive adenomyosis of the uterus-revisited," *American Journal of Obstetrics & Gynaecology*, vol. 112, no. 5, pp. 583–593, 1972
- 3 J. G. Leyendecker, A. Bilgicyildirim, M. Inacker et al., "Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study," *Archives of Gynaecology and Obstetrics*, vol. 291, no. 4, pp. 917–932, 2015.
- 4 J. Struble, S. Reid, and M. A. Bedaiwy, "Adenomyosis: a clinical review of a challenging gynaecologic condition," *Journal of Minimally Invasive Gynaecology*, vol. 23, no. 2, pp. 164–185, 2016.
- 5 Parazzini F, Vercellini P, Panazza S, Chatenoud L, Oldani S, Crosignani PG. Risk factors for adenomyosis. *Hum Reprod* 1997;12:1275–9.
- 6 Reinhold C, McCarthy S, Bret PM, Mehio A, Atri M, Zakarian R, et al. Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation. *Radiology* 1996; 199:151–8.
- 7 C. Reinhold, F. Tafazoli, A. Mehio et al., "Uterine adenomyosis: Endovaginal US and MR imaging features with histopathologic correlation," *Radiographic*, vol. 19, pp. S147–S160, 1999.
- 8 M. Fawzy and Y. Mesbah, "Comparison of dienogest versus triptorelin acetate in premenopausal women with adenomyosis: a prospective clinical trial," *Archives of Gynaecology and Obstetrics*, vol. 292, no. 6, pp. 1267–1271, 2015
- 9 F. Ji, X. H. Yang, A. L. Ai Xing, T. X. Zi, Y. He, and Y. Ding, "Role of levonorgestrel-releasing intrauterine system in dysmenorrhea due to adenomyosis and the influence on ovarian function," *Clinical and Experimental Obstetrics & Gynaecology*, vol. 41, no. 6, pp. 677–680, 2014.

In Chronic Pelvic Pain

^{Rx} LUPRIDE DEPOT ^{1M} ^{3M}

Leuprolide Acetate Depot Inj. 3.75 mg / 11.25 mg

Suppresses Chronic Pelvic Pain & Improves Fertility

ACOG* and RCOG** support the empiric use of GnRH agonist in the diagnosis and management of CPP, even in the absence of confirmation of histology, after exclusion of other causes of pain¹

ESHRE 2014 guideline: management of women with endometriosis²

Guideline development group (GDG), recommends GnRH agonists (Level A) as one of the options, as it reduces endometriosis-associated pain as against hormonal contraceptives (Level B)²

Six months of GnRH agonist therapy immediately following surgery

- Reduces the rate of symptom recurrence⁴
- Increases the length of time before symptoms recur⁵
- It is also more effective in managing endometriosis-related pain after surgery than using oral contraceptives⁶



1. Michele Morelli et al. *Gynecol Endocrinol*, 2013; 29(4): 305-308
2. G.A.J. Dunselman, ESHRE guideline: management of women with endometriosis, *Human Reproduction*, Vol.0, No.0 pp. 1-13, 2014
3. A. E. Schindler, *Gynecol Endocrinol* 2004;19:51-55
4. Hemmings R. *J Reprod Med* 1998;43(3):316-320
5. Schweppe K-W, Hummelshoj L. Recommendations on the use of GnRH in the management of endometriosis. In: Lunenfeld B (ed). *GnRH Analogs in Human Reproduction*. United Kingdom: Francis & Taylor, 2005:53-66
6. Muzii L, Marana R, Caruana P, et al. *Am J Obstet Gynecol* 2000;183:588-592

* American College of Obstetrics and Gynaecology
** Royal College of Obstetrics and Gynaecology

Level A recommendation : Meta-analysis or multiple randomized trials (of high quality)
Level B recommendation : Meta-analysis or multiple randomized trials (of moderate quality)



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