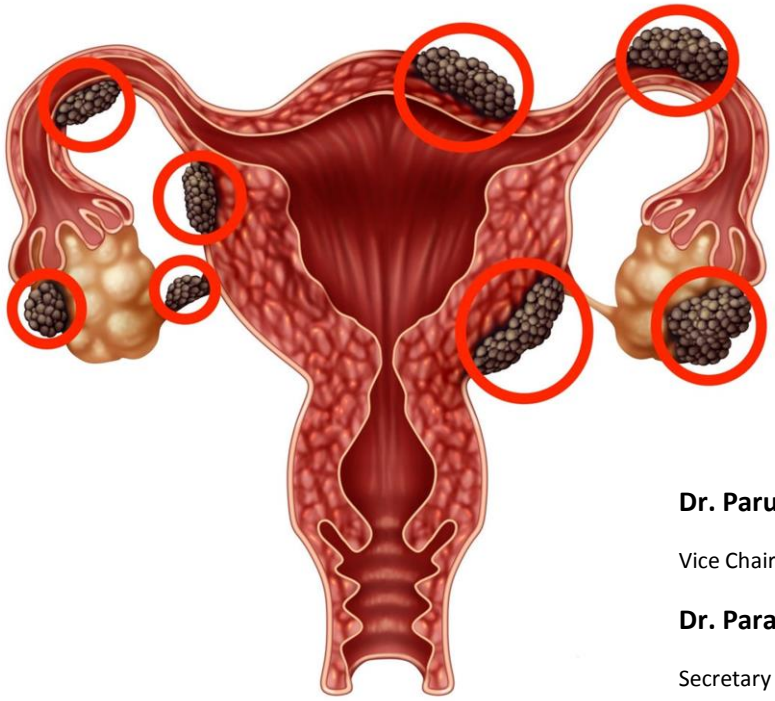
ICOG CAMPUS

On Endometriosis



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ICOG Governing council member

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FROM

PRESIDENT'S DESK

Greetings from FOGSI!

It gives me immense pleasure to release the ICOG CAMPUS booklet on Endometriosis updates as FOGSI President 2020.

Endometriosis is a more common gynaecological disorder which affects 5 – 10 % of the reproductive age group and the incidence increases among infertile women up to 25 – 50%. It is an enigmatic disease with varying symptoms like pain and infertility. Women with endometriosis suffer their entire reproductive age group because of pain which affects the quality of life, productivity, fertility, sexuality and psychological status.

There is a need for management at varying stages depending upon the requirement of the patients whether they need fertility or pain relief. As on date, there are lot of literature evidences and research activities in this particular subject which creates interest among any gynaecologists.

ICOG academic wing of FOGSI is known for publication of different topics which will aid the clinician to update their knowledge.

I would like to congratulate ICOG Chairperson Dr. Mandakini Megh & Dr. T. Ramani Devi, Dr. S. Sampath Kumari Governing Council members of ICOG and their team for publishing this booklet on endometriosis which includes various important topics.

I hope this booklet release will be beneficial to the readers.

Dr. Alpesh Gandhi

President FOGSI 2020

FROM

CHAIRPERSON'S DESK

Greetings from ICOG academic wing of FOGSI. ICOG academic wing was started in 1984 to disseminate knowledge in the field of ObGyn. Team ICOG 2020, proudly brings about an update on endometriosis which is an enigmatic and elusive disorder.

Endometriosis affects 1 in 10 women of reproductive age group, not sparing the adolescents and the perimenopausal women. The main problem with endometriosis is intractable pain and impaired fertility which affects the QOL. The diagnostic delay in early endometriosis may vary up to a period of 4 – 9 years and the patient would have seen minimum of 4 – 5 consultants. There is a lot of economy involved in treating these patients who need lifelong management plan. The patients have to spend a lot and the productivity is lost as well. 30% of patients are subjected to multiple surgeries which should be avoided. They should be managed medically as far as possible. Fertility is improved either by surgery or through ART.

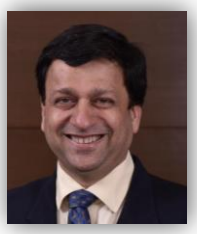
Adolescents are a special group of people who need careful management plan. Recurrence of endometriosis should be handled medically. In Post-menopausal women HRT should be tailor-made.

In this issue the editors have tried to bring about salient topics involved in endometriosis treatment. As the chairman of ICOG, I appreciate the effort taken by the editor, Dr. T. Ramani Devi and co-editor, Dr. S. Sampath Kumari, the governing council member of ICOG, who have compiled this book on ICOG Campus of Endometriosis.

Long live FOGSI – ICOG !

Dr. Mandakini Megh

Chairperson, ICOG



FROM

SECRETARY'S DESK

Greetings from ICOG!

Endometriosis affects between 6-10 % of women of reproductive age worldwide. The condition appears to be present in a developing fetus, but rise in oestrogen level during pubertal years is thought to trigger the symptoms. Symptoms are generally present during the reproductive years. Dysmenorrhea, heavy menstrual bleeding, dyspareunia are common symptoms disturbing woman's life. Most women go undiagnosed, and in the U.S. it can take around 10 years to receive a diagnosis. Allergies, asthma, chemical sensitivities, autoimmune diseases, chronic fatigue syndrome, fibromyalgia, breast cancer & ovarian cancer are linked to women and families with endometriosis.

There is continuous research going on on Endometriosis and newer medical conservative surgical methods are evolving in managing women suffering from endometriosis while management of young women seeking childbearing has also evolved.

I wish to sincerely thank our governing council member Dr Ramani Devi and all experts who has contributed to this ICOG campus. I am sure all our members will be enriched with update in knowledge. After all, we as Gynaecologists always strive for what best we can offer women who are suffering and this issue will be a dreary reckoned for clinicians

Happy reading!

Dr Parag Biniwale

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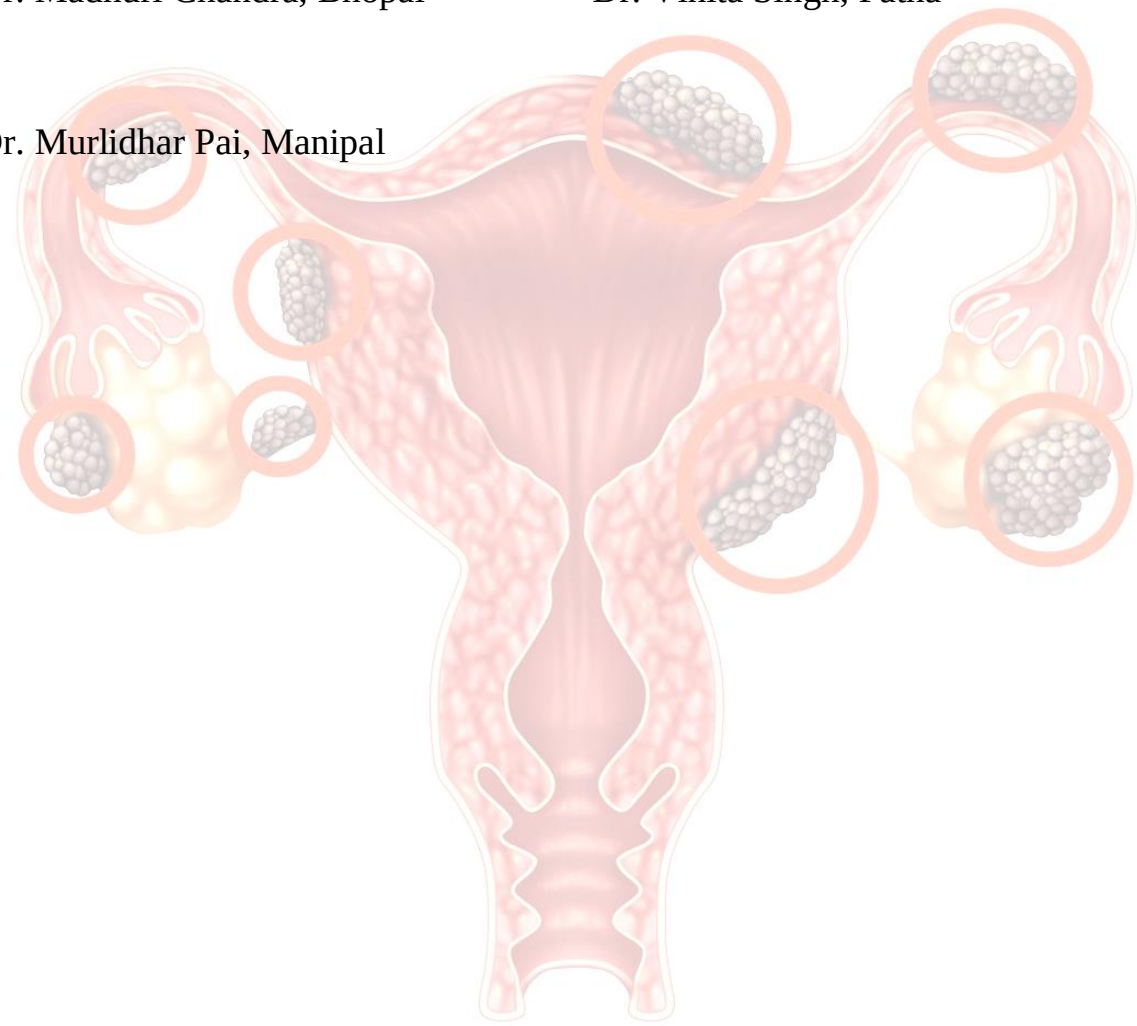

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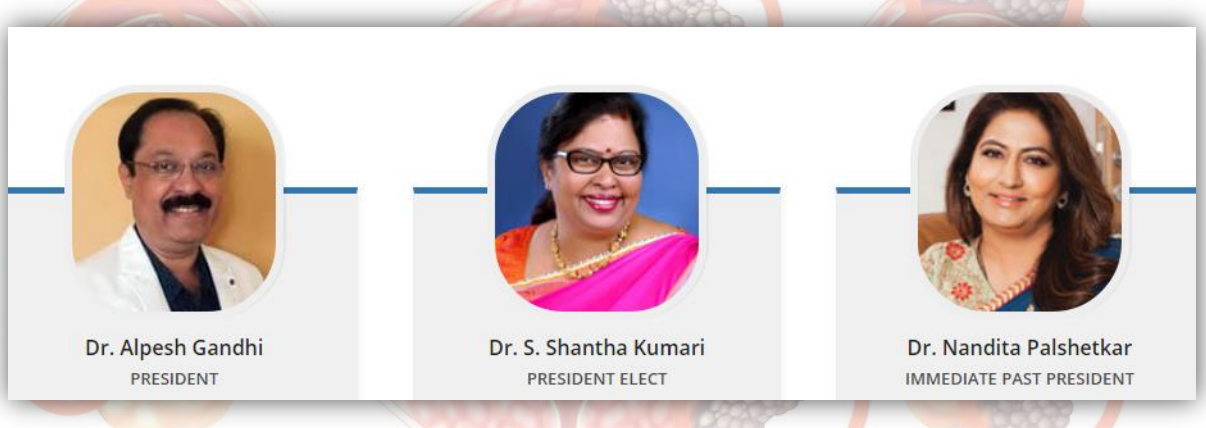

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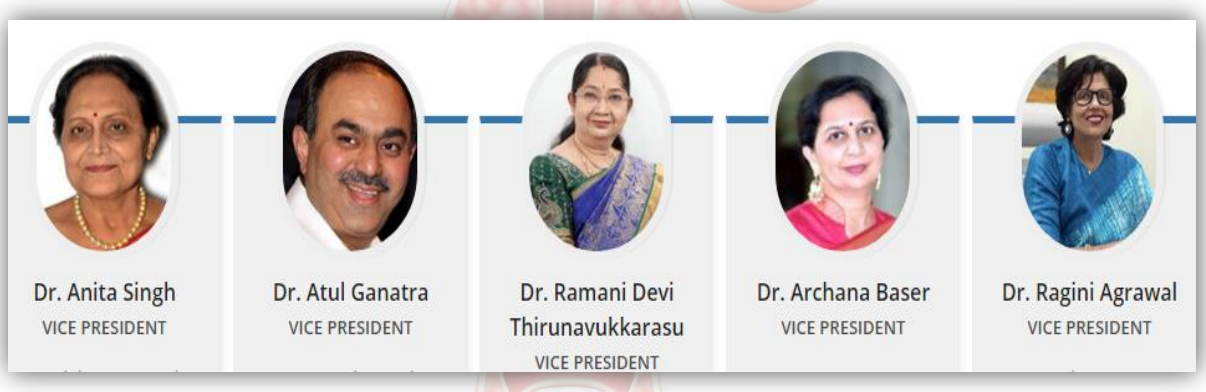

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FROM

EDITOR'S DESK

Endometriosis is an enigmatic disease. According to Prof. Te Linde one who knows endometriosis knows whole gynaecology. Endometriosis not only affects the genital tracts of the female but it spreads its wings to extra genital sites also.

Endometriosis affects the quality of life and fertility. It starts occurring from adolescence to menopause where it has different manifestations, making the diagnosis very difficult.

March is the month of Endometriosis awareness and April is the month of Adenomyosis awareness. Patient with endometriosis suffer from pain of varying degrees which will leads the patient to severe depression. The treatment modalities available are medical, surgical and combination.

Infertility is one arm of endometriosis which has to be handled carefully as repeated surgeries can destroy the future fertility. Earlier shifting of the patients to ART will improve the outcome of fertility. ASRM explains that this is a disease with life-long manifestation which has to be handled medically rather than repeated surgeries.

ICOG academic wing of FOGSI always comes out with various newsletters, booklets and magazines. We as editor's put our efforts to bring an Endometriosis update with latest information regarding aetiology, imaging, management of fertility, pain and recurrence.

I sincerely thank Dr. Alpesh Gandhi, President FOGSI 2020 and Dr. Mandakini Megh, Chairperson FOGSI 2020 for giving us this opportunity to edit this ICOG CAMPUS on Endometriosis updates.

I sincerely thank all authors who have contributed in compiling this booklet. I hope that this booklet will help the clinicians in their daily practice.

With regards,

Editor:

Dr. T. Ramani Devi,

Vice President FOGSI 2020

Governing Council Member ICOG 2018-2020

Dr.S. Sampath Kumari

Chairperson Adolescent Committee 2016-18

Governing Council Member ICOG 2018-2020

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Chapter 1

Genetics of Endometriosis

Dr. Sripriya Pragasam, M.D., FICOG, FICS.

EC Member Endometriosis Committee,

Sri Venkateshwara Hospital,

Trichy.

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG,

National Vice President FOGSI 2020

Governing council member ICOG 2018-20

Consultant Obstetrician and Gynecologist

Director Ramakrishna Medical Centre LLP

Director Janani Fertility Centre

Trichy

Introduction

Endometriosis has always been a complex disease. What predisposes women to endometriosis? Is it a susceptibility gene or a group of genes? Can there be a place for DNA variants? Is there a relationship between phenotype and genotype? How will this affect future genetic research?

Genetics

A genetic contribution to endometriosis risk is well documented! The relationship between DNA polymorphism and endometriosis is unchallengeable!

Today the consensus is that Endometriosis is a polygenic disease and more than one gene and / or genetic variants have predisposed women to endometriosis.

Human genetic variation has introduced a range of mutation that alter relevant cellular or molecular functions and thus affects the multi-layered series of processes that determine endometriosis.

GSTM 1 polymorphism[1], loss of hetero zygosity [LOH] in 9p, 11q, 22q[2], mutation in p 53 gene at codon 220[3], LOH in 17 q[4], monosomy 17[5], mutations in tumour suppressor PTEN gene on chromosome 10q 23[6], KRAS gene mutation[7] have all been identified. Is the relationship really causal or is it casual?

With rapid advances in genomic technology, we are able to do genotyping & gene mapping much faster, more thoroughly and the cost has also come down.

Identification of susceptible genes can be done by two methods – Genetic linkage studies or Association studies.

In Genetic linkage studies, the genes of interest are identified through DNA markers which are physically linked with the putative genes (genes that interest us)

But in spite of all these publications and research, gene studies have been inconsistent and generally they have not delivered clear answers about endometriosis susceptibility. *The genetic basis of endometriosis is complex with a wide range of genes likely to be involved.*

DNA variants

Genes are necessarily the cause of inheritable phenotypes and the phenotypic variations originates exclusively from DNA sequences. We can no longer assume that there is a 1: 1 relation between genetic factor and character. Thus, the DNA variants have an important role to play. In complex disease like endometriosis, we have *confirmed polygenic involvement and genes explain only fractions of variation in the disease*.

The study by Kashima et al among patients with endometriosis, their sisters and normal controls. Can we assume that the particular susceptibility gene is present in that family or is it aggregation of risk factors in that family [like younger age at menarche, body mass index, length of menstrual cycles and the amount of menses.] In controls, does higher fertility, increasing parity and younger age at first birth all have a protective effect[8].

So, the future lies in genetic epidemiologic studies which are more methodological, with proper choice of controls and adjustment for *familial aggregation of risk factors and DNA variants.*

Role of Epigenetics

Understanding the structure of DNA, it has a nucleus which is coated with an equal mass of protein, together forming a complex called chromatin. This chromatin controls gene activity and the inheritance of traits.

The DNA structure can be compared to a puppet. The nucleus of DNA is the puppet and the proteins around are actually the puppet strings which make the puppet come alive.

Proteomics is the study of the protein library and there has been rapid advances now that we have the SELDI – TOF and MALDI – TOF technologies.

Aberration in the epigenetic mechanisms like methylation, histone acetylation and other chromatin remodelling mechanisms can explain the wide spectrum of symptomatology[9].

Abnormal DNA methylation in endometriosis affects homeobox A10 [HOXA 10]. Oestrogen receptor beta [ESR 2], steroid-genic factor 1[NRSA1] and aromatase [CYP 19 A1] which alters steroid signalling and *cause progesterone resistance and hence tissues are resistant to apoptosis*.

The epigenetic mechanisms can explain the remissions, relapses, the variable age of onset and full recovery observed in some mild endometriosis. Aberration in *progesterone receptor- B and DNA methyl-transferases* are also observed

The role of molecular networks

Dioxin [2, 3, 7, 8 – tetra-chloro-dibenzo – p – dioxin; TCDD) and *dioxin – like compounds* (DLCs) (e.g. Polychlorinated biphenyls [PCBs]) has been implicated in the development of endometriosis. DNA variants, environmental and lifestyle factors may act on intermediate, molecular phenotypes and that in turn, induce changes in the higher order disease phenotypes.

Today, there are emergent properties of *molecular networks* that are modulated by *complex genetic loci* and the combined effects of many discretely segregating loci with each contributing a miniscule portion of individual effect.

Identification of each individual locus would be impossible as they are also modulated by *environmental and / or lifestyle factors*[10.]

Thus, to conclude, alterations in the genomic, epigenetic, transcriptional, proteomic and / or signalling networks. Thus all, in a way, increase the susceptibility to endometriosis.

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Chapter 2

Imaging in Endometriosis

Dr.Padmashri.G, MBBS, PG DIP IN USG

Sonologist,

Rao Hospital,

Coimbatore.

Dr. Asha R. Rao MBBS, MD,

Consultant ObGyn and Infertility Specialist,

Rao Hospital,

Coimbatore

Endometriosis is defined by the presence of endometrial tissue occurring outside the endometrial cavity. Endometriosis affects 5-45% of women in reproductive age. Correct diagnosis is essential in defining the best treatment strategy. Ultrasound is the most commonly used diagnostic modality as it is easily available, cost effective with high accuracy. MRI is used as an adjunct.

Transvaginal sonography is the method of choice. High resolution (6-12MHz or 5-9MHz) TVS probe is used. Using Harmonic imaging (HI), Speckle reduction imaging 9SRI0 and cross beam focussing resolution imaging (CRI) improves the quality of grayscale imaging to enable visualization of early ovarian or extraovarian endometriosis. AS and Transrectal ultrasound (TRUS) are used in selected cases.

Types of endometriosis

Superficial Endometriosis

Ovarian Endometrioma

Deep infiltrating Endometriosis

Superficial endometriosis

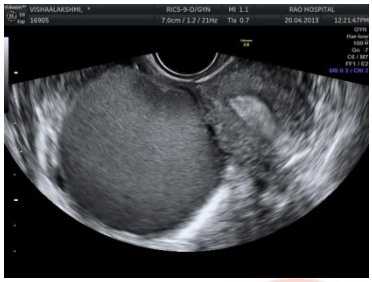
TVS has no role to play in diagnosing superficial endometriosis as the pelvic structures involved are very small. Even MRI cannot delineate the lesion if it is <5mm.

Ovarian endometrioma

TVS has dramatically improved the ability to diagnose ovarian lesions providing reliable criteria and indications for surgery.

Typically, endometrioma presents as thick-walled cyst with ground glass echogenicity, one to four compartments with no papillary structure in premenopausal

women[1].Single best discriminator between endometrioma and other cysts is ground glass echogenicity of cyst fluid. It has a sensitivity 0f 73% and specificity 0f 94% (Fig 1)

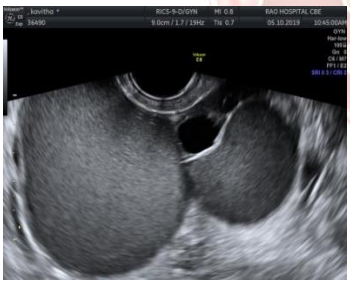


Endometrioma (Fig 1)

Hyper-echoic foci on the cyst wall if seen are indicative of endometrioma These are nothing but cholesterol deposits which are known as Echogenic flecks.

Atypically, endometriomas can show solid areas**.** This is due to the presence of a retracted blood clot seen adjacent to the cyst wall which has a more regular surface without detectable blood flow. Unusually endometrioma can show calcification also.

Kissing' ovaries sign: 1/3 to 1/2 of endometriomas are bilateral. They are commonly associated with adhesions of uterus and ovaries close to each other in POD. Posteriorly placed ovaries adherent to uterus gives the typical Kissing ovaries sign (Fig 2).



Kissing ovaries sign (Fig2)

It suggests that there are severe pelvic adhesions. Bowel and Fallopian tube endometriosis are significantly more frequent in women with kissing ovaries *vs* those without kissing ovaries: 18.5% *vs* 2.5% and 92.6% *vs* 33%, respectively[2].

Post menopausally ovarian cystic or solid cystic mass with a ground glass appearance have a high risk of malignancy[3].Endometriomas have to be differentiated from non-endometriomas which show internal echogenicity e.g.

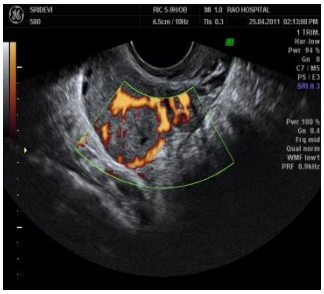
Corpus luteum

Haemorrhagic cyst

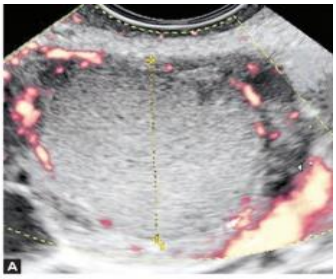
Dermoid cyst

Malignancy

Colour Doppler can help in the differential diagnosis between endometrioma, corpus luteum and malignant lesion. **Corpus luteum** typically shows rich peripheral vascularisation like a ring of fire (Fig 3) whereas Endometrioma will have scattered vascularity over the cyst wall (Fig 4)



Corpus luteum (Fig 3)

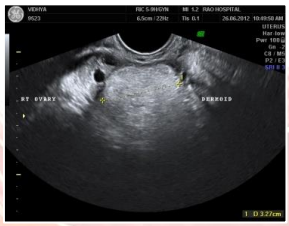


Scattered vascularity (Fig 4)

Haemorrhagic cyst will have organized blood clot of varying stages giving a cobweb appearance and Doppler shows scanty or high resistance flow. Corpus luteum and

haemorrhagic cysts resolve spontaneously in 4-6 weeks. Persistence, points towards diagnosis of endometrioma.

Dermoid cyst may demonstrate a hyperechoic centre while the surrounding demonstrates low level echoes and acoustic shadowing. Dermoid cyst is usually seen n asymptomatic women. (Fig 5)



Dermoid cyst (Fig 5)

Endometriosis and tubal pathology

It is important to assess tubal status in endometriosis. Pelvic endometriosis can involve fallopian tubes resulting in adhesions altering the normal tubal course or occluding the tube. TVS can show dilated fallopian tube with thick walls and incomplete septa seen as a cog wheel (Cog wheel sign). Presence of hydrosalpinx is an indication for surgical removal in infertile women

Decidualisation

Endometriomas may undergo decidualization during pregnancy, in which case they can be confused with an ovarian malignancy on ultrasound examination. Simultaneous presence of other endometriotic lesions may facilitate a correct diagnosis of endometrioma in pregnancy and minimize the risk of unnecessary surgery.

Endometrioma and malignancy

Endometrioma could serve as a precursor of Endometroid Borderline ovarian tumours. Malignant transformation of endometrioma is rare. But can happen with advancing age. Incidence is 0.3-0.8%. Common cancer associated with ectopic endometrium is endometrioid adenocarcinoma. Other sub types such as clear cell carcinoma is rare.

IOTA group simple USG rules

(INTERNATIONAL OVARIAN TUMOUR ASSESSMENT)

Simple	**Malignant**
Unilocular cyst	Irregular multi locular cyst
Presence of solid components, where largest solid component<7mm	Ascites
Presence of Acoustic shadowing	At least 4 papillary structures
Smooth multilocular tumour with largest diameter < 100mm	Irregular multilocular solid tumour with largest diameter >/-100mm
No blood flow	Very high colour content on colour Doppler

Adhesions

Endometriosis is often associated with the presence of pelvic adhesions. Ultrasound diagnosis in the evaluation of pelvic adhesions in the presence of ovarian endometriosis is a diagnostic challenge. In women who are infertile or have chronic pelvic pain and in the absence of ovarian endometriomas, it is important to look for sonographic signs of adhesions.

Normally, the uterus and ovaries are mobile and do not adhere to the surrounding tissues by palpation with the probe, abdominal palpation with the hand, or both. Movement of these organs can be seen on ultrasound (**sliding sign).** The lack of free movement of the pelvic organs while pushing gently on the uterus and ovaries (Negative sliding sign) suggests adhesions or Endometriosis. Endometriomas are usually fixed posterior to uterus. [4]

Assessment of POD mobility:

It can be assessed using real time ultrasound imaging. Gentle pressure is placed against the cervix with the transvaginal probe to establish whether the anterior rectum glides freely across the posterior aspect of the cervix and posterior vaginal wall. Absence of sliding sign indicates POD obliteration. It is useful to identify women who are at increased risk of bowel endometriosis

Site-specific tenderness, reduced ovarian mobility and the presence of loculated peritoneal fluid in the pelvis, are called 'soft markers' for pelvic pathology, including superficial endometriosis[5].

Complications of endometriosis

Torsion of large endometriotic cyst is rare. It can be diagnosed when there are changes in the outline of lesion, differential internal echogenicity and decreased vascularity. Rupture of endometriotic cysts result in subcapsular haemorrhage within the ovary and collapse of the lesion. Endometriosis has also been reported to be associated with spontaneous hemoperitoneum in pregnancy. It is a serious complication with high rates of adverse outcome.

Bladder endometriosis

It may be suspected in patients with dysmenorrhoea and cyclical urinary symptoms- urgency, dysuria and haematuria. TVS with slightly filled bladder improves visualization. TVS reveals solid nodule bulging towards the lumen from the posterior bladder wall close to vesico uterine pouch. Often the diagnosis is not considered at all or mistaken for cystitis.

Deep infiltrating endometriosis (DIE)

It has been defined as the presence of endometrial glands and stroma infiltrating more than 5mm in the sub peritoneal tissue. The prevalence of DIE is estimated to be 1-2% Commonest locations are rectovaginal, vesicouterine, uterosacral ligaments, bladder and bowel. TVS gives a typical sonographic appearance of hypoechoic linear thickening or nodules/masses with or without regular contours. The use of extra gel in the vagina or within the probe cover may create an acoustic window and optimize the ultrasound image of retro-cervical deep endometriotic nodules[6].

Rectal Ultrasound (TRUS) can visualize uterosacral ligament thickness and rectal infiltration.

Conclusion

Real-time dynamic TVS is the primary diagnostic tool in the evaluation of pelvic endometriosis. Visualisation of typical sonographic features, site specific tenderness and the absence of organ sliding are important in detection of endometriosis and optimising diagnostic accuracy.

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Chapter 3

Adolescent Endometriosis

Prof. Dr. S. Sampathkumari,MD, DGO, FICOG, FC Diab, FIME,

Dy. Director & Prof – OG, IOG, MMC,

Chairperson, FOGSI Adolescent Health Committee 2016-19,

President -OG, Board of Studies, TN MGR Med University,

Member, Board of Studies – OG, Meenakshi Medical University,

ICOG Governing Council Member,

Chennai.

The term ‘adolescence’ is derived from Latin ‘adolescere’ meaning to grow, to mature and considered as transition from childhood to adulthood and progression from appearance of secondary sexual characteristics to sexual and reproductive marked feature.

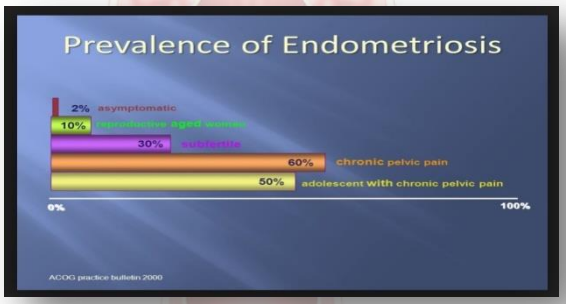
Adolescents are categorized as:

- Early adolescence (10 -13 yrs.): Spurt of growth of development of secondary sex,
- Middle adolescence (14-16 yrs.): Separate identity from parents, new relationship to peer groups, with opposite sex and desire for experimentation
- Late adolescence (17-19 yrs.): Distinct identity, well-formed opinion and ideas.

Menstrual disorders are common in adolescent girls. Periods can be regular or irregular, heavy with or without pain. It may be present for first few years due to immaturity of HPO Axis. Serious pathology is rare; menstrual dysfunction has a significant effect on daily activities and may result in school absence.

Pelvic pain and dysmenorrhoea may be due to a genital tract anomaly and some pathology. Endometriosis though disease in adult women, it is increasingly recognized in adolescent girls [(1)] Studies have found it affects up to 70% of girls with chronic pelvic pain refractory to standard treatment. [(2)] Endometriosis is not always identified on ultrasound and if pain continues despite standard treatments, diagnostic laparoscopy should be performed.

Endometriosis in adolescent is unrecognized, ignored and mislabelled in the adolescent population. This frequently results in chronic pelvic pain, adhesive disease, and infertility. Atypical presentation is more common. Early diagnosis and treatment during adolescence may decrease the disease progression and prevent subsequent infertility.



Incidence

Endometriosis is a common benign and chronic gynaecologic disorder related to the presence of endometrial glands and stroma outside of their normal location. [(3)] The most common cause of secondary dysmenorrhea in adolescence is endometriosis. [(4)] In general

population prevalence is about 0.7 and 44%. In adolescents it is difficult to quantify the incidence among adolescents, [5] but by available studies it is of 47%. [6]

Symptoms

Symptoms of endometriosis in adolescent are acyclical chronic pelvic pain-dysmenorrhoea, Bowel and bladder symptoms. [7]

Acyclic/cyclic pain - 63% Acyclic pain only - 28% Cyclic pain only - 9%

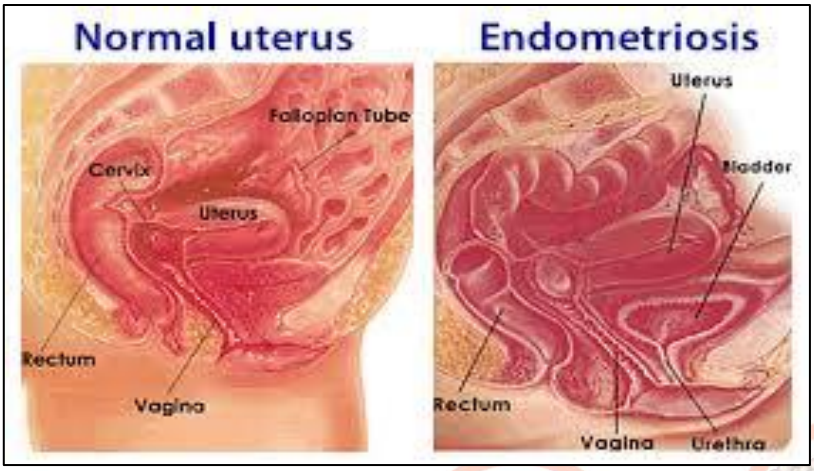
Gastrointestinal pain - 34% Urinary symptoms - 13% Irregular menses - 9%

Vaginal discharge - 6%

Primary (spasmodic) dysmenorrhea refers to recurrent, crampy lower abdominal pain that occurs during menstruation in the absence of pelvic pathology. Colicky lower abdominal pain radiates to supra pubic or inner thigh accompanied by nausea, vomiting, headache, diarrhoea and fatigue.

Secondary (congestive) dysmenorrhea: painful menstruation in the presence of pelvic pathology - dull aching lower abdominal pain due to pelvic congestion - Fibroid, endometriosis

Initial evaluation includes a thorough history, a pain diary documenting severity of pain, relation to bowel and bladder, missing school and social activities, indicates a need for intervention



Stages of Endometriosis

Stage 1: Minimal: - Isolate implants; no significant adhesions

Stage 2: Mild: - Superficial implants less than 5cms in aggregate scattered on the peritoneum and ovaries. No significant adhesions are present

Stage 3: Moderate: - Multiple implants, both superficial and invasive. Peri tubal, peri ovarian adhesions may be evident

Stage 4: Severe: - Multiple, superficial and deep implants, including large ovarian endometriomas, Flimsy & dense adhesions are usually present

Types of endometriosis in adolescent

- Peritoneal endometriosis
- Ovarian endometrioma
- Deeply infiltrating endometriosis
- Severe endometriosis is seen in 32% of adolescent girls.

Risk factors for adolescent endometriosis

Early age of menarche <12 years *(Nnoaham et al,)* polymenorrhoea, menorrhagia, girls with low BMI ,family history of endometriosis(6.9 times higher),severe dysmenorrhoea where OCP is used as analgesic and not as contraceptive, school absenteeism more than 18 days in a year due to use as analgesic and not as contraceptive, school absenteeism more than 18 days in a year due to dysmenorrhoea, pain interfering with daily activities, dyschezia and deep dyspareunia in sexually active girls are considered to be risk factors. These girls have to be watched for development of deeply infiltrating lesions at a later stage. Presence of neonatal uterine bleeding may represent a warning sign of the future development of endometriosis and increase the awareness of devastating disease in the young woman,

Diagnosis

Diagnosing endometriosis in adolescents should include detailed history-taking, an age-appropriate physical examination, and diagnostic imaging.

A health risk screening tool such as the HEADSS assessment [(8)] may assist the health care provider. HEADSS is a framework for history-taking that begins with topics the adolescent may have more comfort discussing and concludes with more sensitive questions: Home or housing, Education and employment, Activities, Drugs, Sexual activity and sexuality, and Suicide and depression.

Physical examination is important. Abdominal examination may not reveal anything significant. Most of the adolescent girls will co-operate for rectal examination. 5 – 11% of the adolescent endometriotic patients will have associated Mullerian anomalies. Q-tip test has to be done to rule out transverse vaginal septum. Adnexal pathologies should also be ruled out by rectal examination. In sexually active adolescent girls bimanual pelvic examination is

feasible. 32 % of the adolescent girls will have utero sacral nodularity, endometrioma and deeply infiltrating endometriosis. Rectal exam can be performed when needed for adolescents who are not sexually active.

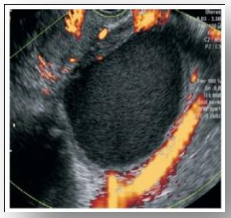
1. Ultrasound diagnosis of endometriosis are:

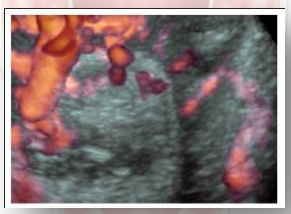
Unilateral / bilateral, Kissing ovaries, Unilocular / Multilocular, Thin/ Thick septae, Mobility restricted, Elicitation of site specific tenderness, Mural echogenic foci, Low level internal echoes and posterior acoustic enhancement called ground glass appearance , Effect of surrounding tissue, Nodular wall thickening.

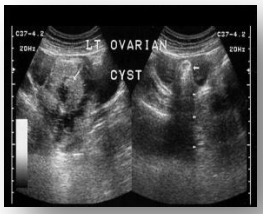
2. Doubtful cases - MRI done

3. 3D/4D /Colour doppler

It can differentiate adnexal pathology like acute haemorrhagic cyst or dermoid or neoplasm. Blood flow in endometrioma is usually peri cystic with resistive index above 0.45.

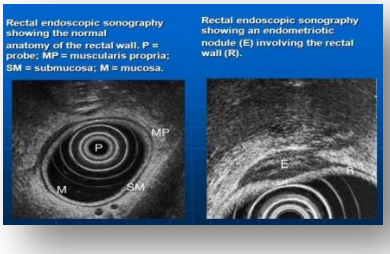




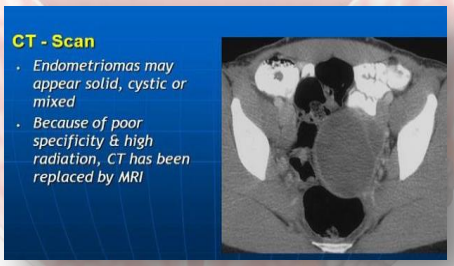


4. Sono-vaginography or saline infusion sonography by trans rectal USG

DIE lesions can be picked up with saline filled vagina. Recto vaginal septum and uterosacral nodularity and posterior bladder infiltration are better picked up than MRI. With a sensitivity of 97% and specificity of 96%.

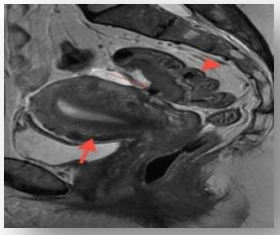


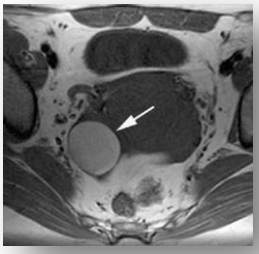
5. CT scan has limited role in diagnosis of endometriosis. CT scan can demonstrate recto vaginal endometriosis (Colon should be distended and vagina packed) → (Virtual Colonoscopy)



6. MRI

MRI is useful for adolescent girls who are not sexually active in diagnosing endometriosis. It cannot pick up peritoneal endometriosis. MRI is a must for deeply infiltrating endometriosis before surgery is planned by the team of urologist, gastroenterologist and laparoscopic gynaecological surgeon. T1 and T2 weighted images along with fat suppression for T1 image is taken along with gadolinium contrast. For diagnosing endometrioma ideal is USG. Only for doubtful cases MRI done. MRI can differentiate cystic teratoma from endometriomas. MRI has 90% sensitivity 98% specificity. (*Chapron.Borghese et al)*





7. Biomarkers

Biomarkers for endometriosis are Interleukin (IL)-6, IL-8 .Tumour necrosis factor-alpha, High-sensitivity C-reactive protein (hsCRP), Cancer antigens CA-125 and CA-19-9, Neutrophil / Lymphocyte ratio, ICAM – 1

Newer biomarkers are

UCN belonging to the family of corticotrophin-releasing factor (CRF), which is involved in the modulation of the immune system and inflammation, physiologically expressed in endometrium during the menstrual cycle, mainly in the secretory phase. Higher concentrations of UCN were found in 88% of cases of endometrioma with a specificity of 90%, while that of Ca-125 increased only in 62% of cases. The measurement of the UCN is a promising marker for early detection of differential endometrioma compared to benign ovarian cysts. [(9)]

Follistin

An active A binding protein that inhibits its function, but is usually expressed in the normal endometrium. Follistin shows a sensitivity of 92% and a specificity of 96% with a cut off of 1433 pg/mL, while Ca-125 shows only 44% of endometriomas with a specificity of 90% [(10)]

Goals of therapy for management of adolescent endometriosis

Adolescent girls should be pain free and there should be no progression of the lesion and preservation of fertility. Management strategies are primary medical, surgical, proper post – operative medical management and follow up. Patients with adolescent endometriosis should be followed life-long.

Management

Endometriosis is a chronic disease that has been shown to be progressive. Adolescent patients with endometriosis confirmed by laparoscopy should receive medical treatment of their disease. The goal of medical therapy is to treat pain from postoperative residual disease and suppress progression.

Endometriosis is the leading cause of secondary dysmenorrhea in adolescents. Endometriosis should be considered in patients with persistent, clinically significant dysmenorrhea despite treatment with hormonal agents and non-steroidal anti-inflammatory drugs, particularly if no other aetiology for chronic pelvic pain or secondary dysmenorrhea has been identified based on history, physical examination, and pelvic ultrasonography

In adolescents, endometriotic lesions are typically clear or red. The goals of therapy include symptom relief, suppression of disease progression, and protection of future fertility.

Medical management

1. Mefenamic acid/ ibuprofen/ naproxen

NSAIDs interrupt cyclo oxygenase-mediated prostaglandin production. NSAIDS are first-line treatment option. Studies prove that NSAIDs are significantly better than placebo in

providing pain relief from primary dysmenorrhea, though safety or efficacy has not been demonstrated. [11]

Least effective dose is administered either before the onset or before the peak of pain

Table 1. Nonsteroidal Antiinflammatory Drugs Used During Menstruation in the Treatment of Primary Dysmenorrhea in Adolescents and Young Adults

Drug	Dosage
Ibuprofen	800 mg initially, followed by 400–800 mg every 8 hours as needed
Naproxen sodium	440–550 mg initially, followed by 220–550 mg every 12 hours as needed
Mefenamic acid	500 mg initially, followed by 250 mg every 6 hours as needed
Celecoxib*†	400 mg initially, followed by 200 mg every 12 hours as needed

*For females older than 18 years
†Cyclooxygenase-2 specific inhibitor
Reprinted from Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. Expert Opin Pharmacother 2012;13:2157–70.

2. Hormonal agents

If pain not reduced with NSAIDS Hormones are tried. Hormones used are combined oral contraceptives, the contraceptive patch or vaginal ring, the single-rod contraceptive progestin implant, intramuscular or subcutaneous depot medroxy progesterone acetate, and LNG-IUS [12]. The mechanism of action for hormonal methods is likely related to prevention of endometrial proliferation or ovulation, or both, thus decreasing prostaglandin and leukotriene production.

A) Combinations hormonal contraceptive patch, or vaginal ring for menstrual suppression (monophasic or multiphasic)

Norgestimate/ethinyl estradiol 0.25 mg/0.035 mg

Norethindrone/ethinyl estradiol 1 mg/0.035 mg

Instead of cyclical contraceptive drugs continuous is prescribed.

B) Progestins Progesterone act by Anti-endometriotic effect causing initial decidualization of endometrial tissue followed by atrophy

E.g.: Medroxy Progesterone Acetate Starting at a dose of 30mg/day

Continuous norethisterone acetate 5 mg (norethindrone) has been shown to be equally effective as a cyclic combined hormonal contraceptive, and data indicate it also decreases dysmenorrhea in women aged 18–23 years [13]

Dose can be individualized for each patient.

Side effects of progestins are nausea, weight gain, fluid retention, breakthrough bleeding due to hypoestrogenism

Progesterone can be given in injection forms also. Eg: DMPA 150mg once in 3 months.

Progesterone receptor modulators use in adolescent endometriosis needs further studies.

Newer progesterone

Dienogest is a newer progesterone which has selective 19-nor and progesterone activity. Dose of 2 mg/day is sufficient and as effective as GnRH analogues. It has anti-proliferative, anti-angiogenic and anti-inflammatory action. It has minimal side effects, good safety profile and tolerability when compare to GnRH. Dienogest can be used for 24 weeks and it gives pain relief up to 11/2 years. (*Srowizki T et al, Hum Reprod 2010)*

Dienogest is a progestin indicated as monotherapy at an oral dose of 2 mg once daily for patients with endometriosis up to 9 months[14].

VISADO study concludes that the treatment of endometriosis in adolescents with 2 mg dienogest once daily for 52 weeks and it has been extended up to 5 years. It was associated with slight decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation

C) Danazol due to androgenic effect not used nowadays.

D) Gonadotropin-releasing hormone agonists are not recommended for empirical use in patients with suspected primary dysmenorrhea because of concerns about their effect on bone mineral density. It causes hypoestrogenic state by down-regulating pituitary receptors. It leads to loss of & down regulation of GnRH activity, resulting in low FSH & LH level → pseudo menopause. The use of GnRH agonist is limited to 6 months because of resultant profound hypoestrogenic state & subsequent effect on bone mineralization. It can be used for girls beyond 16 years.

Side effects: hot flashes, vaginal dryness, ↓libido, osteoporosis, can be corrected with add-back regimen

Add-back therapy

Norethindrone acetate (5mg per day) or conjugated oestrogens/ medroxyprogesterone acetate (0.625/2.5mg per day) to reduce bone loss related to a hypo estrogenic state.

To preserve bone density calcium & vitamin D3 should be taken

Newer drug therapies

Aromatase inhibitors like letrozole and anastrozole can be used along with progestins. Anti-angiogenic drugs like cabergoline can be used in pain relief in early endometriosis.

GnRh antagonist, progesterone antagonist, SPRM, SERM, statins, TNF alpha inhibitors, interferons and ER beta ligands are some of the newer drugs in the pipeline. (*Laufer et al)*

SOGC clinical practice guidelines

Medical Management of Pain associated with Endometriosis

Recommendations

Combined hormonal contraceptives, ideally administered continuously, should be considered as first-line agents. (I-A)

Administration of progestin alone—orally, intra muscularly, or subcutaneously — may also be considered as first line therapy. (I-A)

A GnRH agonist with HT add back or the LNG-IUS, should be considered a second-line therapeutic option. (I-A)

A GnRH agonist should be combined with HT add back therapy from commencement of therapy and may be considered for longer-term use (> 6 months). (I-A)

While awaiting resolution of symptoms from the directed medical or surgical treatments for endometriosis, practitioners should use clinical judgement in prescribing analgesics ranging from NSAIDs to Opioids. (III-A)

Surgical management

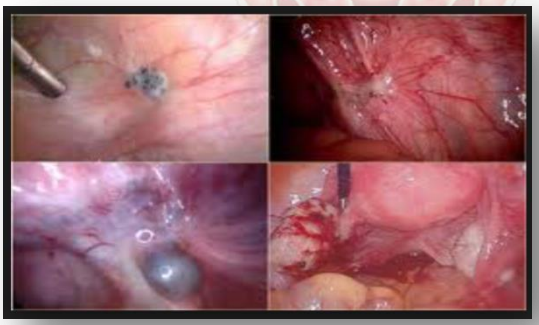
Diagnostic and therapeutic laparoscopy is indicated if trial of NSAIDs and OCP fails

Inspection and palpation with a blunt probe of the bowel, bladder, uterus, tubes, ovaries, cul-de-sac, and broad ligament may show atypical lesions of endometriosis in adolescents: Red,

clear blebs peritoneal defects called as Allen Masters windows or white as opposed to the powder-burn lesion seen commonly in adults. Excise all lesions and restore anatomy. Histologic confirmation may be possible.

Indications for laparoscopy

- Chronic pelvic pain and dysmenorrhea not responding to NSAIDS and OCPs. Diagnostic laparoscopy is indicated. If there is evidence of early endometriosis it has to be treated. This will reduce the pain and disease progression.
- USG and MRI evidence of endometriosis (Endometrioma and DIE) in symptomatic patients. Therapeutic laparoscopy is indicated.
- Endometriosis associated with Mullerian anomalies
- Emergency situations like ruptured endometrioma
- Recurrent endometrioma with severe pain, size greater than 4 cm not responding to medical management and suspicious of malignancy.



Pre-operative evaluation

AMH level should be done to assess the ovarian reserve and choose the type of surgery. CA 125 level should also be done because it is highly sensitive for follow up.

Detailed imaging studies are a must, especially in cases of DIE where the help of Urologist and Gastro- Enterologist are needed during surgery.

Microscopic residual disease needs medical management.

Pre sacral neurectomy, Ablation therapy, Hysterectomy not advised in adolescents.

Alternative therapies

A) Lifestyle modification is important, both Diet and Exercise.

Health benefits of exercise should be counseled. More than 2 hrs./week had lower risk of endometriosis as it lowers estrogen level

Dietary supplements for which there may be limited evidence to suggest a potential benefit include fenugreek, ginger, valerian, zataria, zinc sulphate, fish oil, and vitamin B_1[15]. Vit D also useful

B) Transcutaneous electrical nerve stimulation, acupuncture, herbal preparations, and yoga can be tried[16]

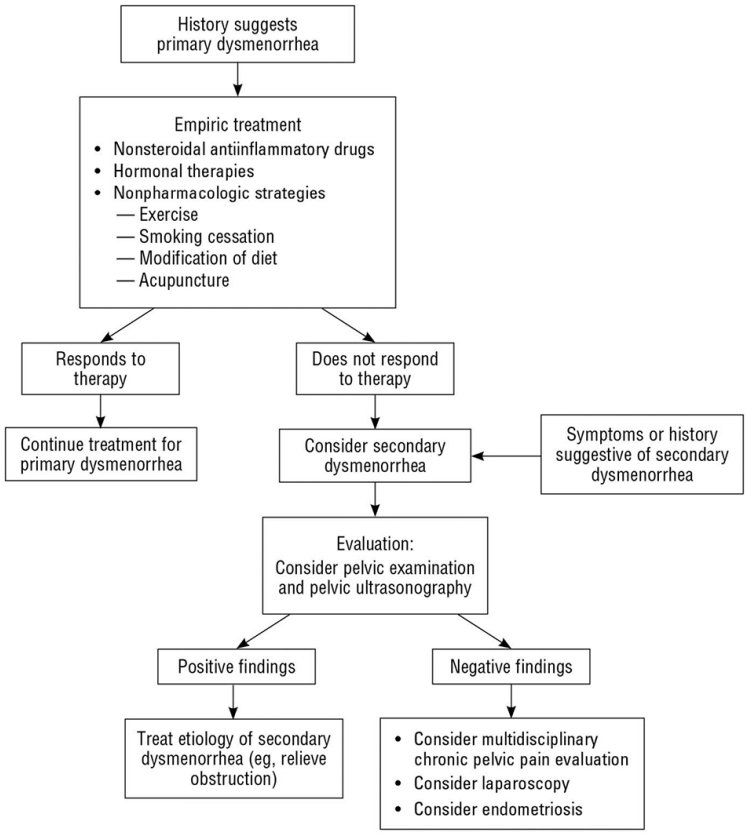


Figure 1. Approach to the adolescent with dysmenorrhea.

Mullerian anomalies & endometriosis

Most studies quote the rate of 5-6% up to 40%, Incidence of anomalies of the reproductive system.72% of the girls with Mullerian anomalies with outflow obstruction have endometriosis.

Clinical outcome in patients with outflow tract obstructions differ from those without such obstructions, because regression of disease usually has been observed once surgical correction of the anomaly has been accomplished

Emergency situations like ruptured endometrioma

Ruptured endometrioma has to be thought when there is severe pain in adolescent girls known to have endometrioma or rupture may be the first manifestation of endometriosis. Emergency laparoscopy is needed. Adhesiolysis and cystectomy should be done.

Role of surgery in recurrent endometriosis

1/3rd of the girls have recurrent endometriosis. They should be handled only by medical management. The exceptions are severe pain not responding to medical management very large endometriomas and suspicious of malignancy which is very rare in adolescents.

Conclusion

Therapy must be individualized; Gynaecologists should consider patient choice, the need for contraception, contraindications to hormone use, and potential adverse effects and counsel the adolescent and her family on treatment options. Coping with endometriosis which is a chronic disease is an important component of management. A multidisciplinary approach is always helpful to improve the quality of their lives

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Chapter 4

Medical Management of Endometriosis

Dr. Kalpana Balamurugan

MD (OG)., FNB (Reproductive Medicine)., FICOG., FICS.,

Consultant in ObGyn and Infertility

Guru Hospital, Madurai

Endometriosis is a chronic gynaecologic disorder that commonly manifests as chronic pain and infertility. It affects 6 to 10 percent of women of reproductive age, and it is present in approximately 38 percent of women with infertility and in up to 87 percent of women with chronic pelvic pain. It is thought to develop from attachment and implantation of endometrial glands and stroma on the peritoneum as a result of retrograde menstruation. Endometrial lesions result from overproduction of prostaglandins and oestrogen, which leads to chronic inflammation.

The mechanism by which infertility occurs in women with early-stage endometriosis is not clear. Oxidative stress and higher concentration of inflammatory cytokines may affect sperm function in several ways, including causing sperm DNA damage. The abnormal peritoneal environment can also cause abnormalities in oocyte cytoskeleton function. In more

advanced endometriosis with ovarian cysts and adhesions, the anatomic abnormalities can impair tubal function.

Medical Management of Endometriosis with Pain

Non-steroidal anti-inflammatory drugs (NSAIDs)

A presumptive diagnosis of endometriosis can often be made on history if the patient has classical symptoms such as pain with periods that is not completely relieved by nonsteroidal anti-inflammatory drugs, pain that begins a day or two before the onset of menses, and acquired or progressive dyspareunia or dyschezia. Medical management to suppress endometriosis and improve quality of life should be started once a presumptive diagnosis is made. Once the diagnosis, either presumptive or definitive, is made, long-term therapy is required as all present medical treatments of endometriosis are suppressive, not curative

Oral contraceptive pills

Oral contraceptive pills have been used empirically to alleviate dysmenorrhoea for many years. ESHRE recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestogens. Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhoea. [(2)] Oral contraceptives produce initial decidualization of endometrial tissue followed later by atrophy. After conservative surgery for endometriosis, the administration of the oral contraceptive pill reduces both the risk of recurrent dysmenorrhoea and the risk of recurrence of ovarian endometrioma.[(1)] Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (oestrogen/progestin) patch to reduce endometriosis

associated dysmenorrhea, dyspareunia and chronic pelvic pain.[3] However, oral contraceptive pills generally do not eliminate non-menstrual pelvic pain or other symptoms of endometriosis such as deep dyspareunia. It is believed that oral contraceptive pills should no longer be used as first line treatment for endometriosis pain and should be replaced by oral progestin-only therapy (ESHRE guidelines). [4]

Progestogens and anti-progestogens

Progestogens [medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, norethisterone acetate or danazol] or anti-progestogens (gestrinone) as one of the options, to reduce endometriosis-associated pain is recommended [6]

The rationale for using progestins in the treatment of endometriosis consists of the fact that these agents have anti-gonadotropic properties and enhance the negative feedback of oestrogen at the hypothalamus determining anovulation and hypogonadotropic hypoestrogenic state. Suppression of ovulation is probably the most important mechanism by which progestins reduce pain in endometriosis [5]. It was originally thought that progestins determine secretory changes in endometriotic lesions followed by decidual transformation and atrophy.

In addition, progestins induce a suppression of matrix metalloproteinases, which are involved in the implantation of the eutopic endometrium.

Break- through bleeding or spotting was noted in 80% of women treated with DMPA

Levonorgestrel-releasing intrauterine system can also be used to reduce endometriosis associated pain. [7] LNG-IUD decreases the severity of dysmenorrhoea, deep dyspareunia and chronic pelvic pain. In addition, it determines a significant decrease in the rectovaginal

endometriotic nodules. The LNG-IUD is also effective in preventing recurrence after conservative surgery for endometriosis,

Danazol

The side effects of danazol have limited its use in the treatment of endometriosis.

Gonadotropin-releasing hormone analogues

Gonadotropin-releasing hormone analogues rapidly induce a hypo-oestrogenic state similar to that of menopause, producing progressive endometrial atrophy and amenorrhea. These drugs can also act through other mechanisms, such as downregulating the expression of inflammatory molecules in the peritoneal cavity. GnRH agonists (nafarelin, leuprolide, buserelin, goserelin or triptorelin), as one of the options for reducing endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.[8] One of the major limitations of the long-term administration of GnRH analogues to premenopausal women with endometriosis consists of several adverse effects due to hypo-oestrogenism.

Add-back therapy reduces the side effects induced by the hypo-oestrogenism without impairing the effectiveness of treatment. Clinicians should be careful when using GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density.

Aromatase inhibitors

In women with pain from rectovaginal endometriosis refractory to other medical or surgical treatment, clinicians can consider prescribing aromatase inhibitors in combination with oral contraceptive pills or progestogens, as they reduce endometriosis associated pain [9] Aromatase inhibitors block oestrogen production by inhibiting the enzyme catalysing the

main step of its synthesis. The adverse effects typically caused by aromatase inhibitors are arthralgia and myalgia, less frequently, these agents may cause headache and gastro-intestinal complaints. They can also cause hypo-oestrogenism and hence, hot flushes, reduction in BMD which requires the addition of OCP and progesterone.

Medical treatment	**Mechanism of action**	**Adverse effects** [13]
Combined oral contraceptives	Inhibit ovulation, decidualise endometriotic tissue	Mood changes, nausea, headaches, hypertension, deep venous thrombosis (rare)
Oral progestogens	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Levonorgestrel intrauterine system	Decidualisation and atrophy of lesion tissue	Irregular bleeding, mood changes, breast tenderness
Etonogestrel implants	Inhibit ovulation, decidualise lesion tissue	Irregular bleeding, mood changes, weight gain, acne
Gonadotrophin releasing hormone agonists	Down-regulate the pituitary-ovary axis and produce a hypo-oestrogenic state, with lesion atrophy	Hot flushes, change in libido, vaginal dryness, headaches, emotional lability, acne, myalgia, decreased breast size
Aromatase inhibitors	Inhibit oestrogen synthesis with lesion atrophy	Hot flushes, arthralgia, myalgia, osteoporosis
Androgens (danazol)	Complex effects on the hypothalamic-pituitary-ovarian axis and uterus,	Acne, hirsutism, voice changes,

	including mild, impeded androgenic action, resulting in lesion atrophy	emotional lability

Pre- operative hormonal therapies for treatment of endometriosis associated pelvic pain

Clinicians should not prescribe preoperative hormonal treatment to improve the outcome of surgery for pain in women with endometriosis. [10]

Postoperative hormonal therapies for treatment of endometriosis associated pelvic pain

ESHRE recommends that clinicians clearly distinguish adjunctive short-term (< 6 months) hormonal treatment after surgery from long term (> 6 months) hormonal treatment; the latter is aimed at secondary prevention.

In women operated for endometriosis, clinicians are recommended to prescribe postoperative use of a levonorgestrel-releasing intrauterine system (LNG-IUS) or a combined hormonal contraceptive for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia.[11]

Hormonal therapies for treatment of endometriosis-associated infertility

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility. [12]

Hormonal therapies adjunct to surgery for treatment of endometriosis associated infertility

In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking.

Some of the treatments presently in development are improvements on current therapy including oral GnRH antagonists (Elagolix) and selective oestrogen or progesterone receptor modulators. However, especially in light of the fertility issues related to endometriosis, future therapies are directed for pain management without suppressing ovulation, or better still result in a cure rather than just temporary suppression of endometriosis. In this regard, immunomodulators and antiangiogenic agents are of interest. Obstacles to this research still involve lack of understanding of the pathogenesis and natural history of the disease.

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Chapter 5

Management of Endometrioma

Dr. K. Subash Mallya

MBBS, D.G.O, D.N.B, MNAMS , Diploma In Gynec Endoscopy(Germany) PGDMLS,

Senior Consultant Gynaecologist,

Infertility Specialist and Laparoscopic Surgeon,

Baby Memorial Hospital, PVS Hospital, Calicut.

Dr. Athira S, MBBS, D.G.O,

Junior Consultant Gynaecologist,

PVS Hospital, Calicut.

Dr. Rajeesh, MBBS, D.G.O, D.N.B

Junior Consultant Gynaecologist,

PVS Hospital, Calicut.

Endometriosis is a common benign gynaecological disease defined by the presence of endometrial glands outside the uterine cavity. It is frequently diagnosed in the third decade of life, affecting 10–12% women of reproductive age. The gold standard for diagnosis of endometriosis is visual inspection by laparoscopy. Endometriosis is highly prevalent and has been estimated that more than 176 million women worldwide suffer from endometriosis and its associated symptoms including infertility, cyclical and non-cyclical abdominal pain, dysmenorrhea, dyspareunia, dysuria and dyschezia. It is generally accepted that no correlation exists between the severity of such pain symptoms and the extent of the disease.

Endometriosis may be categorized into three entities: peritoneal endometriosis, ovarian endometriotic cysts (endometrioma) and deep endometriosis (DE) (previously known as deep infiltrating endometriosis or DIE). Endometriomas are probably the most commonly diagnosed form of endometriosis because of the relative ease and accuracy of ultrasound diagnosis. Although their exact prevalence and incidence are not known, they have been reported in 17–44% of women with endometriosis. The presence of ovarian endometriomas has been reported as a marker for deep endometriosis and multifocal deep vaginal, intestinal and ureteric lesions.

Guidelines

Infertile with stage I/II endometriosis:

- Operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Evidence 1a)

- Consider CO_2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since it is associated with higher cumulative spontaneous pregnancy rates. Aim is to vaporise the endometriotic cyst lining until hemosiderin pigment-stained tissue is no longer visible (until the colour changes from reddish to yellow-white). The entire depth of the cyst capsule does not need vaporisation, as endometriotic tissue is present only superficially. Use intermittent irrigation to maintain good visibility and to remove carbon debris. Ensure the border of the cyst opening is completely vaporised.

Ablation of endometriosis implants may involve either electrocoagulation of the lesion with bipolar energy or laser vaporization or coagulation, which destroys or devitalizes active endometriosis but does not actually remove the lesion. Ablation destroys the lesion without getting a specimen for histologic diagnosis. Resection of endometriosis implants involves complete removal of the lesion from its epithelial surface to the depth of its base.

Resection can be performed with scissors, laser, or monopolar electrosurgery. Resection removes the lesion in its entirety, yielding a histologic diagnosis and allowing you to determine whether, indeed, the entire specimen has been removed.

The question of what is more effective— ablating or resecting endometriosis implants?— was addressed in a prospective study in which 141 patients with endometriosis related pain were randomized at laparoscopic surgery to either excision or ablation/coagulation of endometriosis lesions six months postoperatively, the pain score decreased by, on average, 11.2 points in the excision group and 8.7 points in the coagulation/ablative group.

Technique: How Do We Resect Endometrioma?

It is important to grasp the thinnest part of the cyst wall and progressively strip it, to avoid removing excess ovarian tissue and to reduce the risk of compromising ovarian reserve. After draining the endometrioma of its chocolate-coloured fluid, we irrigate and drain the

cyst several times with warm lactated ringers' solution to promote separation of the cyst wall from underlying stroma and to better identify the dissection plane. The cyst wall is inspected by introducing the laparoscope into the cyst to examine its surface, which is often laden with implants of deep and superficial endometriosis.

If we cannot easily identify the plane of dissection along the edges, we may evert the cyst and make an incision at its base to create a wedge between the wall of the cyst and underlying stroma. The edge of the incised wall is then grasped and retracted to create a space between the wall and the underlying stroma, from which it is progressively stripped from the ovary. To aid dissection and identification of the cyst wall, saline or diluted synthetic vasopressin solution (0.1–1 unit/ml) may be injected under the cyst capsule. The diluted synthetic vasopressin injection has the additional advantage of reduced bleeding during cyst removal. Synthetic vasopressin is not available in all countries and, although rare, it may cause intraoperative cardiovascular complications including bradycardia and hypertension

Traction and counter-traction are the hallmarks of dissection here; sometimes, we use laparoscopic scissors to sharply resect the ovarian stromal attachments that adhere cohesively to the cyst wall. This technique is continued until the entire cyst wall is removed. When follicle-containing ovarian tissue remains attached to the cyst wall, we introduce the closed tips of the atraumatic forceps between the cyst wall and adjacent follicle-containing stroma, spread the tips apart, and recover the true plane of dissection between the thin wall of the cyst and stroma. After the cyst wall is removed, the ovarian crater invariably bleeds because blood vessels supplying the wall have been separated and opened.

Utilizing warm lactated ringers' solution, we copiously irrigate the bleeding ovarian stroma to identify each bleeding vessel and by placing the tips of the micro-bipolar forceps

on either side of the bleeder, individually coagulate each vessel, thus inflicting minimal thermal damage to the surrounding stroma.

Avoid using bipolar forceps indiscriminately to coagulate the bloody stroma in the crater created after cystectomy, because doing so can result in excessive destruction of ovarian tissue or inadvertent coagulation of the hilar vessels that would interrupt the blood supply to the ovary, compromising its function.

Haemostasis

Some surgeons find that fenestration, drainage, and coagulation of the cyst wall is acceptable, but we have concerns not only about incomplete ablation of the endometriosis on the cyst wall, which may be responsible for the higher recurrence rate of disease, but also about the risk of thermal injury to underlying follicles, which may compromise ovarian reserve.

Suturing

Once complete haemostasis has been achieved, the decision to approximate (or not) the edges, preferably with fine absorbable suture, is based on how large the defect is and whether or not the edges of the crater spontaneously come together. For large defects, we usually close the ovary with a 3-0 or 4-0 vicryl continuous suture, imbricating the edges to expose as little suture material as possible to reduce the formation of postoperative adhesions, which is common after ovarian surgery. Last, we ensure that haemostasis is present. Often, we apply an anti-adhesion solution, such as snow or interceed. These agents have been shown to reduce postoperative adhesion formation, especially after laparoscopic surgery for endometriosis.

ESHRE Guidelines

Infertile woman with ovarian endometrioma undergoing surgery:

- Counselling women with endometrioma regarding risks of reduced ovarian function after surgery & the possible loss of the ovary.
- Proper skilful surgical work up during first endometriosis surgery is most important for higher cumulative spontaneous pregnancy rates.
- Decision of repeat ovarian surgery should be considered carefully in women with previous surgery for ovarian endometriosis.
- Endometrioma <3 cm: No evidence that cystectomy prior to treatment with ART improves pregnancy rates
- Endometrioma > 3cm: Recommended to consider cystectomy prior to ART to improve endometriosis associated pain or the accessibility of follicles
- Excision of endometrioma capsule, instead of drainage & electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart et al 2008).
- Coagulation or laser vaporization of endometriomas without excision of the pseudo-capsule is associated with a significantly increased risk of recurrence of the cyst.

Extraovarian Endometrioma

- There will be a false capsule.
- Separating ovary from adherent surface followed by drainage of collected blood rather than trying to find cyst wall is the most important step in the management.
- Complete exposure of deep infiltrating area of endometriotic lesion on ovary.
- Cauterization of exposed surface

- There is not much loss of ovarian tissue during this procedure.
- To prevent recurrence of adhesions: adequate cauterization with complete hemostasis or use Interceed to cover the ovary

Two- or Three-Step Approach for Large Endometriomas

For large endometriomas, a two- or three-step procedure can be considered.

- The first step involves opening and draining the endometrioma as described in the initial stage section.
- Inspect the cyst cavity and take a biopsy.
- Following this initial step, administer a GnRH agonist therapy for 3 months, during which time the thickness of the cyst wall significantly decreases, with atrophy and reduction in stromal vascularisation of the cyst
- Complete the surgery with a second laparoscopy in the form of either cystectomy, CO_2 vaporisation, bipolar diathermy or plasma ablation of the cyst wall lining.

Although women have to undergo two invasive procedures, the potential benefit is that this may facilitate the management of larger ovarian endometriomas, reduce recurrence rates and limit decrease in ovarian reserve.

Endometriosis Surgery and AMH Levels

- Serum AMH concentrations significantly decreased after the operation (1.4±0.2 ng/ml after 3 months and 1.3±0.3 ng/ml after 9 months versus 3.0±0.4 ng/ml before surgery; $p<0.0001$), whereas basal FSH, LH, estradiol and inhibin B concentrations remained unchanged

- The volume of the operated ovary significantly diminished after surgery ($p<0.0001$), whereas the AFC was not significantly altered
- The data shows that laparoscopic stripping of endometriomas reduces ovarian reserve. The significant decrease of AMH after surgery confirms that part of the healthy ovarian pericapsular tissue, containing primordial and preantral follicles, is removed or damaged despite all the surgical efforts to be atraumatic.

Surgery in Deep Endometriosis (DE)

In contrast to superficial endometriosis, which may respond similarly to ablation or resection, deep endometriosis is difficult to ablate either with electrosurgery or a laser because the energy cannot reach deeper layers and active disease is therefore likely to be left behind. Moreover, when endometriosis overlies vital structures, such as the ureter or bowel, ablation of the lesion may cause thermal damage to the underlying organ, and such damage may not manifest until several days later, when the patient experiences, say, urinary leakage in the peritoneum or symptoms of bowel perforation.

- Surgical therapy in DIE is to improve pain rather than fertility
- The effectiveness of surgical excision of Deep nodular lesion before ART in infertile women is not well established with regard to reproductive outcome

Surgical therapies as an adjunct to treatment with ART

The working group recommends documenting the following information:

- The location of DE lesions;
- Uterosacral ligaments, including whether ureters are infiltrated;
- Rectovaginal septum, including involvement of vaginal wall/mucosa;

- Bowel, including involvement of muscularis layer;
- Bladder, including involvement of muscularis and ureteral ostia;
- Other sites in the pelvis;
- Extra pelvic locations;
- Involvement of the ovaries;
- The size of the lesions;
- The number of lesions;
- The degree of involvement of adjacent organs and structures.

Imaging Modalities

- Transrectal ultrasonography (TRUS) may be used for rectosigmoid involvement but could not be adequately assessed for other anatomical sites because of scanty heterogeneous data.
- MRI is usually performed as an additional examination in complex cases or prior to surgery and is highly accurate in the evaluation of endometriosis.
- Diagnostic accuracies were higher for transvaginal ultrasonography (TVUS or TVS) with bowel preparation (TVUS-BP) and rectal water contrast (RWC-TVS) and for 3.0 T MRI than for conventional methods, although the paucity of studies precluded statistical evaluation (TVUS for DE is highly dependent on the experience of the operator and the quality of the US equipment).
- Multi-detector computed tomography enema (MDCT-e) is another technique which might have a high diagnostic performance for rectosigmoid and other bowel endometriosis

If rectal bleeding (haematochezia) is reported by the patient, colonoscopy is indicated for differential diagnosis of any primary bowel disease.

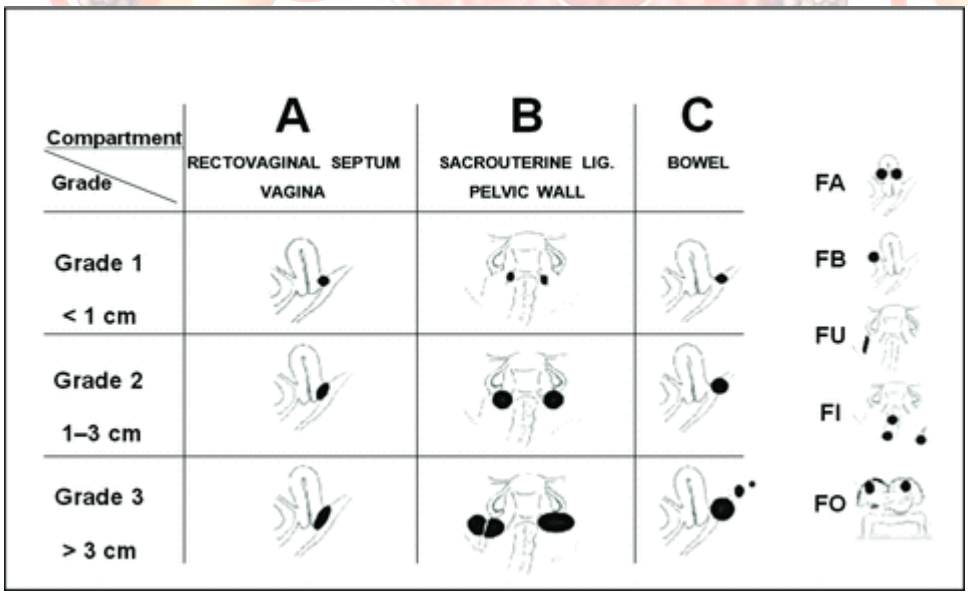
Bladder

TVS is sufficient to diagnose bladder endometriosis in the majority of cases. Typically, lesions are located at the dorsal wall or the fundus of the bladder. They can extend into the vesico-cervical space and the ventral wall of the uterus.

Pre- or intra-operative cystoscopy is recommended for bladder endometriosis as it allows visualization of the bluish, submucosally protruding nodules. It is important to localize the lesion precisely in relation to the ureterovesical junction (UVJ).

Revised Enzian Classification for DE

This classification helps to plan the surgery.



Strategy of the surgical intervention

Each surgeon needs a strategy for the operation, which is influenced by many factors including the size, activity and localization of endometriosis as well as the age and expectations of the patient, and the results of previous interventions.

Advanced endometriosis in a young patient with a desire to have children may be operated differently than in a patient over 40 years of age with pain as the main symptom.

The surgeon is often confronted with the conflict between complete removal of endometriosis and the need for preservation of organs affected by the disease.

Another challenge is tackling multi-organ involvement, which requires a complex intervention possibly in a multidisciplinary setting.

An important limitation is the risk of postoperative complications. For this reason, occasionally a limited radicality or surgery in several steps may be chosen, for example simultaneous segmental resection of intestinal endometriosis and ureteral re-implantation in hydronephrosis may be avoided

Open versus endoscopic surgery (or robotic assisted)

Endoscopic access has become standard for the treatment of endometriosis, including DE. It is obvious that the endoscopic procedures are advantageous due to better view and access to the lesions in the depth of the pelvis, as well as lower postoperative morbidity. However, a laparotomy (sometimes with midline incision) may occasionally be more effective than several inadequate laparoscopies. The advantage of a laparotomy for treatment of severe endometriosis to identify and completely eliminate it lies in the ability of having a better tactile feedback.

Principles for identifying and treating deep endometriotic lesions

- Identify all important anatomical structures (ureters, colon, small bowel, major vessels, adnexae, uterus, bladder, nerves).
- Identify the lesions.

Signs of deep endometriosis include:

a) Fibrosis, with or without characteristic dark spots

b) Dense adhesions

c) Distortion of anatomical structures, infiltrations

d) Reduced tissue elasticity

e) Haemorrhagic cystic structures

- Perform easy steps first as this will facilitate difficult ones.
- Divide adhesions and restore pelvic anatomy in addition to complete excision of endometriosis.
- Free and isolate the lesions
- Start the dissection in areas free of disease.
- Optimise exposure by using manipulators, ovariopexy and additional ports, if necessary.
- Aim for complete excision whenever reasonable and possible.

The following steps may facilitate the surgical procedure: ovariolysis and ovariopexy, sigmoid mobilization, ureterolysis, and the identification of ligaments and rectosigmoid colon.

Second step of surgery for DIE involving the rectovaginal space

DE involving the muscularis layer of the rectum with no vaginal infiltration

In such cases, shaving consists of the separation of the DE nodule from the ventral part of the rectum.

Discoid excision

If the rectal wall is still infiltrated by implants of DE after shaving, it will appear hollow, rigid and thickened when palpated with a laparoscopic probe and/or a rectal probe.

In these circumstances, to achieve a macroscopically complete excision, a full-thickness discoid excision of the shaved area may be performed, followed by suturing the defect in one or two layers.

Summarising

Surgery is an important treatment option for women with DE. However, like medical intervention, surgery is not always successful and is also associated with clinically relevant risks.

Surgical treatment failure can be partially attributed to the heterogeneity of endometriosis, but it is also correlated with factors such as surgical experience, the complexity of each case, and anatomical locations of the disease.

- Laparoscopic surgical removal of Endometriosis is an effective First-line Approach for treating pain related to Endometriosis (Strong evidence).
- Although current RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially deep endometriotic lesions (weak evidence).
- Laparoscopic surgery for endometriosis should always be undertaken in preference to laparotomy, where possible (Strong evidence).
- The addition of Laparoscopic Uterine Nerve Ablation (LUNA) to laparoscopic removal of endometriosis does not improve pain relief (Strong evidence).

- Although Pre-Sacral Neurectomy (PSN) might benefit a small number of women, the benefits are likely to be outweighed by the potential for harmful effects (Strong evidence).
- Laparoscopic excision (cystectomy) for ovarian endometriomas is preferred if possible, to minimise symptom recurrence and endometrioma recurrence (Strong evidence).

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Chapter 6

Pain management of Endometriosis

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG,

National Vice President FOGSI 2020

Governing council member ICOG 2018-20

Consultant Obstetrician and Gynecologist

Director Ramakrishna Medical Centre LLP

Director Janani Fertility Centre

Trichy

Dr. D. Gayathri, MBBS,

Junior Resident, Ramakrishna Medical Centre LLP

Trichy

Introduction

Endometriosis is an enigmatic disease which has two components namely pain and infertility. ASRM defines endometriosis as an oestrogen dependent, chronic inflammatory disease which requires a life-long management plan aiming at maximizing the use of medical treatment and avoiding repeated surgical procedures. Treatment should be focused on alleviating pain, promoting fertility, reducing recurrence and improving the quality of life.

Globally, in women of reproductive age, the incidence of endometriosis is 1 in 10[1]. 30 to 50% of women with endometriosis are infertile[2]. 25 – 35% of infertile women have endometriosis.

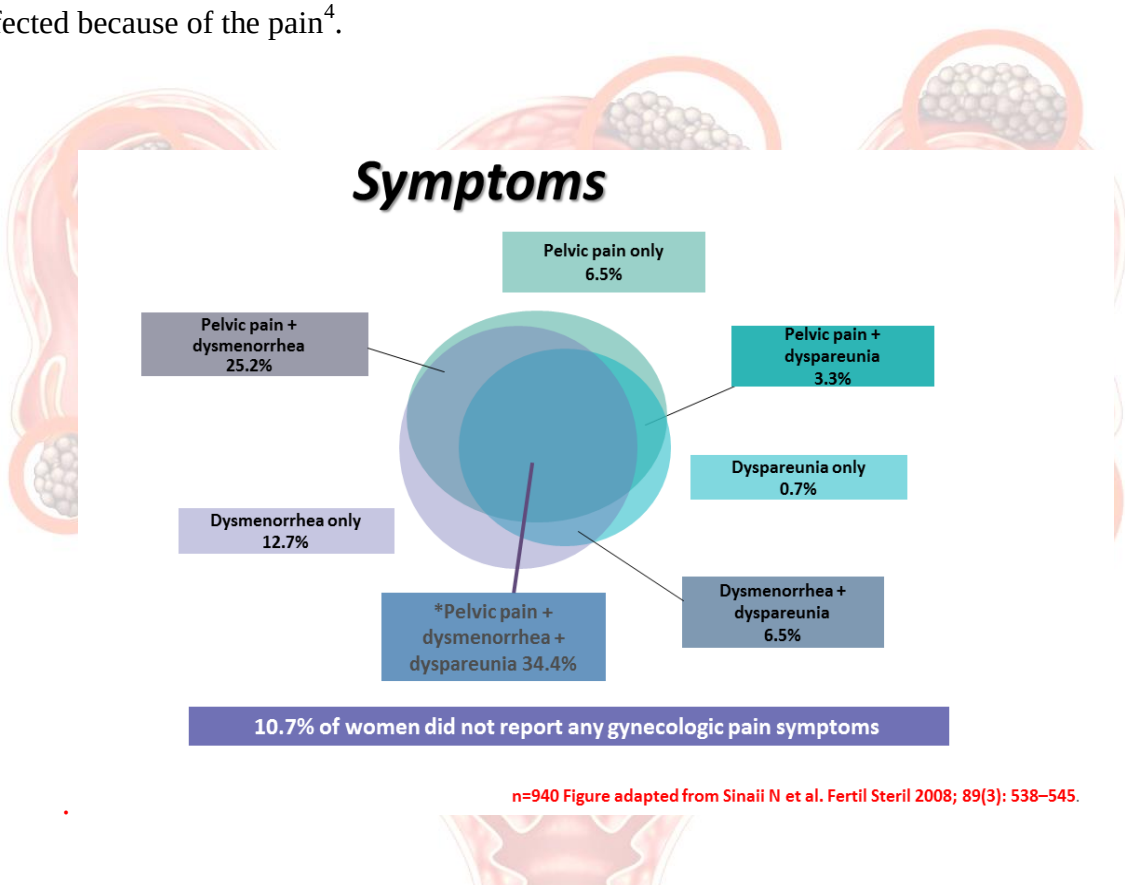
In India approximately 26 million women suffer from endometriosis[3]. Study by Endometriosis society of India in the year 2017 says more than 50 million women in India could have been affected.

Sites involved in Endometriosis

The underlying cause for endometriosis remains enigmatic. There are three types of endometriosis namely peritoneal, ovarian endometrioma and deeply infiltrative lesions (DIE) [currently known as Deep Endometriosis - DE]. Ovaries, utero sacral ligament, peritoneum, Pouch of Douglas (POD), vagina, bladder, bowel, and ureters are commonly involved in endometriosis. Lungs, umbilicus, abdominal wall and brain are few rarer sites of extra genital endometriosis. Endometriosis can appear as clear vesicles, erythematous lesions, dark pigmented lesions, white scarring etc depending upon the age of the endometriosis. Each lesion produces pain in different ways.

Symptoms of Endometriosis

Can be grouped under 7D's (Dysmenorrhoea, dyspareunia, dyschezia, dysuria, diffuse abdominal pain, D(A)UB and difficulty in conception). A 2008 cross-sectional survey showed that there is no clear relationship existing between pain, severity and the extent of the disease. There is often overlapping of symptoms. Most of the women are psychologically affected because of the pain[4].



Main causes of chronic pelvic pain other than recurrence of endometriosis

Gynaecologic	Non Gynaecologic
Adenomyosis	Irritable Bowel Syndrome (IBS)
Pelvic adhesions	Interstitial cystitis
PID (Pelvic Inflammatory Disease)	Fibromyalgia
Tumours of the ovaries or tubes	Musculoskeletal disorders
	Pelvic floor dysfunction

Mechanism of pain in Endometriosis

Production of growth factors and cytokines by alternately activated macrophages and other cells associated with functional endometriotic implants contribute majority to the pain associated with endometriosis. Irritation of pelvic floor muscles, direct invasion of pelvic nerves by endometriotic implants, especially in the lower pelvis and cul-de-sac, direct and indirect effects of active bleeding from endometriotic implants contributes to dysmenorrhea, dyspareunia and chronic pelvic pain in endometriosis[5].

Primary Mechanism of Endometriosis Associated Pelvic Pain (EAPP)

Peritoneal lesions induce inflammatory reactions and secrete prostaglandins, cytokines, histamine and kinins. DIE destroys tissues and nerves; ruptured chocolate cyst may irritate peritoneum and leads to fibrosis. Restricted mobility of organ secondary to lesions, adhesions to bowel, disturbed anatomical relations, induration of sacral ligaments leads to dyschezia and dyspareunia.

EAPP affects the quality of life and needs immediate treatment. DIE causes pain due to destruction of tissues and entrapment of nerves. There is increasing evidence that nociception and neuronal involvement contributes largely to EAPP.

Pathogenesis of cell survival and inflammation in endometriosis

Estradiol enhances the survival or persistence of endometriotic tissue. Prostaglandins and cytokines mediate pain and inflammation. Estrogen receptor β suppresses progesterone receptors (PRs), leading to progesterone resistance and deficient inactivation of estradiol leading to infertility. In endometriotic tissue, estradiol and PGE2 are produced in large quantities and enhance cell survival and inflammation[6].

Other factors contributing to pain in endometriosis include

1. Peripheral nociceptive effect of endometriotic lesions[7]
2. Amplified pain signalling from the periphery[8].
3. Associated Myofascial trigger points[9].
4. Psychological co-morbidities[10].

Diagnosis of Endometriosis

History plays an important role in diagnosing endometriosis. Age of menarche, cycle frequency, regularity, history of neonatal bleeding, previous pregnancies, surgeries, oral contraceptive pills or hormonal treatment for dysmenorrhoea, family history, pain unrelated to primary dysmenorrhea and presence of triple dysmenorrhoea are few notable factors considered in diagnosing endometriosis. Endometriosis can be diagnosed 80% through proper clinical examination. Presence of fixed retroverted uterus, palpable utero sacral ligaments, recto vaginal septum, nodules in POD, adnexal masses are suggestive of endometriosis.

Optimizing the diagnosis through

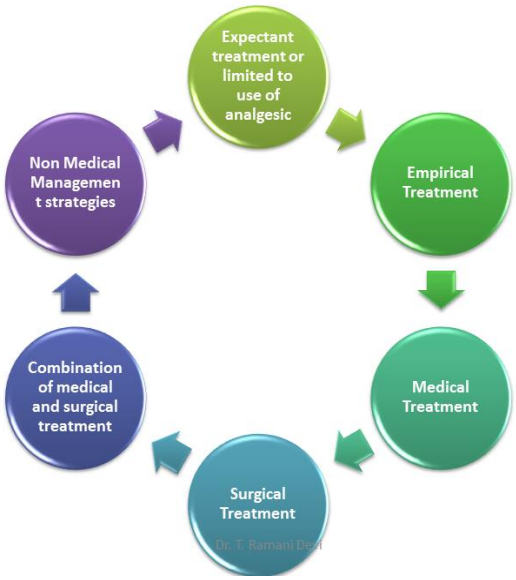
- Blood routine
- Physical examination
- Imaging TV USG / MRI
- Trans rectal USG
- Colonoscopy
- Cystoscopy may be required.

MRI scan remains the main stay in diagnosis of DIE as it can pick up ureteral and rectal endometriosis as well.

Pain management in Endometriosis

- Pain management should consist of empirical, medical, surgical, combination or alternative medical therapy as per suitability of patient. [Evidence level GPP ESHRE guidelines][11].
- Clinicians should be aware that endometriosis should be viewed as a chronic disease that requires life-long management plan with the goal of maximizing the medical treatment and avoiding repeated surgical procedure [ASRM recommendations]

Method of treatment



Depends upon age, fertility issues, previous treatment, nature and severity of pain, severity of disease and type of lesion.

Medical management

Currently available medical treatments include NSAIDs and hormonal contraceptives for mild symptoms. Progesterone – (Medroxy Progesterone Acetate, Cyproterone acetate, norethisterone, Dienogest, levonorgestrel-releasing intrauterine system (LNG-IUS)), danazol and GnRh analogues for moderate to severe symptoms.

- Empirical treatment can be given to patients with suspected EAPP with NSAIDs, COCs and Progestogen [Evidence level GPP][11].
- NSAID (Mefenamic acid) is given to women who are desirous of fertility.
- Continuous oral progestin therapy is effective for treatment for EAPP [MPA, Norethisterone acetate, Cyproterone acetate, Dienogest and Danazol] [Evidence level A][11].
- Dienogest has been used for managing the EAPP at any age group at the dose of 2 mg per day. It can be used for many years without much side effects. [Evidence level A][11].
- Depot MPA is effective for endometriosis associated pelvic pain [Evidence level A]* comparable to GnRh agonist.
- LNG-IUS is effective for endometriosis associated pelvic pain and comparable to GnRH with fewer side effects [Evidence level A][11].
- Oral Danazol is effective in treatment of endometriosis associated pelvic pain but serious side effects have limited their use. [Evidence level C][11].

- Danazol, (Ring, IUCD, intra cervical injections) are other options for treatment of endometriosis associated pelvic pain but currently not available in India [Evidence level B][11].

- GnRH agonist is most effective in the treatment of endometriosis associated pelvic pain. However, its side effects limit its prolonged use. [Evidence level A][11].

- Add back therapy is recommended to prevent the side effects [Evidence level GPP][11].

- The use of aromatase inhibitors in combination with progestins especially in DIE to reduce EAPP is recommended as second line drugs. [Evidence level B][11].

- GDG recommends that clinician should take patient preference, side effects, efficacy, cost and availability into consideration when choosing hormonal treatment for endometriosis associated pelvic pain. [Evidence level GPP][11].

- Elagolix is an oral non-steroidal gonadotropin releasing hormone (GnRH) antagonists that decreases estrogen production and is used to treat endometriosis associated pelvic pain 150mg to 200 mg per day can be used. This drug has been recently approved for use in EAPP[12,13,14].

- Failed medical management is an indication for surgery. [Evidence level GPP][11].

Nerve pain and medications

Pelvic nerve pain can be caused by damage to nerves or nerve endings. This causes nerves to send pain signals to spinal cord without needing a specific stimulus, or in response to something that wouldn't normally hurt, such as gentle stroking of your skin. In cases of endometriosis, normal urination, having bowel movements, sexual activity and everyday activities can cause pain.

Amitriptyline is an antidepressant drug but at lower doses it is widely used for long-term pain caused by arthritis, nerve pain or fibromyalgia. Dosage can start as low as 10mg at bedtime, and increased up to 75mg. An added benefit is that it can be used to help insomnia and sleep issues due to pain. Side effects include dry mouth, drowsiness, cardiac arrhythmias, seizures, constipation, and confusion.

Gabapentin (Neurontin), Pregabalin (Lyrica) works by dampening down the activity in the nerves that are irritated or damaged in the pelvis. It must be taken for 3-4 weeks before effects can be seen. Dosages can be titrated slowly or quickly based on side effects. Promising effects are seen. Common side effects include dizziness, drowsiness, increased appetite, weight gain, mood changes and constipation.

Tri-cyclical anti-depressants and anti-epileptics can reduce central sensitization and hence they can be of use in some patients. Multidisciplinary approach like physiotherapy and psychological therapy may also help in pain relief[15].

Narcotics in Endometriosis Treatment

Addiction and opioid tolerance are conditions that can negatively impact effective pain management with narcotics. Prolonged administration of narcotics or opiates can result in a paradoxical increase in atypical pain that appears to be unrelated to the original reason for medications in the first place. For better understanding a small review of how pain receptors work may help.

Australian Parliament House has amended the use of medical marijuana and then over whelmingly approved medical cannabis legislation act on March 14-16, 2016.

Surgical management

Surgery is preferred over medical management in relief of pain as the effects of drugs are short lived and it is more expensive. Surgical management is preferred in the following conditions

- For pain management, not responding or contraindicated to medical management.
- Acute pain like adnexal torsion or rupture
- DIE not responding to medical management

Surgical management of mild to moderate endometriosis

Laparoscopy should only be therapeutic and not diagnostic. Laparoscopic surgery is gold standard for management of endometriosis among patients with CPP not responding to medical management. Excision of visible endometriosis has the advantage of the specimen but technically difficult and peritoneal surface is lost. Bipolar ablation of lesions and adhesiolysis may relieve the pain.

While managing endometrioma excision of the capsule instead of drainage and electrocoagulation increases the spontaneous pregnancy rates and reduces the pain[16]. [Evidence level A][11].

Following surgery in patients with associated infertility, expectant management may be considered up to 6 months depending upon the age, ovarian reserve, tubal or male factor. Laparoscopy improves pregnancy rates in all stages of the disease and even after failed ART[17].

There is no evidence to recommend performing surgical excision of DIE prior to ART in infertile women with endometriosis, to improve reproductive outcomes. However, these

women often suffer from pain, requiring surgical treatment. The effectiveness of surgical excision of deep nodular lesions before treatment with ART is not well established with regards to reproductive outcome. It is indicated more for relief of pain.

Management of pain with severe endometriosis

In patients who have completed family with unilateral endometrioma, can be suggested unilateral salphingo-oophorectomy followed by insertion of LNG-IUS[18].

Hysterectomy with BSO is indicated when the patients have completed family over medical management. If hysterectomy is planned, we should be careful about the ureters as hydronephrosis can occur due to retro peritoneal fibrosis. Removal of ovaries and all visible endometriotic lesions should be done. However, women should be informed that hysterectomy will not necessarily cure the symptoms or the disease. [Evidence level A][11].

Indications for Hysterectomy with BSO are endometriosis in elderly, recurrence of endometriosis, chronic pelvic pain not responding to conservative surgery and medical management.

HRT is indicated in young patients who have undergone hysterectomy with BSO. Isolated estrogen is not preferable. Combination of estrogen and progesterone or tibolone may be ideal[19].

How to handle recurrence?

Endometriosis recurs because the basic pathophysiology cannot be corrected. Treatment only aims at symptom relief and removal of the disease as much as possible.

Delaying pregnancy and persistence of the pathological mechanisms act synergistically. In cases of aggressive disease, recurrence is more common with adverse prognosis. Post-

operative recurrence rate is 21% at the end of 2 years and 40 – 50 % at the end of 5 years even in expert hands[20]. Incomplete surgery might increase the incidence of recurrence. Recurrence can be either pain or lesion and pain is more common than the lesion.

Decision for repeat surgery should be carefully done as there is reduced ovarian reserve and counseling is needed [Evidence level GPP][11].Repeat surgery is more definitive treatment and simplifies the management for the clinician. Laparoscopy can destroy the lesions and excision of deeper fibrotic lesions and restoration of pelvic anatomy. Ureteric dissection has to be done to prevent complications.

Recurrent lesion should be handled medically, failure of which surgery is indicated which involves surgical re-excision and nerve ablation surgeries (pre-sacral neurectomy) which can have their side effects.

Infertility treatment of women with recurrent endometriosis, ART is preferable over repeat surgery. [Evidence level A][11].

Sudden increase in the size of endometrioma, appearance of new symptoms should alert the clinician towards the onset of malignancy. [Evidence level GPP][11].

Alternative treatments for pain

- Dietary changes – Endometriosis diet
- Pelvic floor Physical Therapy, TENS, reflexology, massage,
- Lifestyle modifications have proven its role in lowering the risk of endometriosis. Studies have shown that exercising two hours per week, adding omega 3 fatty acid to diet reduces the risk.

- Dairy products, refined sugar, red meat, wheat, soy by-products, caffeine, saturated fats and oils have proven to increase the risk of endometriosis[21].
- Complimentary treatments are used in 30-50%
- Yoga and meditation can be adjuvant therapy in treatment of EAPP
- Acupuncture may be useful in severe dysmenorrhea.
- Chinese herbal medicines attracted Cochrane review. It may be advised to patients who are keen on using them.
- There is limited use of neuromodulators, anesthesia, behavioral therapy, reflexology, homeopathy and psychological therapy in treatment of EAPP.

Conclusion

- Endometriosis Associated Pelvic Pain warrants immediate attention for improving quality of life. Empirical start of medical treatment in the form of NSAIDs, COCs and Progestins are justified in most settings.
- There is wide range of medical treatment available for EAPP management. Selection of therapy should be individualised.
- GDG recommends clinician to counsel women with symptoms presumed to be due to endometriosis thoroughly and to empirically treat them with adequate analgesia, combined hormonal contraceptive or progestogen [Evidence level GPP][11].
- Surgical treatment is considered in case of endometrioma, infertility and pain not responding to medical treatment.

- Post-operative adjuvant medical treatment reduces the chance of recurrence but compromises fertility. No consensus on duration and follow up of post-operative adjuvant treatment is available currently.

- Definitive surgery should be considered in symptomatic endometriosis if child bearing is completed. Oophorectomy reduces the chances of recurrence and pain. Endometriosis needs life time management plan and has to be individualised.

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Chapter 7

Recurrent endometriosis

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG,

National Vice President FOGSI 2020

Governing council member ICOG 2018-20

Consultant Obstetrician and Gynecologist

Director Ramakrishna Medical Centre LLP

Director Janani Fertility Centre

Trichy

Dr. N. Gayathri, MD, DNB OG.,

Consultant Shyamala Nursing Home,

Trichy

Introduction

Endometriosis is a relatively common disease affecting about 10% of women in reproductive age. The percentage is higher in infertile women. It is characterized by extra uterine implantation of endometrium like tissue, triggering chronic inflammatory reaction which clinically manifests with pelvic pain, pelvic mass and / or infertility. Because the endometrial cells are hormonally influenced, symptoms of endometriosis often worsen during menstruation.

Recurrent endometriosis is a frequently encountered benign disorder, where approximately 30% of patients need to undergo repeated surgeries, adversely affecting their quality of life. Recurrence rate reported worldwide ranges between 6 – 67%[1,2].

The rate of recurrence of endometriosis is 20% after 2 years and 40 – 50% after 5 years in a study by Sun Wei et al. According to the staging of endometriosis, after 2 years recurrence rate for stage I and II endometriosis is 5 – 7% and for stage III and IV being 14.3%. Various studies have suggested recurrence rate between 6-67%[1,2].

Recurrence occurs in the form of pelvic pain, dysmenorrhea, dyspareunia, pelvic mass or other pelvic lesions. Pain is by far the most common symptom in recurrence.

Factors affecting recurrence

Location

Time from primary surgery

Laterality

AFS Score

Age of patient/ age at primary surgery/ age at menarche

Parity

Previous / post-surgery medical treatment

BMI

Size of lesion at surgery

Extent of primary surgery

Fertility after primary surgery

Risk factors for recurrence

LOW RECURRENCE RISK[3]	HIGH RECURRENCE RISK[3]
rAFS score <70	**rAFS score >70**
pregnancy / parous woman	**Infertility, Nulliparous**
OCP	**Bilateral lesion**
Endometrial abalation	**Suboptimal surgery**
Unilateral lesions	**No post op medical therapy**
Complete surgery	**Pre-op medical management**
Post op medical management	**Young age**
Low BMI	**Ovarian conservation at primary surgery**
Older age at diagnosis / surgery	**High BMI**
Parous woman	

The risk of recurrence depends on the primary location of lesion. Busacca et al[3] studied 144 recurrence cases and reported that at the end of 4 years recurrence rates as 24.6% for ovarian, 17.8% for peritoneal, 30.6% for deep and 23.7% for peritoneal endometriosis. Following 8 years recurrence rates were 42,24.1, 43.4 and 30.9% respectively[4].

Li et al followed up 285 patients for a period of 36 months and reported the following parameters as risk factor for recurrence - bilaterality, pelvic involvement of endometriotic lesion, tender nodularity at Cul de sac, previous surgeries, pre-operative (rAFS) score and young age.

Recurrence mainly develops due to either of the 2 factors. First factor is newer lesions developing after surgery (patient has an increased tendency compared to general population and the basic pathogenesis is persistent). Second factor is reactivation and /or persistence of existing lesions[4].

It may be interesting to note that pre-operative medical therapy, increased the risk of recurrence. This could be due to suppression of small lesions or rendering some lesions very small that they cannot be completely excised. These lesions, after primary surgery, in the absence of post-operative therapy, tends to get reactivated early.

Parazzini et al[5] showed that the advanced stage disease initially had a higher recurrence rate and Bussacca et al[6] reported young age, deep endometriosis, stage III or IV and interval following surgery were additional risk factors for recurrence.

Many authors reported that pregnancy after surgery serves as a protective factor for recurrence as increased progesterone levels suppresses the activation and growth of lesions thereby inhibiting inflammation.[7]

Pathophysiology

Primary surgery aims at removing all lesions but the underlying pathology - genotype or phenotype of the patient, which dictates the tendency of the patient to form more lesions remains the same. Thus, persistence of retrograde menstruation, high premenstrual uterine tone, retrograde uterine contractions (frequency and amplitude) are few theories behind the development of newer lesions.

Lympho-vascular involvement could also be another cause for recurrence, most commonly rectovaginal endometriosis.[5] Immunological theory (NK cell suppression) also plays a role in recurrence[6].

Increased aromatase expression leading to increased oestrogen biosynthesis in peripheral tissue by aromatase is not inhibited.

Recurrence

In most studies, the recurrence of pain at 1 year after surgery has been much higher (45%), while reappearance of lesion or disease was lower at 1 year (about 9 – 15%). After conservative surgery followed by 6 months medical treatment 26% had pain which recurred 1 year later and 8% had detectable disease after 1 year.

Clinical recurrence usually presents in the form of endometriotic cyst more than 10 mm in the ovaries.

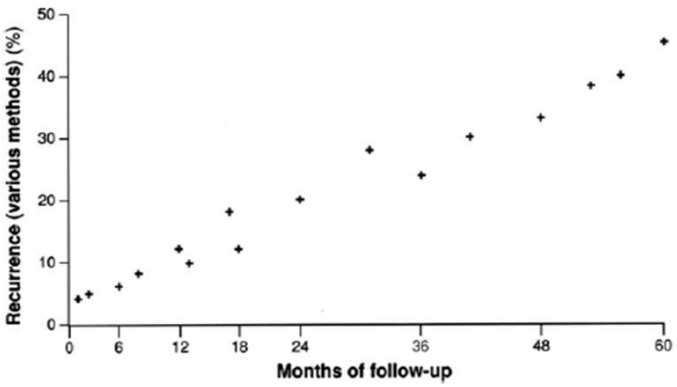


Figure 1 Cumulated literature data from studies reporting recurrence of endometriosis showing a gradual but steady increase in recurrence figures over the first 5 years of follow-up. From Evers et al. (1991). Reproduced with permission from the publisher.

Site

Recurrence occurred in same ovary, untreated contralateral ovary, or both. Incidence of recurrence in same ovary (81%) was much higher than the contralateral ovary (11%) or bilateral disease (8%) (Exacoustos et al (2006))[7]. 20% of patients showed recurrence after 1st surgical procedure and 17% after 2nd procedure at the end of 5 years [13]

Diagnosis usually depends on reappearance of symptoms, clinical examination, USG evidence, Biomarkers, laparoscopy and presence of biopsy proven endometriosis. Imaging modalities like USG and MRI picks up recurrent lesions, but their extent cannot be made out.

Management

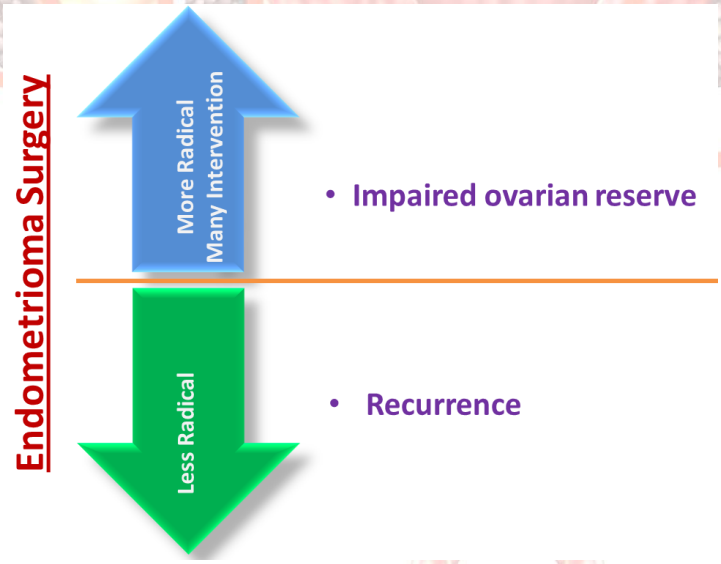
Laparoscopy is the gold standard in diagnosis as well as treatment of recurrent endometriosis. 3 goals of treatment include delaying recurrence, reducing pain and treating infertility. Therefore, the main aim is providing complete cure[8].

Preventing recurrence

Extent of surgery: By ablating or excising all visible lesions and looking for atypical lesions, recurrence can be avoided.

Timing of surgery: Surgeries in follicular phase had 2 fold decreased recurrence compared to luteal phase surgeries.

Technique: Excision, coagulation, vaporization of lesion and laser may delay recurrence. USG guided or laparoscopic drainage of endometrioma had 80 to 100% recurrence. Cystectomy had lesser recurrence. In DIE, resection of recto vaginal nodule relieves pain rapidly. Radical surgery is often required in preventing recurrence, in patients who have completed family.



Protective factors: Pregnancy, OC Pill usage, Post-operative progestins use, GnRH analogues – few factors to prevent or postpone recurrence[9].

Post op medication: As adjuvant minimizes risk of recurrence and extend pain free period in severe disease after conservative surgery

Main focus is eliminating the residual endometriotic cells[9]. But effect of drugs given post-operatively vanishes soon after stopping the drugs. Hence, it is only for temporary protection. According to ESHRE Guidelines 2014, long term OCPs, Dienogest, GnRH analogues, LNG-IUS are best in preventing recurrence and can be given in women not wanting pregnancy.

Medical Adjuvant Therapy

OCPs: Ovarian suppression, decreasing retrograde menstruation, inhibiting proliferation of endometriotic tissue. Continuous therapy is preferable to intermediate therapy[10]. The recurrence rate is reduced by the end of 1 year but not at the end of 2 or 3 years (similar to placebo)[9,11]

Dienogest: 2mg OD for 6 months can be given to prevent recurrence.

GnRH analogues: Reduces inflammation and adhesion formation and can be given for 6 months. Therapy beyond 6 months will need add-back therapy. It is associated with significant reduction of pain, especially in stage I and stage II disease. The effect is much lesser in stage III and Stage IV disease[12].

LNG – IUS: It has anti-inflammatory, immune modulatory effect and down regulates proliferative endometrial cells leading to endometrial glandular atrophy. Especially useful in reducing dysmenorrhea and as effective as GnRh analogues in its effect[13].

Danazol: Studies have reported reduced pain scores in patients given danazol in low doses 100 mg /day for six months[14] after primary surgery. Effect is seen better when used for more than 6 months. Androgenic side effects limits its routine use.

DMPA: Causes atrophy of endometriotic tissue. It is preferred in women who also need a contraceptive (dual use)

Tibolone: Atrophies endometrial tissue and has the same effect on ectopic tissue as well. Has promising results in preventing recurrence following hysterectomy when the women need HRT.

With all the above treatment options, it is important to individualize the plan of management according to the patient characteristics and side effect profile. Thorough counselling actively involving the women in her choice of treatment is advisable.

Pain Management

NSAIDs: Commonly used for symptomatic relief of pain. No drug within the group was found to be better than the other. Various NSAIDs are used in various centres as per the local protocols.

Surgical Management: Superior to medical management as far as pain is considered. Disadvantages include short term effect and more expensive besides being invasive with associated anaesthesia risks. According to ESHRE Guidelines 2014, pre sacral neurectomy is effective but not without its own set of long-term effects and complications.[15,16]

Infertility Management

Primary surgery in infertile women has to be done meticulously, giving her the best possible clearance. First look is the best look. As subsequent surgeries are not preferred in infertile women as they are associated with greater reduction of ovarian reserve. According to ESHRE Guidelines 2014, in case of recurrence, ART is preferred to repeat surgery.

Indications for surgery in recurrence are only for severe pain not responding to medical management, difficulty in oocyte pick up and suspicion of malignancy.

HRT after Hysterectomy and Oophorectomy

Fear of reactivation of the hormone receptive endometriotic tissue and malignant transformation of residual tissue limited the use of HRT in these patients. But most recent guidelines, from ACOG Practice Bulletin 2010, state that HRT is not contraindicated in these patients and can be given when benefits outweigh the risks.

Conclusion

Endometriosis when it recurs, affects the quality and fertility of a woman severely. For the sub fertile population, ART is preferred over repeated surgeries. Indication for repeat surgery are few when there is difficulty in oocyte pickup or pain. In general population who have recurrence of lesion or pain should be managed medically and improve the quality of life. If not responding to medical management, surgery should be the last option. Optimal management at primary surgery and post op medical adjuvant therapy can prevent recurrence. These patients need life-long follow up.

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Chapter 8

Endometriosis and Infertility

Dr. Rajapriya Ayyappan, MD, FRCOG.,

Consultant ObGyn and Infertility,

Srinivas Priya Hospital,

Chennai.

Endometriosis a disease of reproductive age females, affecting 10-20%. It is defined as presence of ectopic endometrial tissue, which is estrogen responsive and leads to low grade chronic inflammatory disease. There is no single universally accepted theory for etiology of endometriosis. It is recurrent in nature and is a leading cause of infertility by affecting various phases of reproduction from dyspareunia to failure of implantation. Multiple factors include altered tubo-ovarian relationship, ovulation dysfunction, poor oocyte quality, tubal dysfunction, reduced fertilization, suboptimal embryo development and reduced implantation and increased miscarriage. The fecundity rate per se is lower in endometriosis affected individuals, from 20% it drops to < 5% depending on age and stage of endometriosis.

The pathophysiology of the disease is unclear and ranges from genetic, anatomic, hormonal to immunologic. The ectopic endometrium giving rise to different stages of disease depends on survival, adhesion, proliferation, vascularization and invasive nature. The altered

molecular level mechanisms lead to increased local estrogen, pro inflammatory cytokines, prostaglandins and matrix-metalloproteinases together with altered immune system leading to key presentation of varied forms of pain and infertility. NSAIDs are given for pain among infertility patients and it is preferable to give COX 1 inhibitor as COX 2 inhibitor affects ovulation.

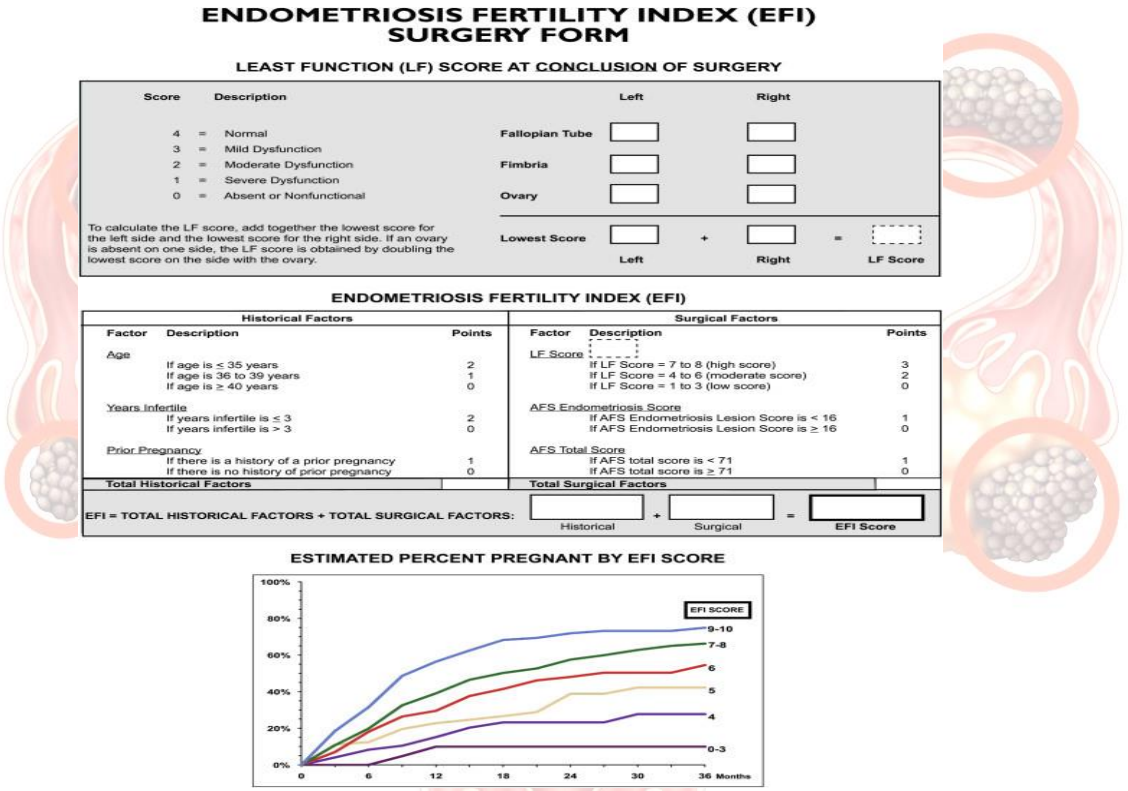
ASRM has stated that, "Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures."

The medical measures induce pseudo menopause or pseudo pregnancy. It leads to ovarian suppression, apoptosis and decidualization of endometrial tissue. The surgical measures include removal of pathogenic tissue and restoration of pelvic anatomy. Inadequate clearance of disease or development of new lesions pave way for recurrence post operatively. Hence the patients, must be counselled about the nature of this disease. Follow up is key and it helps to plan the treatment for infertility.

Medical management works by suppression and doesn't help in treating infertility. Wide variety of hormonal agents available to treat endometriosis at different levels include GnRh analogues, antagonists like Elagolix, Selective Progesterone Receptor Modulator like ulipristal, mifepristone, Selective Estrogen Receptor Modulator like bazedoxifene, progestin monotherapy like dienogest, norethindrone acetate, medroxy progesterone acetate, levonorgestrel releasing intrauterine system, Etonogestrel subcutaneous implant, aromatase inhibitors, anti-angiogenics, immunomodulators and botanicals like curcumin. In women needing fertility treatment medical management is not useful.9 (ESHRE guidelines)

The ideal way to diagnose and treat is laparoscopy. There is a new validated scoring system called Endometriosis fertility index (EFI), which helps to evaluate the infertility

aspect. A good descriptive laparoscopic documentation of lesions affecting tubes, ovaries and pelvis like powder burn lesions, fibrosis, red implants, clear vesicles or scarring , discoloration of peritoneum, ovarian endometrioma, deep infiltrating endometriotic nodules >5mm into the peritoneum which may also invade bowel, bladder, ureters, vagina and uterosacral ligaments etc. are needed to validate the EFI.



ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube		
3	= Mild Dysfunction			
2	= Moderate Dysfunction	Fimbria		
1	= Severe Dysfunction			
0	= Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

Lowest Score: Left + Right = LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

ESTIMATED PERCENT PREGNANT BY EFI SCORE

The imaging tools MRI and USG in addition to laparoscopy, helps to classify endometriosis into, Ovarian, Peritoneal and Deep infiltrating endometriosis. Histopathology is not mandatory to initiate treatment but it is essential for endometrioma to rule out occult malignancy. CA 125 also is not only pathognomonic for diagnosis of endometriosis, but also aids in follow up.

Surgical treatment by laparoscopy needs expertise, specialized equipment and skill. Sometimes multidisciplinary input from gastro or urosurgeons aid in performing a complete satisfactory management of complicated disease. At times, strategies like sandwich therapy

may help though individualization is important. Conservative surgery is the initial aim when it comes to managing infertility. There is no longer a role for diagnostic laparoscopy. It is essential to actively treat the endometriotic implants by ablation and adhesiolysis even if minimal endometriosis to improve fertility outcomes. Cystectomy is preferred over drainage of endometrioma as it reduces the recurrence rate of around 20-30%. In a Cochrane review, Hart et al. (2008) concluded from three RCTs that excisional surgery of ovarian endometriomas provides a more favorable outcome. Histopathology proof is available. However, there is 3 % chance of premature ovarian failure. Using surgery and drugs judiciously helps in handling recurrent disease and help patients to attain motherhood when optimal conditions prevail. Patient has to be counselled regarding the reduction in the ovarian reserve, especially when she under goes redo surgery. When combining live birth rate and ongoing pregnancy after 20 weeks, a meta-analysis demonstrated an advantage of laparoscopic surgery when compared to diagnostic laparoscopy only. The odds ratio (OR) was 1.64 (95% confidence interval (Cl) 1.05 to 2.57) in favour of laparoscopic surgery. There are no studies demonstrating that one surgical energy sources (electrosurgical, laser, ultrasonic, or robotic) is superior to another. It is not mandatory to surgically treat asymptomatic chocolate cyst prior to IVF to improve results.

The only option is active management before disease becomes active or aggressive. It behaves like a benign malignancy. The prudent use of operative laparoscopy and medical pre-treatment to control endometriosis gives better results for assisted reproduction either intrauterine insemination (IUI) or IVF/ICSI.

ESHRE guidelines suggest IUI with gonadotrophin stimulation works better. The results improve from 8 % to 26 %. RCOG guideline recommends IUI to improve pregnancy in minimal and mild endometriosis. Ideally, fertility treatment must be started soon after any endometriosis surgery in a woman desiring pregnancy without resorting to medical

management. Pre-treatment for 3-6 cycles with GnRh analogues in certain situations improves the outcome by promoting the implantation. There is an increased need of gonadotrophin dose to stimulate these follicles following suppression therapy. Instead, 1 or 2 doses of GnRH analogues can be given followed by ART. Frozen embryo transfer can be done following GnRH analogues treatment to promote implantation.

In vitro fertilization or Intra cytoplasmic sperm injection is indicated whenever associated with tubal or male factor, failure of 3-4 cycles of IUI, if age >35 years with low reserve or in moderate to severe stage even if age <35 years. Judicious use of surgery has to be done prior to IVF only when symptomatic or size >4 cm or suspicious of malignancy or when there is difficulty anticipated in oocyte pick up. Aspiration of ovarian endometrioma through USG guidance carries the risk of infection and hence caution is essential.

A very debatable topic is that, what is the best way to achieve pregnancy in case of recurrent moderate to severe endometriosis? Currently, ASRM states that IVF is better than surgery, if asymptomatic. It is clear that infertility associated with endometriosis is best treated by primary Surgery and immediate Assisted reproduction techniques. An individualized treatment plan should be developed, taking into account the age and duration of infertility. The major advantages of surgery are effectiveness compared with one IVF cycle, without increased risk of multiple pregnancies and the possibility of achieving subsequent pregnancies. In addition, pain symptoms could be significantly alleviated and diagnosis histologically confirmed. Recurrent endometriomas with infertility are better managed by ART.

To improve fertility outcomes in endometriosis, it is important that you make the first surgery the best, to time it, so as to get best fertility outcome in reproductive age. Simple steps to follow to safeguard the reproductive potential will be to know the ovarian reserve

using Antral Follicles Count and Anti Mullerian Hormone, pre-treatment with the right medical agent, timely decisions for IUI or IVF. Fertility preservation by cryopreservation of ovarian cortex or oocytes among young girls may help to achieve pregnancy at a later stage. Young adolescent girls should be educated regarding the value of good life style modification to prevent the disease progression.

Conclusion

In women with minimal and mild endometriosis, surgical excision or ablation of endometriosis is recommended as first line with doubling the pregnancy rate. In patients with moderate and severe endometriosis surgical excision also is recommended as first line. In patients who failed to conceive spontaneously after surgery, assisted reproduction is more effective than repeat surgery. In women who have failed assisted reproduction, further management remains controversial in the present time.

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Chapter 9

Endometriosis and Malignancy

Dr. Kavitha Sukumar

MD (OG), MCh (Surgical Oncology)

Associate professor of Surgical Oncology

Institute of Obstetrics & Gynaecology, Egmore

Chennai

Endometriosis is defined by the presence of ectopic endometrium (including glands and stroma) in extrauterine locations such as the ovaries, peritoneal surfaces, rectovaginal septum and occasionally distant sites, affecting approximately 6–10% of women of reproductive age. It shares many features with ovarian cancer, such as the invasive growth, hormone dependency and recurrence (1). Epidemiological, histopathological and molecular data suggest a possible malignant potential of endometriosis. The majority of the published studies on endometriosis-associated ovarian cancer have reported that ovarian cancer risk among endometriosis patients is moderately increased (RR, SIR or OR 1.32–1.92) (2). The overall frequency of malignant transformation of endometriosis is estimated to be from 0.3% to 0.8%.(3)

Endometriosis as a cancer precursor: the historical perspective:

A number of gynaecologic cancers are thought to originate from endometriosis. In 1927, Sampson first published a report of a malignancy associated with endometriosis (4) wherein he described specific criteria for endometriosis-associated ovarian cancers

1. Evidence of endometriosis in association or close proximity to the cancer
2. Histology of the tumour must be consistent with an endometrial origin
3. No other primary tumour site must exist

In 1953, RB Scott amended Sampson's original criteria, to add an additional criterion stating that the endometriosis associated with cancers must show a morphologic progression from benign to malignant in a contiguous fashion. In 1988, La Grenade and Silverberg identified what appeared to be a precursor lesion, the so-called atypical ovarian endometriosis. (5)

Jiang et al described some of the first studies suggesting a molecular basis linking endometriosis with cancer development in 1998. They demonstrated the same loss of heterozygosity (LOH) events in endometriotic lesions and adjacent endometrioid ovarian cancers in 82% of cases examined.

Malignant transformation of endometriosis

The malignant transformation of endometriosis is a rare event, mostly involving the ovary; however, malignant transformation of endometriosis has also been observed in extra-ovarian endometriosis(6) .About 80% of EAM (Endometriosis associated Malignancies) have been found in the ovary, whereas 20% are localized in extragonadal sites like intestine, rectovaginal septum, abdominal wall, pleura and others.

Endometriosis-associated ovarian malignancies are most commonly Endometroid or Clear cell cancers, rarely other ovarian malignancy types like borderline tumours, endometrial stromal sarcoma or adenosarcoma may arise on a background of endometriosis (7). Recently published pooled analysis of case-controlled studies by Pearce et al. reported an increased risk for low-grade serous ovarian cancer among endometriosis patients as well (RR 2.11) (7) however, there is no association with high grade serous cancers as on date. According to Kurman, and Shih's classification, in which ovarian cancers are designated as type I and type II based on morphologic, molecular, and histogenic characteristics, endometriosis is commonly linked to the tumorigenesis of type I ovarian carcinomas, but is rarely seen in type II ovarian carcinomas.

Van Gorp et al. (8) classified ovarian cancer associated with endometriosis into 3 categories: (C1) ovarian cancers with histologic proof of transition from endometriosis to ovarian cancer based on the definition of Sampson and Scott; (C2) ovarian cancers with endometriosis in the same ovary, but without histologic proof of transition; and (C3) ovarian cancers with concomitant endometriosis at any location in the pelvis. On the basis of these categories, most histologic analyses of EAM fall into the C3 category. More extensive sampling of ovarian endometrioid or clear cell carcinomas will likely increase the probability of detecting C1 or C2 cancers.

Pathogenesis

Atypical endometriosis is a heterogeneous condition, histologically characterized by hyperplasia of endometrial glands with cytological atypia or presence of atypical hobnail cells within ovarian endometriosis. They are found in 80% of cases of endometriosis associated ovarian cancers and are hence believed to be their precursor lesion.

The postulated mechanism of malignant transformation is chronic inflammation and oxidative stress due to heme iron present in areas of accumulated blood in endometriotic lesions. The recurrent oxidative stress in turn induces genetic alterations which ultimately may result in development of EAM.

Approximately 90% of synchronous tumours from ovary and endometrium will be endometrioid. Studies have shown that there is a high prevalence of coexisting endometriosis in these concurrent ovarian and endometrial carcinoma (9). The findings suggest that common genetic background plays an important role in the tumorigenesis of endometriotic-associated carcinoma, in addition to inflammation or microenvironment.

Numerous mutations in genes linked to carcinogenesis have been identified in endometriotic lesions. Defects of pTEN, p53, Loss of heterozygosity, ARID1A, Wnt/β-catenin pathway defects, kRAS, Bcl-2, hMLH1 etc have frequently been identified in Endometriosis associated cancers and their surrounding areas of endometriosis.

Risk factors for transformation to malignancy

Many studies report an increased risk of ovarian cancer in women with endometriosis, especially in those with a longstanding history of endometriosis (>10 years) and with endometriosis diagnosed at a young age (<30 years) (10).

The size of endometrioma as well as postmenopausal status were demonstrated to be independent predictive factors for the development of ovarian cancer among endometriosis patients. In the study by Kobayashi et al (11), the risk of ovarian cancer in 6398 women with ovarian endometriomas, tumour size ≥ 9 cm in diameter was shown to be associated with increased ovarian cancer risk.

Both endogenous or exogenous hyperoestrogenism is another risk factor for malignant transformation. Obesity as well as therapy with unopposed oestrogens after hysterectomy for endometriosis were shown to be a significant risk factor for the development of EAM. (12) However, hormonal contraception, tubal ligation or hysterectomy were found to reduce the ovarian cancer risk among patients with endometriosis (13)

Clinical Features

Endometriosis associated malignancies occur at an earlier age group as compared to those not associated with endometriosis. Aris et al reported in their retrospective cohort trial that the mean age of women with EAM was 48.3 ± 10.8, on average 5.5 years lower. (14)

By and large, Endometriosis associated malignancies are well differentiated tumours and present at an early stage, without ascites. Consequently, their prognosis is better when compared with similar subtypes without associated endometriosis (15).

The diagnosis of EAM is often difficult because of the overlap of imaging findings and raised ca 125 values found in endometriosis per se. However, a high index of suspicion is necessary in certain clinical scenarios such as sudden increase in size of an ovarian mass in longstanding endometriosis, especially in postmenopausal women or when there are suspicious imaging findings in cases of endometriosis.

Imaging

MRI is the Imaging modality of choice in cases of suspected endometriosis. For those where an EAM is suspected, a contrast MRI is ideal. The typical morphologic appearance of an endometriosis-associated carcinoma is that of a unilateral large cystic mass that contains haemorrhagic fluid and mural nodules. The mural nodules appear contrast enhanced on postcontrast T1-weighted images. Dynamic subtraction MR imaging is useful for detecting

small contrast-enhanced nodules in the hyperintense endometrioma on T1-weighted images. Enlargement of the endometrioma with the disappearance of shading on T2-weighted images are suggestive of malignant transformation.

Management

These tumours are managed as per the guidelines of management of epithelial ovarian cancers. Though there is a suggestion that these tumours may be less responsive to chemotherapy than the non-endometriosis associated cancers, there is currently no difference in indications for chemotherapy for EAM.

Prevention

For those women who are having surgery for endometriomas close to menopause salpingo-oophorectomy must be considered, especially if the endometrioma cannot be completely removed by cystectomy as most cases of EAM arise from endometriomas.

Because of the malignant potential, endometriosis patients should, if indicated, receive a combined oestrogen-progestin therapy (HRT, hormone replacement therapy) or tibolone even after hysterectomy; unopposed oestrogens should generally be avoided in these patients. Regular use of the oral contraceptive pill for 5 years results in a 20–30% reduction in Endometroid and clear cell carcinoma risk [16]. Similarly, tubal ligation is at least as effective as the oral contraceptive in reducing the risk of EAM, showing a reduction in risk of almost 50% [17]. As the fallopian tube is the likely conduit for key factors resulting in the aetiology and propagation of endometriosis, tubal occlusion is an important consideration for those women looking for permanent contraception. In these women, opportunistic salpingectomy also has the potential to reduce their risk of serous ovarian cancers and should be considered [18,19].

Future perspectives

Several epidemiological studies, case reports and case series on EAM have been published in the literature to date. However, a systematic analysis of a large population of patients with EAM is still missing. Thus, a systematic retrospective study on endometriosis-associated malignancies (EAM study) is currently being conducted by the Endometriosis Research Foundation together with the study groups on ovarian and uterine tumours of the working group for gynaecological oncology (AGO)

Additional research should be directed to the discovery of biomarkers that identify cases of endometriosis with oncogenic potential, the goal being to identify premalignant lesions and then study subsequent interventions in order to reduce the incidence of EAM and improve patient outcomes.

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Chapter 10

Endometriosis & Menopause – An Inscrutable Disease

Prof. N. Hephzibah Kirubamani,

M.D., D.G.O., F.I.C.O.G., F.R.C.O.G., Ph.D., D.Sc.

Saveetha Medical College, SIMATS

Chennai.

Endometriosis symptoms usually subside after menopause, but not always. Endometriosis does occur in postmenopausal women but usually, less common and less active.

Dr.Martha K.Richardson stated that "Endometriosis often, but not always, improves after natural or surgical menopause."

"Endometriosis at menopause should not be considered as final but women need to be followed up."

The prevalence of endometriosis in menopause is 2.4%.

There are two major issues in endometriosis and menopause

1. Occurrence and recurrence of Endometriosis after menopause

2. Menopausal symptoms are due to surgical menopause, medical menopause or natural menopause with history of prior endometriosis.

Pathogenesis of Endometriosis in Menopause

It may be due to activation of pre-existing residual ovarian remnants or incomplete definitive surgery or other risk factors such as hyper estrogenoemia and obesity may play larger roles.

Can it develop as de Nova Lesions?

Asymptomatic lesions may well progress in the postmenopausal period and become clinically evident. Oestrogens can be derived from exogenous administration of Menopause Hormone Therapy, Phytoestrogens or Endogenous extra ovarian excess production from adipose tissue, adrenal glands, through aromatization of androgens and aromatase activity in eutopic and ectopic endometrium. Theory of recurrence – A genetic predisposition in association with environmental factors, medication or fat redistribution increases the risk of endometriosis after menopause.

The administration of exogenous oestrogen is not a pre-requisite for the presence of endometriosis in postmenopausal women.

Postmenopausal endometriotic lesion has the same immune chemical profile as the disease occurring in premenopausal women and has the potential to reactivate when given the appropriate stimulation. Local estradiol production by the endometriotic lesions drives the disease through its autocrine and paracrine effects.

Presentation of post-menopausal endometriosis may be varied depending upon the site. Symptoms may be pelvic pain or mass. Many different locations have been described namely, intestinal, ureteral, hepatic and even cutaneous endometriosis have been reported.

Endometriosis should be considered in the differential diagnosis of postmenopausal cystic lesions of the ovary. Endometriosis after menopause can get reactivated and residual endometriotic lesions undergo may malignant transformation, although this risk is very small.

Management of Post-menopausal Endometriosis

1. Surgery: Due to the risk of malignancy, surgery is the first choice of treatment. These patients are high risk for surgery due to their age, comorbid conditions and previous surgeries.
2. Aromatase Inhibitors (AI): Has the potential to improve symptoms either as first-line treatment or when surgery is contraindicated or as a second line one for recurrence following surgical treatment. Since AI could cause a decrease in bone mineral density and increase the rate of bone fractures, supplemental bisphosphonate therapy has to be provided.

Menopause Hormone Therapy (MHT) in Women with Previous Endometriosis

Menopausal symptoms in endometriosis can arise due to surgical menopause or medical menopause which can be early or age-appropriate. Premature and early menopause due to decreased ovarian reserve and decreased levels of anti-mullerian hormone (AMH) in stages 111-1V endometriosis. As per an Italian study, the age of menopause in endometriosis ranges from 32-52years. Conservative ovarian surgery may lead to premature ovarian failure due to the removal of healthy ovarian tissue, vascular injury or aggressive coagulation.

Women with endometriosis are usually younger and they will invariably have either induced or surgical menopause. Surgical menopausal state is a hyper-gonadotrophic state and hypo-estrogenic state. Medical menopause induced by GnRH injection is a hypogonadotropic state. This decline may relieve endometriosis-related symptoms, but can simultaneously trigger menopausal symptoms. Risks of premenopausal surgical menopause are sexual dysfunction, genitourinary symptoms and severe vasomotor symptoms which are long-lasting

and may not be completely relieved. This is often accompanied by sleep disturbances and mood swings. There is a seven-fold increase in Cardiovascular risk following surgical menopause before 50 years (R.R-4.45) and less than 45 years. There is a linear relationship between earlier age at menopause and lower density in later life - (Gallagner: 2017). Quality of life is significantly more affected in surgical menopause. To alleviate menopausal symptoms, they may require hormone therapy.

Non-Pharmacological Options for Management of Symptoms

a. Regular exercise and diet,
b. Weight management and
c. Cognitive behavioural therapy

Two Specific Concerns in the Management of Menopausal Symptoms in Women with Previous Endometriosis

First, there is a possibility that endometriotic growth may get reactivated with exogenous oestrogen and

Secondly, exogenous oestrogen may promote malignant transformation of residual endometriotic tissue.

Though the role of hormone therapy in endometriosis is debatable, denying hormonal therapy may worsen the long-term consequences of hypoestrogenism.

Currently, there are no data to indicate the absolute risk of malignant transformation in this group of women. (Fujiu et al 2010, Bhat et al 2014) (L.C. Gemmell et al 2017)

There is little high-quality data to answer these questions, so the absolute risk of disease reactivation and malignant transformation cannot be quantified, but instances of its occurrence are available in literature.

Appropriate MHT for Women with Previous Endometriosis

1. *Combined oestrogen and Progestin regimens:* Instead of unopposed oestrogens, preferably continuous combined therapy with micronized progesterone both in hysterectomised and non-hysterectomised women to prevent the risk of recurrence and malignant transformation.
2. *Tibolone* has an estrogenic effect on menopausal symptoms and bone, yet a progestogenic effect on tissues, has some androgenic property, might be a safer alternative to traditional HRT in patients with residual endometriotic disease.

Data regarding MHT are limited but it is safer to give continuous combined oestrogen and progestogen or Tibolone.

The risk of recurrence is probably increased when there is residual disease after surgery, hence women should be monitored for symptoms of recurrence.

Timing

Initiation and Duration of MHT:

For those on GnRH analogues, clinicians are recommended to commence add-back HRT with the start of GnRH agonist therapy to prevent bone loss and hypo-estrogenic symptoms.

Data are also lacking on the optimal time to commence HRT following surgical menopause but should be continued till the natural age of menopause.

When oestrogen is contraindicated, they should be advised about alternative pharmacological treatment for menopausal symptoms and skeletal protection.

When women are unable to tolerate oral progestogens, LNG-IUS in conjunction with a systemic oestrogen could be an option (in women with a uterus and on medical menopause).

Combinations of oestrogens and Dienogest have been proposed as new HRT but evidence in the literature is still sparse and could be reliable options with a double role in controlling menopausal symptoms and endometriosis recurrence.

Dietetic Oral Isoflavone supplement was associated with reduced risk of endometriosis recurrence, but Noel et al have suggested that there is a relapse of endometriosis with the use of oral isoflavones.

Recommendation by EMAS

1.	In women with surgically induced menopause, because of endometriosis, oestrogen/progestogen therapy or tibolone can be effective for the treatment of menopausal symptoms (Al Kadri, et al., 2009).	B
2	The Guideline Development Group (GDG) recommends that in postmenopausal women after hysterectomy and with a history of endometriosis, clinicians should avoid unopposed oestrogen treatment. However, the theoretical benefit of avoiding disease reactivation and malignant transformation of residual disease should be balanced against the increased systemic risks associated with combined estrogen/progestogen or tibolone	GDG
3	The GDG recommends that clinicians continue to treat women with a history of endometriosis after surgical menopause with combined oestrogen/progestogen or tibolone, at least up to the age of natural menopause.	GPP

Approach to Postmenopausal Women for MHT with Past History of Endometriosis

- The clinician must balance the benefits of MHT to bone and cardiovascular health against the potential risks of recurrence or malignancy,
- The decision when to initiate after surgical menopause must be individualized, considering her age and past medical history,
- Benefits and risks of MHT should be evaluated for every individual patient, considering age, previous disease severity, family history, co-morbidities, and BMI,
- Actively engage the patient in the decision-making process and understand our limitation as providers to quantify specific risks,
- If a decision to initiate MHT is taken, choose combined MHT or Tibolone,
- Beware of possible risk for malignant transformation (although the incidence is likely to be very small) and
- Consider obtaining tissue for histology if there is any suspicion of malignancy.

Follow-up

Though data about the timing of follow-up are lacking, regular follow up is recommended. In every visit symptoms of recurrence (chronic pelvic pain, dyschezia, dysuria and dyspareunia) should be elicited. If recurrence is ascertained MHT should be stopped and should be investigated.

Future Research

2018 trial conjugated oestrogen and bazedoxifene - tissue selective estrogen complex (TSEC) showed improvement in vasomotor symptoms and protective against osteoporosis and has antiestrogenic activity on the uterus and breast

Studies with SERMS such as ospemifene and bazedoxifene, and combining these agents with oestrogens (especially bazedoxifene/conjugated oestrogens) may be promising and may represent a future alternative to conventional HRT.

Conclusion

It is a real challenge to treat women with menopausal symptoms with a history of endometriosis since it is difficult to decide between the treatment of menopausal symptoms and the risk of endometriosis recurrence. Many women would have suffered years of debilitating symptoms before diagnosis, and then proceeded to undergo multiple treatments and operations in an attempt to regain some quality of life and would have attained either natural, medical or surgical menopause. Hence these women deserve to have accurate individualized and specific information about the risk of recurrence with different menopausal treatments, so that they can make an informed decision about their treatment.

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Chapter 11

Iron metabolism in endometriosis

Dr Vidya A Thobbi, MD, DGO., FICOG.,

Professor and head,

Department of OBG,

Al Ameen Medical college,

Bijapur.

Dr Nidaa Khan

Resident,

Department of OBG,

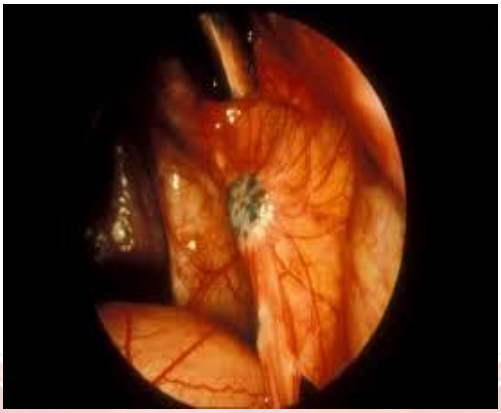
Al Ameen Medical college,

Bijapur.

Introduction

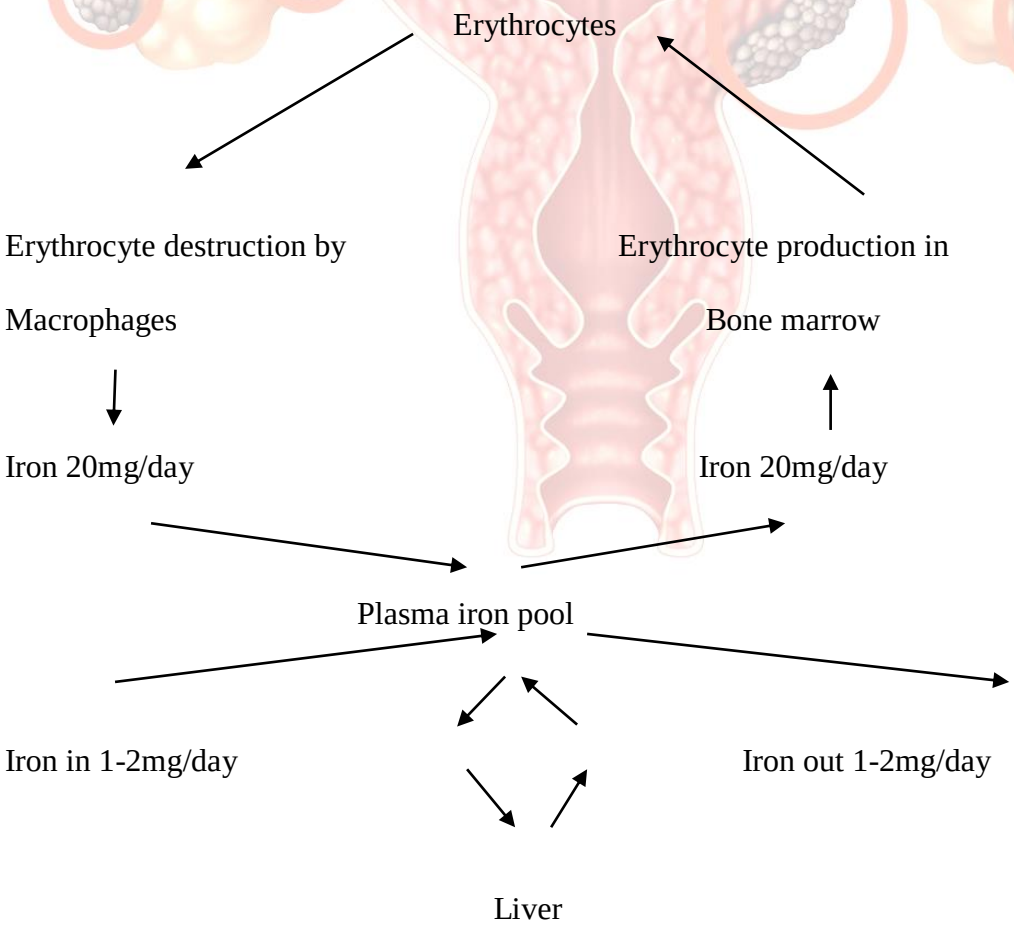
Higher levels of iron, which is probably released after lysis of erythrocytes, have been found in the peritoneal fluid of patients with endometriosis and the concentration of iron is related to the severity of disease. Free iron, which is a strong prooxidant, may act as a proinflammatory factor in the peritoneal cavity and promote the development of pelvic endometriosis. However, how the peritoneal environment copes with the presence of erythrocytes and iron has been discussed.

Iron overload is seen in different components of the peritoneal cavity of endometriosis patients (peritoneal fluid, ectopic endometrial tissue, peritoneum adjacent to lesions and macrophages).



The above picture shows early peritoneal implants.

Iron metabolism in body



Iron enters body in the same amount as much as it exits i.e. 1- 2 mg/day. Because there is no effective means of excretion of iron – except exfoliation of cells and menstruation, iron metabolism is controlled by its absorption. Liver and bone marrow are the stores.

Iron metabolism in endometriosis

Peritoneal fluid[5]

In the peritoneal fluid of patients with endometriosis, higher levels of iron, ferritin, transferrin and Haemoglobin was seen. Saturation of Tf was found to be higher in the peritoneal fluid of endometriosis patients.

Endometriotic lesions and peritoneum[5,6]

In the stroma of endometriotic lesions and peritoneum, cytologic and histochemical data revealed the presence of iron and macrophages heavily laden with ferric pigment. In endometriotic cysts too, iron concentrations in cystic fluid were considered to be an indicator of endometriosis. Studies have showed that endometriotic lesions were able to synthesize and secrete Haptoglobin.

There is strong expression of heme oxygenase-1 (HO-1), catalysing heme degradation, in ectopic endometrium.

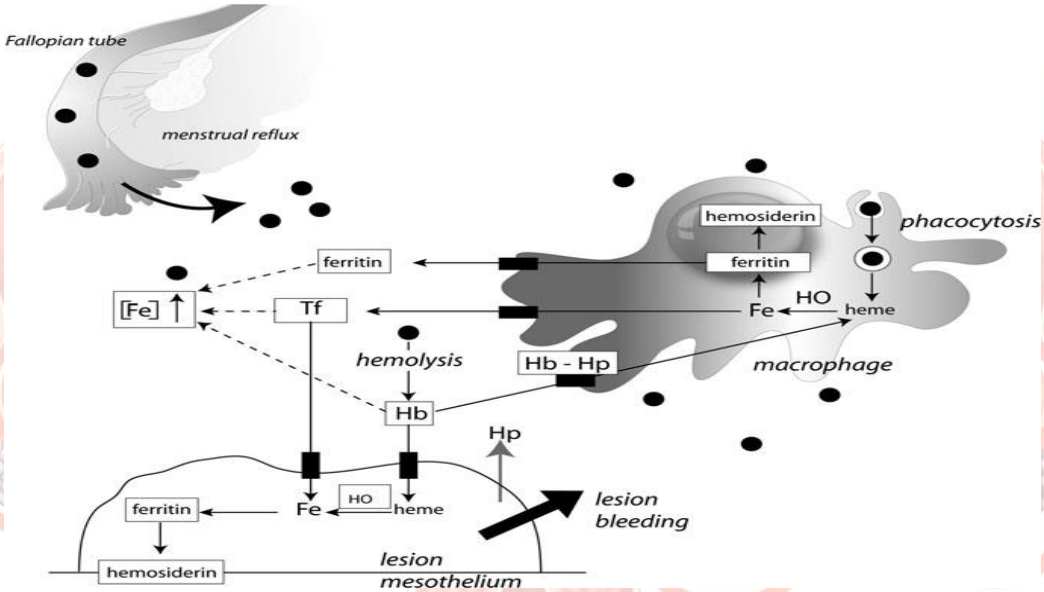
Peritoneal macrophages[1]

Iron metabolism by macrophages appears to be enhanced in the case of endometriosis due to presence of siderophages (iron-storing macrophages) heavily laden with hemosiderin inside the pelvic cavity. There is increased iron storage (ferritin load) in the peritoneal macrophages of endometriosis. Bilirubin pigment, a normal metabolite of Hb identified inside macrophages. Peritoneal macrophages were found to express more Tf receptors and to be Haptoglobin-saturated. Iron overload involves all the components of the peritoneal cavity in endometriosis patients. However, it is strongly localized and does not affect body iron content.

Endometriosis patients often experience longer and heavier menstrual periods resulting in anaemia.

Most cells protect themselves from iron toxicity by expressing inducible HO-1 and scavenger proteins, such as Hp and hemopexin, binding Hb and heme, respectively.

Origin of iron in pelvic cavity



Erythrocytes are carried into the pelvic cavity by retrograde menstruation and haemorrhaging foci of ectopic endometrium. They are phagocytosed by peritoneal macrophages. Metabolism of haemoglobin (Hb) by heme-oxygenase-1 (HO) releases iron. Macrophages store some iron in the form of ferritin or hemosiderin, and release some that binds to Tf. Macrophages are also able to release ferritin into peritoneal fluid, whereas lysis of erythrocytes releases haemoglobin into peritoneal fluid. Hb forms a complex with Hp, which is in part secreted by ectopic lesions. The Hb–Hp complex is then endocytosed by macrophages. Increased pelvic iron concentrations result from Tf, ferritin and Hb accumulation in peritoneal fluid. Tf and Hb may be assimilated by ectopic endometrial cells, resulting in the formation of iron deposits (ferritin or hemosiderin) inside lesions.

Effect of iron overload on endometriosis development

Iron, macrophages and oxidative stress[5,7,8]

Peritoneal macrophages are known to play an important role in the initiation, maintenance and progression of endometriotic lesions. They may demonstrate differences in phenotype, due to higher expression of oestrogen receptors-a and -b, differentiation markers (CD68, NCL-MACRO and HAM56) and inflammatory cytokines (interleukin-1b, tumour necrosis factor-a and IL-6). Activation of macrophages is an essential defence mechanism (acute inflammation), but in pathological conditions, such as endometriosis, their activation may become exacerbated and inflammation become chronic.

Continuous delivery of iron to macrophages, increases the capacity of ferritin to store and sequester the metal, causing oxidative injury to the cells.[7] Iron can act as a catalyst in the Fenton reaction to potentiate oxygen and nitrogen toxicity by the generation of a wide range of free radical species, including hydroxyl radicals, OH or the peroxynitrite anion.

Hydroxyl radicals react with amino-acid residues and purine and pyrimidine bases of DNA, as well as attacking membrane lipids to initiate a free radical chain reaction known as lipid peroxidation. Excessive release of ROS not only induces cellular damage, but may also alter cellular function by regulating protein activity and gene expression. Indeed, ROS play an essential role in the regulation of the transcriptional factor NF-kB which induces expression of multiple genes encoding pro-inflammatory cytokines, growth and angiogenic factors, adhesion molecules and inducible enzymes, nitric oxide synthase (iNOS) and cyclooxygenase (COX-2).[7] These induce endometrial fragment adhesion, proliferation and neovascularization.

HO-1 detoxification system[1,9]

Haemolysis releases Hb and free heme into peritoneal fluid. Heme is essential to the activity of a wide range of enzymes, including COX-2 and iNOS. In large amounts, it can become toxic by mediating oxidative stress and inflammation.

HO-1 is a heme-degrading enzyme strongly up-regulated by heme. HO protects cells from heme-induced oxidative stress by generating beneficial molecules like CO, bilirubin and ferritin.[9] HO-1 induction is accompanied by increased ferritin synthesis, scavenging of free iron and, subsequently, protection against the adverse effects of iron. Bilirubin is an important antioxidant, providing potent protection against oxidative injury and inflammation, whereas CO is a soluble gas acting as a signal molecule.

In the case of endometriosis, Hb concentrations were increased in the peritoneal fluid, and higher HO expression was observed in ectopic endometrium, especially in red lesions, compared with eutopic endometrial and mesothelial cells.

However, since inducible HO-1 was poorly expressed by macrophages and mesothelial cells, constituting the majority of cells in the peritoneal cavity, and because there was no concomitant increase in peritoneal fluid bilirubin, its final by-product, it strongly suggests that detoxifying systems, although present, might be insufficient to metabolize haemoglobin in the case of endometriosis. Accumulation of heme in the peritoneal cavity might induce oxidative stress, stimulation of cell adhesion and cytokine production by macrophages.

Effect of iron overload on endometrial tissue adhesion[11]

The mesothelial lining, like other epithelium, might serve as a barrier to prevent adhesion of menstrual endometrial fragments to the peritoneal lining. But, some studies have shown that endometrial cells can adhere to mesothelium. This may be because the mesothelium is a fragile membrane, which can be damaged by ectopic menstrual endometrium or inflammatory cells creating adhesion sites on its surface, facilitating the

development of endometriosis.[11] Oxidative stress was suggested to be responsible for local destruction of the peritoneal mesothelium, producing adhesion sites for ectopic endometrial cells.

Effect of iron on endometriotic lesion proliferation[2]

After implantation onto the mesothelium, proliferation of lesions promotes the further development of endometriosis. Proliferation of epithelial cells and their differentiation into glandular structures are key events, likely to be under the control of factors in the local environment. Mitogens produced by stromal cells, like hepatocyte growth factor and inflammatory cytokines present in peritoneal fluid, have shown to promote epithelial cell proliferation and ectopic endometrial cell growth. Iron could be one of the factors promoting further growth of implanted ectopic endometrial tissue.[3]

Effect of iron on endothelial cells[12]

Endometrial tissue implantation and subsequent growth require an adequate angiogenic response. Pro-oxidant iron has been shown to generate free radicals in endothelial cells and promote monocyte adhesion to these cells by inducing adhesion molecules such as intracellular adhesion molecule and vascular adhesion molecule.[12]

Involvement of iron in endometriosis-associated subfertility

Endometriosis and infertility are commonly associated. A decrease in acrosome reaction rates was associated with increased iron concentrations in peritoneal fluid. Excessive activation of macrophages is considered to be an etiological factor of infertility. Furthermore, iron ingested by peritoneal macrophages could be responsible for their increased spermiophagy and contribute to the subfertility observed in endometriosis.[13]

Iron chelators as endometriosis treatment[10]

Treatment with desferoxamine (DFO), a common iron chelator, has proved beneficial. Treatment with an iron chelator like DFO prevents iron overload in the pelvic cavity, thereby

diminishing its possible deleterious effects. Iron overload observed in these patients is generally localized in the pelvic cavity, whereas body iron content may actually be decreased due to abundant menstruation. For this reason, iron chelator treatment should be applied locally, only inside the peritoneal cavity, by means of intrapelvic implants that release DFO over several months or years.

Conclusion

In endometriosis patients, retrograde menstruation is often increased and may overwhelm peritoneal protective mechanisms, resulting in iron overload in all the components of the peritoneal cavity (peritoneal fluid, endometriotic lesions, peritoneum and macrophages).

Iron overload may affect a wide range of cell types, including endometrial cells (stromal and epithelial), mesothelial cells, endothelial cells and immune cells impairing their functionality and thereby contributing to the development of the disease.

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Chapter 12

GnRH Antagonist

Dr. T. Ramani Devi, MD, DGO, FICS, FICOG,

National Vice President FOGSI 2020

Governing council member ICOG 2018-20

Consultant Obstetrician and Gynecologist

Director Ramakrishna Medical Centre LLP

Director Janani Fertility Centre

Trichy

Dr. D. Gayathri, MBBS,

Junior Resident, Ramakrishna Medical Centre LLP

Trichy

Introduction:

Elagolix is an oral non-steroidal gonadotropin releasing hormone (GnRH) antagonists that decreases estrogen production and is used to treat endometriosis associated pelvic pain.

History:

First described in literature in the year 2005.

In June 2010, Neurocrine bioscience and Abbott announced a global agreement to develop Elagolix for treatment of endometriosis. In November 2016, the medication completed phase III clinical trials for endometriosis. In September 2017, Abbvie filed a New Drug Application (NDA) for Elagolix for treatment endometriosis associated pelvic pain associated with endometriosis in USA. In 23rd July 2018, FDA approved Elagolix for the treatment of endometriosis associated pelvic pain.

Elagolix is the first and currently only member of a new class of GnRH modulators described as "second generation" non-peptide orally acting drug which offers advantages over currently available injectable peptide-based treatments.

Pharmacodynamics

Elagolix acts as potent and selective competitive antagonists of GnRH receptor.

It blocks GnRH receptor in the pituitary gland and suppresses GnRH induced secretions of LH, FSH from anterior pituitary, thereby reducing the production and circulating levels of sex hormone by the gonads.

Elagolix has the ability to suppress Estradiol (E2) concentrations in a dose- dependent manner. It suppresses estrogen production and levels there by decreasing endometrial growth which leads to decrease in endometriotic symptoms like chronic pelvic pain.

Elagolix is a short acting GnRH antagonist with a half-life of 4 – 6 hours. Because of short half-life of Elagolix in the body, the deactivation of GnRH receptors by GnRH is not fully blocked throughout the day, with once daily administration. As a result, gonadotropin and sex hormones are only partially suppressed when drug is taken once per day.

In addition, the degree of suppression can be dose dependently adjusted as needed. Because of its short duration in body, effects of Elagolix are rapidly reversible upon discontinuation.

Also due to its partial and incomplete suppression of estradiol levels, symptoms such as hot flushes, decreased BMD are all lower than with 1st generation GnRH modulators.

Median levels of estradiol were partially suppressed to 42pg/mL (Follicular phase) with 150mg once daily and fully suppressed to 12pg/mL (Postmenopausal levels) with 200mg twice daily.

In a 21-day study in premenopausal women, the effects of Elagolix on FSH levels were found to lie maximal at a dosage of 300mg twice a day and above, whereas its effects on LH and estradiol levels were maximal at a dosage of 200mg twice a day and above.

Progesterone levels were maintained at anovulatory levels (<2mg/mL) across the 21-day study period at dosages of 100mg twice a day and above.

A dosage of 400mg twice a day appears to produce no greater suppression in gonadotropins or estradiol levels, than a dosage of 300mg twice a day in pre-menopausal women.

Suppression of gonadotropin and sex hormone levels with Elagolix occurs rapidly within hours and upon discontinuation of Elagolix, gonadotropin, sex hormone levels remain suppressed for at least 12 hours, but slow recovery within 24 to 48 hours.[1,2] By the virtue of

its suppression of gonadotropin and sex hormone levels, Elagolix inhibits ovulation. Over the course of 3 menstrual cycles, ovulation returns at 50% with a dosage of 150mg once daily and 32% at 200mg twice daily.

Because ovulation is triggered by a surge in estradiol levels at mid cycle, estrogen exposure during Elagolix therapy might be greater around this time in some women.

In addition to its activity as GnRH antagonists, Elagolix is a weak to moderate inducer of CYP3A and an inhibitor of P- glycoprotein.

Pharmacokinetics:

Animal research shows oral bio availability of 5.8% in rats, 11% in monkeys.[3]

Elagolix is orally rapidly absorbed with peak concentration occurring after 0.5 to 1.5 hours.

Drug accumulations ratio is 0.98 at 150mg once a day and 0.89 at 200mg twice a day.

This indicates the drug is not accumulated in the body with continuous administration.

Taking this drug with a high fat meal has found to decreases its peak levels by 36%.

The drug is metabolized in the liver with major pathway being CYP3A and minor pathway CYP2D6, CYP2C8 and UDP glucuronosyl transferase.

Pharmacokinetics of Elagolix were unaffected by body weight and body mass index. Drug exposure is not affected by renal impairment or mild hepatic impairment, but is increased by 3-fold in women with moderate hepatic impairment and by 7-fold in women with severe hepatic impairment.

Medical uses:

1. It is indicated in management of moderate to severe pain associated with endometriosis in premenopausal women. It significantly decreases dysmenorrhea, non-menstrual pelvic pain and dyspareunia.
2. Other off label uses includes uterine fibroids, breast cancer in men, precocious puberty in children, hormone therapy in transgender and adults.
3. It is in phase III clinical trials for usage in treatment of uterine fibroids.[4]

Contraindications:

1. Contraindicated in women who are pregnant (Due to risk of early pregnancy loss).
2. In women with osteoporosis (Due to risk of bone loss) and severe hepatic impairment
3. In patients taking strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g.: cyclosporine and statins)

Warning and precautions:

1. **Bone loss:** Causes dose-dependent decrease in BMD which is greater with increasing duration of use and may not be completely reversible after stopping treatment. Limit the duration of use to reduce the extent of bone loss.
2. **Abnormal menstrual pattern:** Women taking Elagolix experience a change in menstrual bleeding pattern which includes decrease in intensity and duration of bleeding and hence reduced ability to recognize pregnancy. Perform pregnancy testing if pregnancy is suspected and discontinue Elagolix if pregnancy is confirmed.
3. **Mood changes:** Suicidal ideation, mood changes, depression has occurred in subjects treated with Elagolix in endometriosis clinical trials.
4. **Hepatic transaminase elevations:** In clinical trials, dose dependent elevation of serum ALT at least 3 times the upper limit of reference range occurred with Elagolix. Use the lowest effective dose and instruct patients to promptly seek medical attention

in cases of symptoms and signs that may reflect liver injury such as jaundice. Low dose regimen is recommended for women with moderate liver dysfunction (Child – Pugh class B cirrhosis) and Elagolix is contraindicated in patients with advance cirrhosis.

5. **Reduced efficacy with estrogen containing contraceptives**: Based on mechanism of action, estrogen containing contraceptives are expected to reduce efficacy of Elagolix. The effect of Progesterone Only Pills (POP's) on Elagolix is unknown. So advice women to use non-hormonal contraceptives during treatment and for one week after discontinuing Elagolix.
6. **Supplementation of Calcium and Vitamin D3:** Concomitant use of Calcium and Vitamin D3 along with Elagolix may help to strengthen the bone.

Common side effects:

Side effects	Low dose (%) (150mg/ day)	High dose (200mg/day)
Hot flushes, night sweats	**24**	**46**
Amenorrhea	**4 – 17**	**7 – 57**
Headache	**17**	**20**
Nausea	**11**	**16**
Insomnia	**6**	**9**
Mood swings	**6**	**5**
Depressive symptoms	**3**	**6**

Safety and effectiveness in patient < 18 years is not established.

Elagolix is not contraindicated in breast feeding mothers, but it's unknown whether it is excreted in the breast milk or it has adverse effects upon lactation and breast fed newborn. So, the use has to be considered carefully weighing both benefits and risks.

Conclusion:

Elagolix is a short acting non-peptide GnRH antagonist which rapidly suppresses pituitary ovarian hormones. It produces a dose dependent suppression of ovarian estrogen production that varies from partial to full suppression, depending on the frequency and dose given.

Elagolix does not result in an initial increase in symptoms like the flare effect of GnRH agonists. More over GnRH agonists has to be administered either intra nasally or by injection, whereas Elagolix is an oral medication. In this way Elagolix scores over GnRH agonists.

Available dose:

1. Typical doses 150mg once daily for up to 24 months (Low dose therapy). This is prescribed for endometriosis condition alone.
2. 200mg twice daily for 6 months (High dose therapy). If patients are to be treated for endometriosis and dyspareunia.

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