FOGSI FOCUS on
ENDOMETRIOSIS AND ADENOMYOSIS
NEWER UPDATES

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Dedicated to

The courageous women who battle against endometriosis and treating fellow doctors.
May this book bring awareness, comfort, and hope.

President's Message

Dear Fogsians,

It gives me immense pleasure to present to you this FOGSI FOCUS on Endometriosis and Adenomyosis. Endometriosis affects 1 in 10 women worldwide and has devastating effects on the sufferers.

This handbook is a crisp compilation of chapters on clinically relevant topics by stalwarts in this field from across the country. These chapters are therefore rich with the recent evidence and a vast experiences of the author, hence full of practical tips and points which the readers will find beneficial.

FOGSI has forever played a vital role in spreading the knowledge both among doctors and patients. This year my FOGSI slogan is Swasthya Nari, Sukhi Nari. My CSR activity is defined as BADLAAV (Change) including three arms- Ekikaran (integration of thought and action), Samanta (equality of treatment irrespective of economic status) and Takniki (technology to achieve these objectives). These focuses are a step towards my goal of improving women's health in our country, by providing updated information about the relevant topics in women care.

I congratulate Dr Asha Rao and Dr Anu Chawla for their sincere efforts to write, collate, edit and publish this focus.

I sincerely hope that this book will benefit and empower all the FOGSIANS.

Wish you all a Happy Reading.

Hrishikesh D Pai
President, FOGSI (2022-2023)

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Preface

Endometriosis is a chronic and often debilitating condition that affects millions of people worldwide. Despite affecting an estimated 10% of women of reproductive age, endometriosis is often underdiagnosed and undertreated, leaving many sufferers to suffer in silence.

This book aims to shed light on endometriosis providing with the latest research and medical information; will help readers understand better, the complexities of endometriosis and how to manage it effectively.

A new twist .....the tale of Adenomyosis, it's diagnosis by user friendly ultrasound and current approaches to optimize reproductive outcomes in Adenomyosis has also been discussed.

Editors

Asha R Rao
Anu Chawla

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We would like to express our deep gratitude to our co-authors for their invaluable contributions to the creation of this book. Their insights, expertise, and dedication have been instrumental in shaping this work into its final form.

Together, we overcame many challenges and worked through countless revisions to produce the **FOGSI FOCUS on Endometriosis and Adenomyosis - Newer Updates**.

We sincerely thank the team of Evangel Publishing Pvt Ltd, New Delhi, India and other professionals who supported us throughout this journey.

Finally, we would like to thank FOGSI, for all the encouragement and support.

Asha R Rao
Anu Chawla

Contents

Chapter 1

What is New in the Management of Endometriosis?

Hrishikesh D Pai,
Anu Chawla

INTRODUCTION

In 2022, the European Society of Human Reproduction and Embryology (ESHRE) guidelines have updated the Guidelines on the Management of Endometriosis and some points potentially influence the practice. There were 35 PICO Questions - (patients, interventions, comparison, outcome), 7 Questions in the narrative form, 109 Research Recommendations/Good Clinical Practice points, and 30 Research Recommendations. Based on these guidelines as well as other Updated Newer Literature, it is worth noting that according to the ESHRE guidelines, the Degree of Recommendation may not necessarily correlate with the level or quality of evidence.

IMAGING MODALITIES

Laparoscopy is not a recommended Diagnostic Gold Standard any longer. It is only recommended in cases with imaging results as negative, in situations when an empirical treatment has been not successful or not appropriate.

When we use imaging modalities in the diagnosis for endometriosis, a negative outcome does not exclude endometriosis, especially not at least a possibility of a superficial peritoneal disease.

FERTILITY MANAGEMENT OF ENDOMETRIOSIS PATIENTS

The extended administration of gonadotropin-releasing hormone (GnRH) agonist prior to in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment.

Secondly, it is stressed in this guideline that it is probably going to affect the Fertility Management of Endometriosis patients. Prolonged use of GnRH Agonist right before IVF/ICSI treatment, to improve Live Birth Rates, especially in the form of Ultra-long protocol is not recommended anymore, because of the yet unclear benefits.

ENDOMETRIOSIS FERTILITY INDEX

Although it is not still largely adopted in practice to fill the endometriosis fertility index (EFI) sheet and hand it over to the patient after her surgery for endometriosis, especially when the surgeon and the Fertility Clinician are not the same Treating Doctor of the patient, but this point is stressed that EFI, first described by Adamson et al. in 2010, was included as an additional step in the treatment as it can possibly help in the decision making and choosing a reasonable option to enhance the pregnancy rates after the surgery.

TREATMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN

Studies on GnRH antagonist treatments support their use as an additional (second line) treatment option.

The use of medical treatment after the surgery, could be of benefit towards pain management. Also, it has a place, tobe offeredto women who do not plan an immediate pregnancy.

It is recommended to offer the following modalities as hormone treatment as one of the options to reduce endometriosis-associated pain:

- Combined hormonal contraceptives
- Progestogens
- GnRH agonists or GnRH antagonists.

To reduce endometriosis-associated dyspareunia, dysmenorrhea, and nonmenstrualpain.

It is recommended in the updated ESHRE Guidelines,women can be prescribed a combined hormonal contraceptive modalities (oral/vaginal ring / transdermal).

For cases with complaints of endometriosis-associated pain, women can be prescribed levonorgestrel-releasing intrauterine system (LNG-IUS) or an etonogestrel-releasing implants.

It is also recommended to prescribe women GnRH agonists to reduce endometriosis-associated pain, although evidence is limited regarding dosage or duration of treatment.

REFRACTORY PAIN

Pain that is refractory to medical/surgical treatment, it is recommended to prescribe aromatase inhibitors, as they reduce endometriosis-associated pain.

Aromatase inhibitors can possibly be combined with oral contraceptives orprogestogens or GnRH agonists/GnRH antagonists.

SURGERYTO REDUCE ENDOMETRIOSIS-ASSOCIATED PAIN

Surgery is surely, an option to reduce endometriosis-associated pain; however, of note is that, it is not advisable to prescribe preoperative hormone treatment to improve the immediate outcome of surgery for pain.

It is of note that the following modalities are not anymore included in guidance, but still mentioned in the text:

- Danazol
- Anti-progestogens
- Laparoscopic uterosacral nerve ablation (LUNA) and presacral neurectomy (PSN)
- Anti-adhesion agents
- Biomarkers: It has been stressed as a Strong Guidance to not use biomarkers in endometrial to diagnose endometriosis.

Ovarian suppression treatment to improve fertility- significantly so, in subfertile women with endometriosis, clinicians should not prescribe ovarian suppression treatment to improve fertility.

Also, subfertile patients planning apregnancy, should not be prescribed postoperative hormone suppression with the only aim to increase pregnancy rates.

SURGERY PRIOR TO ASSISTED REPRODUCTIVE TECHNOLOGY

It is not a guidance, to plan surgery prior to assisted reproductive technology (ART) to improve live birth rates in women with revised American Society for Reproductive Medicine (rASRM) stage I/II endometriosis, as the benefits are still not clear.

Also, it is not advisable to routinely perform surgery for ovarian endometrioma prior to ART with an aim to improve live birth rates, as the evidence shows no benefits yet.

Surgery is likely to have rather a counter productive impact on ovarian reserve. Let us not forget to talk about fertility preservation!

FERTILITY PRESERVATION WITH WOMEN WITH ENDOMETRIOSIS

In case of ovarian endometriosis, it is of prudence to discuss the pros and cons of fertility preservation with women with endometriosis. The true evidence-based data about the benefit of fertility preservation in women with endometriosis remains unknown.

It can be cultural, but of grave importance that clinicians are aware that they avoid making advise to a patient to achieve pregnancy with the only purpose of treating endometriosis, as pregnancy does not necessarily lead to improvement of symptoms or even the reduction of disease progression, and that it is her personal and social decision, which has a lot to do with herself and her support system.

EARLY PREGNANCY LOSS IN ENDOMETRIOSIS

Clinicians should be aware that there may be an increased risk of first trimester miscarriage and ectopic pregnancy in women with endometriosis.

ENDOMETRIOSIS RECURRENCE

Any hormone treatment or surgery can be offered to treat recurring pain symptoms in women with endometriosis as a weaker recommendation.

Clinicians should reassure women with endometriosis regarding the risk or probability of developing a malignancy associated with the use of hormonal contraceptives.

POOR RESPONDER ENDOMETRIOSIS PATIENT

OC Pills increase the total number of days of stimulation as well as the total dose required – hence not the best Pre-IVF treatment for such patients.

The observation of postoperative decrease in anti-mullerian hormone (AMH) may be due to inadvertent removal of ovarian tissue or destruction of follicles from excessive use of electrosurgery. The amount of tissue removed increases with:

- endometrioma dimension
- use of preoperative suppressive therapy, and perhaps surgeon experience.

Techniques to alleviate the risk of injury:

- Minimal or no usage of instruments of electrosurgery
- Achieving hemostasis
- Use of hemostatic agents or suture.

If Pre-IVF, OC pills are combined with Agonist trigger, it might fail, due to a low endogenous LH. Dual stimulation is not a very attractive option with the practical evidence gathered so far but still under review.

GAINING FOCUS ON EUPLOID BLASTOCYST

There has been a few papers in the literature, recently by Paul Pirtea, in which the author has brought the focus on the fact that as long as a Euploid Blastocyst is transferred in a woman, all other perils of Endometriosis can be bypassed in the best possible way; however, it is too early to accept this hypothesis till the required evidence is gathered.

INDICATIONS FOR PRE-IVF SURGERY

It is of note that according to both ASRM and ESHRE Recommendations, the only indications for pre-IVF surgery are:

- Severe pelvic pain and/or
- To improve access to follicles (cut off ≥ 4 cm).

ADD-ONS /INTERVENTIONS FOR POOR RESPONDERS

There is not much evidence to favorany specific add-on however, Adjuvant androgens (DHEA or testosterone) and Adjuvant growth hormone - are the two

modalities gaining evidence in carefully selected patient population as they may improve live birth or ongoing pregnancy rates.

Excision is advised as preferred modality over ablation. Another new addition is, there are some flow algorithms included, which are suggested to be a part of the local standard of procedure (SOP) in our practice.

Ovaries need not be removed in all cases, along with uterus, in cases where hysterectomy is selected as the treatment modality.

Progesterone should be a part of HRT in cases of menopause hormone replacement therapies, and not just estrogen, in cases where uterus is present.

Ovarian, breast, and thyroid cancers are at an increased risk in cases of endometriosis; however, the overall risk still remains small. There is no evidence of screening for cancers in these cases unless a significant personal or family history is present.

Conclusion

Endometriosis, is still, not fully understood and the evolving understanding of this disease makes it important for us to follow evidence, in our practice. The social aspect is also a crucial element in this pathology. It is common that patients are sometimes told that it is all in their minds, and this delays the diagnosis by an average of 8 years. One important take home message would be, many times, it is not in their minds, but in their pelvis.

Suggested Reading

1. Andres MP, Arcoverde FVL, Souza CCC, et al. Extrapelvicendometriosis: a systematic review. J Minim Invasive Gynecol. 2020;27(2):373-89.
2. Chamie LP, Ribeiro DMFR, Tiferes DA, et al. Atypical Sites of Deeply Infiltrative Endometriosis: Clinical Characteristics and Imaging Findings. Radiographics. 2018;38(1):309-28.
3. ESHRE Guidelines for Endometriosis 2021.
4. Gidwaney R, Badler RL, Yam BL, et al. Endometriosis of abdominal and pelvic wall scars: multimodality imaging findings, pathologic correlation, and radiologic mimics. Radiographics. 2012;32(7):2031-43.
5. Hirata T, Koga K, Kitade M, et al. A National Survey of Umbilical Endometriosis in Japan. J Minim Invasive Gynecol. 2020;27(1):80-7.
6. Horton JD, Dezee KJ, Ahnfeldt EP, et al. Abdominal wall endometriosis: a surgeon's perspective and review of 445 cases. Am J Surg. 2008;196(2):207-12.
7. Johnson MM. Catamenial pneumothorax and other thoracic manifestations of endometriosis. Clin Chest Med. 2004;25(2):311- 9.
8. Joseph J, Sahn SA. Thoracic endometriosis syndrome: new observations from an analysis of 110 cases. Am J Med. 1996;100(2):164-170.
9. Rousset P, Rousset-Jablonski C, Alifano M, et al. Thoracic endometriosis syndrome: CT and MRI features. Clin Radiol. 2014;69(3):323-30.
10. Yarmish G, Sala E, Goldman D, et al. Abdominal wall endometriosis: differentiation from other masses using CT features. AbdomRadiol (NY). 2017;42(5):1517-23.

Chapter 2

Newer Concepts in the Understanding of Etiopathogenesis of Endometriosis

Manju Khemani

INTRODUCTION

The incidence of endometriosis is very high. Endometriosis is estimated to affect 10% of reproductive-age women.[1] Its treatment is symptomatic; currently, there is no known cure for it. Chronic pain and infertility caused by the disease have a high social and economic impact. The pathogenesis of endometriosis is still not fully defined. There are various theories to explain its etiology; no single theory can explain all the lesions. Endometriosis can have different presentations ranging from superficial peritoneal lesions of varying color, endometrioma, and deep endometriosis, often accompanied by fibrosis and adhesions, to extrapelvic lesions.[1] There are various theories to explain the etiology of endometriosis and the most accepted theories are retrograde menstruation, hematogenous or lymphatic spread, celomic metaplasia, and extrauterine-sourced stem cells.

RETROGRADE MENSTRUATION

Retrograde menstruation theory was proposed by Simpson one century ago. The observation that endometriosis is more commonly seen in women with outflow obstruction and retrograde menstruation is commonly seen in a high percentage of women supports this theory.[2,3] This theory can explain superficial endometriosis, endometrioma, and fallopian tube lesion, but cannot explain deep endometriosis and lesions in adolescents and women suffering from Rokitansky–Kustner-Hauser syndrome. It has been suggested that endometrial cells in retrograde menstruation enter the ruptured corpus luteum and are trapped in it. These cells get blood supply from it and the estrogen environment helps them to grow and form an endometriotic cyst.[2] Retrograde menstruation is observed in up to 90% of women, but endometriosis is not so common; so, there must be additional factors, such as genetic predisposition, environmental toxins, hormonal factors, and immune dysfunctions, to cause this aberrant ectopic growth of endometrial tissue.[3]

HEMATOGENOUS/LYMPHATIC SPREAD THEORY

Point to ponder here is that can menstrual endometrium containing both epithelium and stromal cells pass through the angiolymphatic circulation without disruption and that it is still able to undergo extravasation from the vessels in order to be located within the muscular layers of organs and grow.[3]

CELOMIC METAPLASIA THEORY

Celomic metaplasia theory was described by Gruenwald in 1942.[4] This theory explains that celomic walls (peritoneal serosa or serosa-like structures) are embryologically related to Müllerian ducts; hence, because of metaplasia, endometriosis can develop in all celomic wall derivatives. All those cases which cannot be explained by retrograde menstruation can be explained by this theory.[5]

STEM CELL RECRUITMENT THEORY

Stem cell recruitment theory has gained popularity and acceptance in the recent years. Stem cells are undifferentiated cells and have the capability of converting in any type of daughter cells.[5] Deeply infiltrating endometriosis (DIE) and endometriosis outside the abdominal cavity both can be explained by this theory. According to this theory, stem cells of endometrial origin may gain entry into the angiolymphatic space during menstruation and, thus, enter into the circulation system to find a suitable environment for them to grow.[2] It also fits the retrograde menstruation model.

The origin of stem cells could be uterine endometrium or bone marrow. In the uterus, there are two kinds of stem cells.

Epithelial Stem Cells

Epithelial stem cells are supposed to be present in the basalis layer of the endometrium near the functional layer; and, hence, are protected from regular menstruation. These stem cells could be responsible for the regeneration of the epithelium of the functional layer during the proliferative phase in response to estrogen. Unfortunately, no specific markers have been isolated for these epithelial stem cells.[5]

Endometrial Mesenchymal Stem Cells

Endometrial mesenchymal stem cells are present in the perivascular area of both the basalis and functionalis and are responsible for generating functionalis stroma. Specific marker for mesenchymal stem cells is molecular markers, such as CD146, and these stem cells can be isolated from endometrial biopsy by this marker.[5] So far, scientists have not been able to find any direct evidence that endometrial stem cells are involved in the pathogenesis of endometriosis.

Bone Marrow Stem Cells

During menstruation and the proliferative phase, many bone marrow-derived stem cells increase in circulation and help in the regeneration of epithelium and stroma of endometrium. According to this theory, if bone marrow-derived stem cells instead of going to endometrium go into other soft tissue, then endometriosis can develop.[2]

Recently, by using next-generation sequencing techniques, somatic mutation analyses of DIE, endometrioma, and eutopic normal endometrium have been done and redefined the stem cell theory. It is now suggested that stem/progenitor cells of at least two different origins, epithelium and stroma, contribute to the creation of endometriosis.[6]

EMBRYOGENETIC THEORY

Signorile PG proposed this theory based on his work suggesting the persistence of residual embryonic cells of Wolffian or Müllerian ducts during embryogenesis which may develop later into endometriotic lesions in response to estrogen.[7] In a critical period, during embryogenesis, relocation of the Müllerian ducts could cause the spread of primordial endometrial cells in their migratory pathway across the posterior pelvic floor.[5] These embryonic rest cells remain dormant till puberty and under the influence of estrogen later can differentiate in endometriosis. This theory can explain DIE. This theory can also explain endometriosis in patients with Rokitansky–Kustner-Hauser syndrome and in adolescents before menarche.

Signorile PG by doing an autopsy on female fetuses has shown the presence of ectopic endometrial cells.[8] These ectopic endometrial cells were confirmed by histological and immunohistochemical studies.[9] The data from their study clearly demonstrate ectopic endometrium is located outside the uterine cavity during the earlier steps of organogenesis and this has been proven by the histological and immunohistochemical analysis.[5] The pouch of Douglas, the rectovaginal septum, the mesenchymal tissue close to the posterior wall of the uterus, the rectal tube at the level of muscularis propria, and the wall of the uterus were the anatomical sites of these ectopic endometrial structures. All these anatomical locations are very well-known sites for endometriosis in women.[5]

These findings have also been confirmed by the work of De Jolinière et al. They confirmed that epithelial components of these ectopic endometrial glands showed positive staining for estrogen and progesterone receptors.[8]

IS ENDOMETRIOSIS AN EPIGENETIC DISEASE?

Women having first-degree relatives with severe endometriosis are six times more likely to have endometriosis as compared with those with unaffected relatives.[3] But still, it has not been proven that it is a genetic disease. Three meta-analyses have failed to show that endometriosis is a genetic disease. There is a

subtle but distinct difference between hereditary and genetic 'disease concepts.' Since protein/enzyme aberrations that characterize the disease are ultimately governed by gene expression; so, one can say that at the molecular level, almost all diseases are genetic. Still, a disease that is genetic is not necessarily hereditary. On the other hand, a disease that is hereditary may not be entirely genetic.[3]

Epigenetics refers to the stable inheritance of phenotypes of cells and organisms without changes in deoxyribonucleic acid (DNA) base sequence or DNA content (Greer and McCombe, 2012).[3] Epigenetic means modifications that are induced developmentally or environmentally but that do not alter the genetic code but instead control how information encoded in DNA is expressed in a tissue context-specific manner (Ivashkiv, 2013).[3] So, through epigenetic aberrations, some apparently hereditary traits may result without any change in DNA sequences. This may happen with transgenerational epigenetic transmission (Di and Guo, 2007).

It is believed that endometriosis could be an epigenetic disease. Ultraviolet light radiation, pathogens, toxic agents, steroid hormones, oxidative stress, air pollutants, and some unknown factors can disrupt epigenetic regulations.[3] The following are the evidences that endometriosis could be an epigenetic disease:

- There is a difference in the putative promoter of (HOXA10) gene in the endometrium of women without endometriosis as compared to women with endometriosis. The putative promoter of (HOXA10) gene is hypermethylated in endometriosis (Fambrini et al., 2013).[3]
- We all know that there is progesterone resistance in women with endometriosis.[3] This is because the promoter of progesterone receptor-B (PR-B) is hypermethylated in endometriosis (Wu et al., 2006).
- In endometriosis, three genes coding for DNA methyltransferases (DNMTs) which are involved in genomic DNA methylation, are all overexpressed (Wu et al., 2007).
- In normal endometrial stromal cells, steroidogenic factor-1 (SF-1) which is essential for the biosynthesis of estrogen is undetectable. We all know that endometriosis is an estrogen-dependent disease. In endometriotic cells, both SF-1 factor and estrogen receptor-beta (ER ß) promoter are hypomethylated. This accounts for its overexpression in endometriosis.[3]
- In epithelial tumor cells, protein E-cadherin is a known metastasis-suppressor protein. E-cadherin is hypermethylated in endometriosis and its deregulation also seems to be associated with the invasiveness of endometriotic cells. Endometriotic cells lack the protein E-cadherin. This explains why they behave like cancer cells.[3]
- MicroRNAs (miRNAs) play a key role in altering innate and adaptive immune responses and they also respond to steroid hormones. Many miRNAs have been identified which play a key role in the epigenetics of endometriosis.[3]

In the pathogenesis of endometriosis, two important factors are dysregulation of immunological and hormonal factors leading to increased immune tolerance, hyperestrogenism, and progesterone resistance. The common denominator in both these is epigenetic changes. So, one can say that the main factor in activating the etiopathogenetic mechanisms for endometriosis development may be epigenetic alterations.[3]

MOLECULAR GENETIC CHANGES IN ENDOMETRIOSIS

In 2017, Anglesio et al., in their study in which by next-generation sequencing showed that 83% of benign DIE lesions contained somatic mutations. A total of 26% harbored cancer driver mutations, including in *KRAS*, *PIK3CA*, *ARID1A*, and *PPP2R1A*, all of which were confined to the epithelium.[2] This unexpected observation prompts new avenues of investigation in the pathogenesis of endometriosis and may in the future tell us about prognostication.

Pathogenesis and Pathophysiology

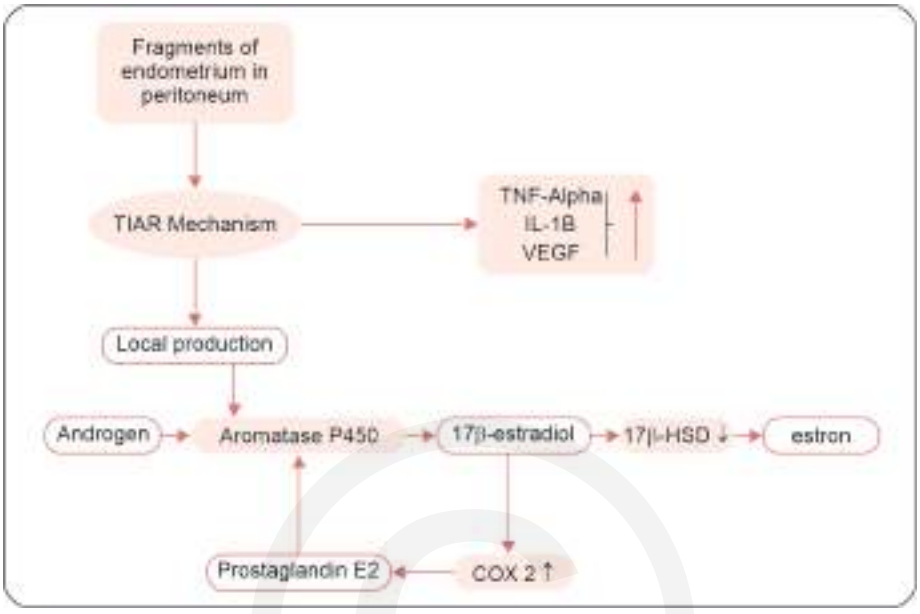
For the development of endometriosis, the involvement and interaction of endocrine, proinflammatory, immunologic, and proangiogenesis processes are required.[1] Whether these are causative factors or features of pathophysiology detected years after the symptoms of the disease are present is still unknown.

So, explained simply, the potential origin of endometriosis may be via retrograde menstruation, celomic metaplasia, or vascular and lymphatic dissemination. Once deposited, these endometriotic cells are deposited in ectopic locations and for further development needs several factors. Development and maintenance of superficial and deep endometriosis require interacting molecular mechanisms which will promote cellular adhesion and proliferation, systemic and localized steroidogenesis, immune dysregulation, localized inflammatory response, and neovascularization and innervation.[1]

Retrograde menstruation is common, but every patient does not develop endometriosis. So, patients with endometriosis must be having some other factors for these cells to get adherent to the peritoneal surface, to proliferate, and to grow. Eutopic endometrium contains stem cells and if these are shed in retrograde menstruation, these may play a role in the development of the endometriotic lesion. In women who have endometriosis, their stromal cells in the endometrium have altered integrin profiles; and, hence, endometrium shows adhesive capacity.[10] Cellular adhesion in endometriosis is due to localized inflammatory response.

Endometriosis is an estrogen-dependent chronic inflammatory disease and its proliferation requires systemic estrogen. Endometriotic lesions produce local estrogen for their growth and for the same, they have increased expression of aromatase and steroidogenic acute regulatory protein. 17β-hydroxysteroid

Flowchart 1: Diagrammatic representation of pathogenesis of endometriosis



Abbreviations: 17B-HSD, 17beta-hydroxysteroid dehydrogenase; COX-2, cyclooxygenase-2; IL-1B, interleukin-1 beta; TIAR, tissue injury and repair; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor

dehydrogenase type 2 converts E2→E1 and testosterone to androstenedione in the endometrium. The expression of 17β-hydroxysteroid dehydrogenase 2 is decreased in endometriotic lesions. Estrogen receptor β, shows increased expression in the endometriotic lesion **(Flowchart 1)**.[11] This has been shown to promote lesion growth by the following mechanisms:

- Inhibiting apoptosis induced by tumor necrosis factor α (TNF-α),
- Increasing interleukin-1β levels,
- Increasing cellular adhesion.[1]

It is known that there is progesterone resistance in endometriosis. Suppression of the progesterone receptor is seen in both eutopic and ectopic endometrium of patients with endometriosis. Progesterone resistance is enhanced in ectopic endometrial cells by epigenetic differential methylation of PR-B.[1] Thus, endometrial decidualization is dysregulated; decidualization is the process by which the endometrial lining prepares for pregnancy.

A localized immune and inflammatory response is elicited by endometriotic lesions.[1] In the secretory phase, the macrophages increase in number in normal endometrium. The physiological role of these macrophages is the clearance of cell debris over the course of the menstrual period. In endometriosis patients, this increase in macrophage number does not happen in eutopic endometrium,

but a global augmentation (hormonal cycle-independent) of macrophages (in particular of M1 macrophages) has been observed, as compared to the endometrium of non-endometriosis women. A high number of angiogenesis-supportive M2 macrophages are found in the ectopic tissue in endometriotic lesions. Compared to healthy women, in women with endometriosis M2 macrophages is present in lesions, peritoneal cavities, and peritoneal fluid. Blood monocytes once differentiated into tissue macrophages increase the proliferation of endometrial cells isolated from women affected by EM, whereas monocytes derived from healthy women inhibit endometrial cell proliferation.[12]

In patients with endometriosis, natural killer cell activity is decreased. Decreased natural killer cell activity leads to immune evasion of endometrial cells. In endometriosis, dysfunction of the immune system is seen, but it is not known whether this initiates endometriosis or is only a pathophysiological hallmark of the disease.

In patients with endometriosis, the following changes are seen:

- Decreased phagocytic capacity of macrophages in the peritoneal cavity
- Increased activation of proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6)
- Increased activity of proangiogenic factors (vascular endothelial growth factor)
- Increased activity of growth factors and adhesion molecules.[1]

Type 17 helper T-cell concentrations are increased in the peritoneal fluid of women with endometriosis which results in increased interleukin-17 expression and promotes chronic inflammation.[1] In endometriotic lesions, compared with eutopic endometrium, several key inflammatory mediators, including cyclooxygenase-2 (COX-2), IL-1β, IL-8, TNF-α, prostaglandin E2 (PGE2), and E2, are elevated and these factors promote chronic inflammation.[2] In contrast to normal endometrium, uterine endometrium from women with endometriosis exhibits increased levels of COX-2 expression, and the endometriotic tissue has even higher COX-2 levels. Elevated PGE2 levels in endometriotic stromal cells induce the production of E2, and this, in turn, promotes local inflammation. A positive feedback loop is created between excessive E2 and PGE2 which, in turn, promotes persistent inflammation, immune responses, angiogenesis, and survival of endometriotic tissue.[2]

Inflammatory mediators stimulate nerve fibers which are present in endometrium and endometriosis. There is central sensitization which is the heightened responsiveness of nociceptive neurons to normal or subthreshold afferent input. This is due to the ascending nociceptive signals received in the central nervous system constantly.[1] There may be poor postsurgical pain relief in many affected women because of cross-organ sensitization (pain perception from adjacent structures due to the convergence of neural pathways).

Conclusion

In spite of so much research, we still do not know how endometriosis develops and it is still a disease of theories. As there is not enough evidence that it could be a genetic disease stem cell theory and theory of fetal origin or embryonic theory has joined the bandwagon of its origin. It could be an epigenetic disease and there is microRNA alteration in endometriosis. Though the origin of endometriosis may not be very clear, its pathogenesis and mechanism of infertility are clearer now. There is higher estrogen receptor (ER)β levels, and enhanced ERβ activity and this stimulates the growth of endometriosis and adhesion and proliferation properties. ERβ overexpression could increase endometriosis-associated infertility by preventing the decidualization response. There is also progesterone resistance. More research in its origin may help in early diagnosis and individualized treatment of this disease in different patients.

References

1. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med. 2020;382(13):1244-56.
2. Wang Y, Nicholes K, Shih L-M. The origin and pathogenesis of endometriosis. Annu Rev Pathol. 2020;15:71-95.
3. A Kokcu. A current view of the role of epigenetic changes in the aetiopathogenesis of endometriosis. J Obstet Gynaecol. 2016;36(2):153-9.
4. Gruenwald P. Origin of endometriosis from the mesenchyme of the celomic walls. Am J Obstet Gynecol. 1942;44(3):470-4.
5. Signorile PG, Viceconte R, Baldi A. New insights in pathogenesis of endometriosis. Front Med (Lausanne). 2022;9:879015.
6. Maruyama T. Revised stem cell theory for the pathogenesis of endometriosis. J Pers Med. 2022;12(2):216.
7. Laganà AS, Garzon S, Götte M, et al. The pathogenesis of endometriosis: molecular and cell biology insights. Int J Mol Sci. 2019;20(22):5615.
8. Signorile PG, Baldi F, Bussani R, et al. Ectopic endometrium in human foetuses is a common event and sustains the theory of müllerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. J Exp Clin Cancer Res. 2009;28(1):49.
9. de Jolinière JB, Ayoubi JM, Lesec G, et al. Identification of displaced endometrial glands and embryonic duct remnants in female fetal reproductive tract: possible pathogenetic role in endometriotic and pelvic neoplastic processes. Front Physiol. 2012;3:444.
10. Klemmt PAB, Carver JG, Koninckx P, et al. Endometrial cells from women with endometriosis have increased adhesion and proliferative capacity in response to extracellular matrix components: towards a mechanistic model for endometriosis progression. Hum Reprod. 2007; 22(12):3139-47.
11. Han SJ, Jung SY, Wu S-P, et al. Estrogen receptor β modulates apoptosis complexes and the inflammasome to drive the pathogenesis of endometriosis. Cell. 2015;163(4):960-74.
12. Agostinis C, Balduit A, Mangogna A, et al. Immunological basis of the endometriosis: the complement system as a potential therapeutic target. Front Immunol. 2021;11:599117.

Chapter 3

Rising Focus on Adolescent Endometriosis in Modern Gynecology Practice

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INTRODUCTION

Dysmenorrhea is defined as menstrual pain. Dysmenorrhea may be due to a primary or secondary cause. Primary dysmenorrhea is defined as painful menstruation without underlying pelvic pathology. The most common cause for dysmenorrhea in adolescent girls is primary in etiology, which is seen within 6–12 months postmenarche. Primary dysmenorrhea is usually responsive to treatment with oral contraceptive pills (OCPs) or nonsteroidal anti-inflammatory drugs (NSAIDs). Secondary dysmenorrhea is defined as menstrual pain due to underlying pathology of the uterus. The most common form of secondary cause found in adolescents is endometriosis.[1]

Chronic pelvic pain is defined as pain in the pelvic region that lasts for at least 6 months, and it can be cyclical, noncyclical, constant, or intermittent. Classically, cyclic pain is associated with adult endometriosis, whereas adolescents with endometriosis are more likely to present with noncyclical pain.[1]

PREVALENCE OF ENDOMETRIOSIS

Endometriosis affects 6–10% of reproductive-age women. The prevalence of adolescent endometriosis is difficult to determine due to the invasive method of a definitive diagnosis of endometriosis via laparoscopy and the absence of large-scale studies within this population. But, it is seen that approximately 60% of adult women with endometriosis usually experience symptoms before the age of 20. In adults, the time duration between the onset of symptoms and diagnosis of endometriosis is reported to be approximately 7 years, whereas it is more than 12 years if the onset of the disease was in adolescence.[2]

PATHOPHYSIOLOGY

Endometriosis is a multifactorial condition and the exact pathophysiology is not fully understood yet. Three proposed mechanisms are generally accepted: direct implantation via retrograde menstruation, lymphatic and vascular dissemination of endometrial cells, and coelomic metaplasia.

The most widely accepted theory is the Sampson theory which is the direct implantation of viable endometrial cells via retrograde menstruation through the fallopian tubes into the peritoneum leading to direct implantation of endometrial tissue outside of the uterus. Though a majority of healthy women have retrograde menstruation, only 10% of them develop endometriosis.[3] Other theories of retrograde menstruation leading to endometriosis include a genetic predisposition, progesterone resistance, estrogen dependence, and inflammation. The theory of lymphatic and vascular dissemination of endometrial cells accounts for extraperitoneal locations of endometriosis such as lymph nodes, pleural cavity, brain, and kidney. The coelomic metaplasia theory suggests that metaplasia of coelomic epithelium covering the peritoneum and ovary can lead to pelvic endometriosis, which may account for the development of endometriosis in prepubertal girls and adolescents.[3]

RISK FACTORS

There are many risk factors associated with endometriosis in adolescents such asgenetic, anatomic, and hormonal factors. Few recent studies show that there is a genetic link to endometriosis in adolescents, as seen in adult patients. Obstructive Müllerian anomalies can lead to retrograde menstruation and that has been shown to increase the risk for endometriosis in adolescents. This is supported by the findings of spontaneous resolution of endometriosis in adolescent patients after the obstruction is surgically corrected. Early menarche is associated with a high risk of endometriosis due to increased exposure to estrogen and increased duration of retrograde menstruation.[4] Early onset of dysmenorrhea and chronic pelvic pain at the time of menarche also increases the probability of having endometriosis.[5] Low body mass index (BMI) also is correlated with an increased risk of endometriosis.[4]

CLINICAL PRESENTATION

Endometriosis has to be suspected in adolescents when they have severe dysmenorrhea interfering with daily activities, chronic pelvic pain resistant to medical treatment, nausea associated with pelvic pain, gastrointestinal symptoms, such as constipation, dyschezia, and intestinal cramping, may also be experienced. If the adolescent is sexually active, dyspareunia may be present.[6] Suspect endometriosis when young girls present with cyclical absenteeism from school.[7]

CLINICAL EXAMINATION

A vaginal examination may show a retroverted uterus with limited mobility; however, a vaginal examination may be inappropriate in the case of a non-

sexually active adolescent. Rectal examination may reveal tender uterosacral ligament with rectovaginal nodules.[8]

IMAGING

Pelvic ultrasound can detect ovarian endometriomas; however, it is not useful in detecting superficial endometriosis. A normal ultrasound does not rule out endometriosis. If a transvaginal scan is not appropriate, magnetic resonance imaging (MRI), transabdominal, transperineal, or transrectal scan may be considered. This may confirm diagnosis only in advanced lesions, early lesions may not be picked out.

DIAGNOSIS

Diagnosis in adolescents are through careful history taking and physical examination including vaginal examination after taking into consideration the acceptability, age and cultural background, risk factors, and family history combined with imaging technologies as the diagnostic accuracy of physical examination is low.

Serum biomarkers like CA-125 are not recommended for diagnosing endometriosis in adolescents. For adolescents with suspected endometriosis, where imaging is negative and medical treatments have not been successful, diagnostic laparoscopy may be considered. If laparoscopy is performed, it is always recommended to take biopsies to confirm the diagnosis histologically, although negative histology does not entirely rule out the disease.[7]

STAGING OF ENDOMETRIOSIS

Staging of endometriosis is done by the Revised American Society for Reproductive Medicine (rASRM) scoring system. It is done based on the appearance, location, type, and depth of invasion of the lesion. **Table 1** shows the different staging of endometriosis.[9]

Table 1 Staging of endometriosis

Stage	*Description*	*Points*	*Appearance*
1	Minimal	1–5	Few small implants, wounds, or lesions
2	Mild	6–15	More implants, deeper into the tissue, with/without scarring
3	Moderate	16–40	Deep implants with small cysts (chocolate cysts) seen in both ovaries; the presence of scarring tissue
4	Severe	>40	Widespread distribution with larger cysts in both ovaries; thicker scarring tissues

There is large variability in the rASRM staging in adolescents. Adolescent endometriotic lesions appear as red or clear vesicular lesions and may be difficult to see, as compared to adult endometriotic lesions which are classically described as "powder burn" lesions, which appear black with white scarring. Red and clear lesions have increased metabolic activity resulting in increased prostaglandin production, which manifests in increased pain among adolescents.

MANAGEMENT

Treating endometriosis in adolescents is very important as it has got control over symptoms and prevents disease progression, which may reduce long-term consequences such as infertility.[10]

The first-line medical treatment includes hormonal contraceptives or progestogens [systemically or via levonorgestrel-releasing intrauterine system (LNG-IUS)] as the first-line hormone therapy because of their safety profile and effectiveness. Newer progestins, such as dienogest, help to relieve pain in adolescent girls and can be used for a longer period. The VISADO study (VISanne study to assess safety in ADOlescents, 2017) used dienogest for up to 52 weeks and has shown substantially reduced pain, mild reduction in bone mineral density (BMD) (1.2%), which improved partially after treatment discontinuation.

Nonhormonal therapy, such as NSAIDs, can be used with hormonal therapy to decrease pelvic inflammation and pain.[11]

In adolescents with endometriosis, especially those whose diagnosis was confirmed via laparoscopy and associated pain in whom hormonal contraceptives or progestogen therapy failed, gonadotropin-releasing hormone (GnRH) agonists may be considered for up to 1 year, with add-back therapy. This can be considered only after a discussion of potential side effects and long-term risks with a practitioner in a secondary or tertiary care setting.

Surgical therapy for endometriosis is typically necessary for intractable pelvic pain despite medical therapy. Surgery should be performed laparoscopically by an experienced surgeon, and if possible, complete laparoscopic removal of all endometriotic lesions should be performed. Postoperative hormone therapy should also be considered as that may suppress the recurrence of symptoms. All candidates before surgery should be informed of the potentially detrimental effect of ovarian endometriosis and surgery on ovarian reserve and future fertility.[7]

Fertility preservation options should be considered in selected patients, like those with bilateral ovarian endometriomas or those with unilaterally operated endometriomas with a contralateral recurrence. If fertility preservation is carried out in young women, it is suggested that fertility preservation can precede ovarian surgery. Although true benefit, safety, and indications in adolescents with endometriosis for fertility preservation remain unknown.[9]

Conclusion

Endometriosis should be strongly suspected in adolescent females with pelvic pain refractory to medical treatment. Negative imaging does not rule out endometriosis. Early diagnosis and management with medical or surgical management may prevent disease progression and also significantly benefit their future quality of life.

References

1. ACOG Committee Opinion No. 760: Dysmenorrhea and endometriosis in the adolescent. Obstet Gynecol. 2018;132(6):e249-58. Available from:https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/12/dysmenorrhea-and-endometriosis-in-the-adolescent
2. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789-99.
3. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012;98(3):511-9.
4. Shafrir AL, FarlandLV, Shah DK, etal. Risk for and consequences of endometriosis: A critical epidemiologic review. Best Pract Res Clin Obstet Gynaecol. 2018;51:1-15.
5. Sarıdoğan E. Endometriosis in teenagers. Womens Health (Lond). 2015;11(5):705-9.
6. DiVasta AD, Vitonis AF, Laufer MR, et al. Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood. Am J Obstet Gynecol. 2018;218(3):324.e1-11.
7. ESHRE Endometriosis Guideline Development Group.2022. Available from: https://www.eshre.eu/Guideline/Endometriosis#:~:text=Issued%3A%202%20February%202022&text=The%20guideline%20is%20a%20full,and%20post%2Doperative%20hormone%20therapy
8. Sarıdoğan E. Adolescent endometriosis. Eur J Obstet Gynecol Reprod Biol 2017;209:46-9.
9. Giudice LC. Clinical practice: Endometriosis. N Engl J Med. 2010;362(25):2389-98.
10. Dowlut-McElroy T, Strickland JL. Endometriosis in adolescents. Curr Opin Obstet Gynecol. 2017;29(5):306-9.
11. deSanctis V, Matalliotakis M, Soliman AT, et al. A focus on the distinctions and current evidence of endometriosis in adolescents. Best Pract Res Clin Obstet Gynaecol. 2018;51:138-50.

Chapter 4

Noninvasive Diagnosis in Endometriosis

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INTRODUCTION

Endometriosis is a lifetime disorder, starts at adolescence and continues till menopause sets in. Though the exact incidence is difficult to document, it occurs in approximately 3–15% of women. The incidence is approximately 40–50% in patients with infertility and it is seen in approximately 50–70% of female with chronic cyclical pelvic pain.

In endometriosis, there are functional ectopic endometrial glands and stroma. They respond to the changing hormonal milieu and undergo cyclical bleeding. This stimulates reactionary inflammation and fibrosis. Evaluation of this complex multifocal disease is important because there is significant morbidity associated with it and clinical diagnosis remains challenging.

Transvaginal ultrasound (TVS) is the prime diagnostic imaging modality. It is important in not only diagnosing the disease but also helps to map the disease significantly with reasonable sensitivity and specificity. Hence, it helps immensely in to planning the management. The advantage of TVS is that it is noninvasive , has higher accuracy, and allows dynamic assessment. Diagnostic tools other than TVS remain laparoscopy and magnetic resonance imaging (MRI).

The presenting complaints of the patients are dysmenorrhea, dyspareunia, infertility, and chronic pelvic pain. The clinical examination may show a mass, tenderness, and nodules, and may even be normal. Additional compounding fact is that the complaints and clinical findings do not always corroborate with the severity of the disease. Hence, the diagnosis is difficult, delayed, or missed. So, the clinicians need a noninvasive screening diagnostic modality with high precision.

The accuracy and reliability of TVS has been authenticated by the European Society of Human Reproduction and Embryology (ESHRE). To ensure standardization of the diagnostic protocol, a consensus protocol – the International Deep Endometriosis Analysis (IDEA) protocol was agreed by a team of multidisciplinary experts. The IDEA protocol[1] to assess pelvic endometriosis requires evaluation of:

- uterus, ovaries and adnexa

- evaluation of deep infiltrating endometriosis - DIE
- sliding sign
- presence of ultrasound soft markers.

COMPONENT 1

Uterine Evaluation

A growing school of thought believes that adenomyosis is having a deep association with endometriosis, more often associated with severe endometriosis. Currently, the detection of adenomyosis has significantly improved with the increased resolution of the current-day ultrasound machines. Also, once believed to be a disease of the middle age, it is now seen with increasing incidence in the reproductive-age group.

Crucial to its pathology, in adenomyosis, there are functional ectopic endometrial glands and stroma in the myometrium. These hormonally sensitive ectopic glands bleed cyclically and induce a hyperplastic reaction in the surrounding myometrium. The ensuing changes seen in adenomyosis are heterogeneous myometrium, focal or diffuse myometrial hyperplasia which is often asymmetrical. This heterogeneous myometrium has a venation blind striated appearance. There is an ill-defined endometrial myometrial junction with pseudowidening of endometrium. There are endometrial striations extending from the endometrium to the myometrium. There are hyperechoic nodules in the myometrium which display cyclical changes similar to the endometrium in the same cyclical fashion. These can later on change to myometrial cyst.

Ovaries

Endometrioma has a characteristic morphology on ultrasonography (USG). It is a complex cyst with homogeneous low-level homogeneous echoes – the ground-glass echoes. It is usually unilocular, can be multilocular (number of locules vary from 2–5). But, usually, multilocular appearance is because of closely abutting cysts. It lacks calcification, solid elements, or internal vascularity. The size should be measured in three planes. The presence of bilateral masses should be noted. The morphology is so characteristic on ultrasound that the ESHRE endometriosis special interest group[2] has labeled level A evidence that TVS has a high sensitivity and specificity in diagnosing endometriomas and that it requires little training. A note should be made of the visible antral follicle count (AFC). Other than assessing the endometriomas, the ovarian margins should be assessed. Superficial endometriosis and adhesions cause blurring of the ovarian margins. There may be adhesions between the endometrioma and the peritoneum because of endometriosis of the peritoneum covering the ovarian fossa. A typical endometrioma is seen as unilocular solid mass with ground-glass

echogenicity, papillary projection, a color score 1 or 2, or no flow in the papillary projection. Endometriomas may undergo decidualization in pregnancy and need to be differentiated from malignancy.

The differentials of an endometrioma are – corpus luteal cyst, dermoid cyst, cystadenoma, follicular cyst. Corpus luteal cyst is differentiated by its changing morphology and associated peripheral high vascularity with low pulsatility index (PI). Dermoid cyst has calcified elements with acoustic shadowing, hyperechoic dots, and mesh of hyperechoic mass. Cystadenomas are multilocular. Follicular cysts are usually functional and disappear on treatment or spontaneously.

Clinical Significance

Size of endometrioma is important as the infertility groups recommend a surgery if size is >4 cm [American Society for Reproductive Medicine (ASRM), ESHRE]. But, most assisted reproductive technology (ART) consultants recommend ART instead of surgery as there is a compromise in egg reserve post-surgery. When there are bilateral endometriomas and ovaries are fixed to each other, endometriosis is severe and grade 4 and is less amenable to surgical correction. Here, ART is recommended instead of a corrective surgery.

Adnexal Evaluation

Adnexal evaluation requires exclusion of hydrosalpinx, hematosalpinx, and peritoneal inclusion cyst.

Hydrosalpinx results because of serosal and subserosal deposits resulting in peritubal adhesions resulting in tubal dilatation. Hydrosalpinx is a tubular cystic structure with salpingeal folds simulating a cogwheel appearance in transverse scans. In hematosalpinx, there are low-level internal echoes. The presence of hematosalpinx is often considered as an indicator of endometriosis and sometimes maybe the only finding in endometriosis.

Peritoneal inclusion cyst is a septated cystic structure conforming to the shape of the peritoneum. The ovary is located eccentrically within this loculated collection.

Peritoneal inclusion forms around the ovary in the presence of adhesions when the latter hinder the absorption of fluid.

COMPONENT 2

Deep Infiltrating Endometriosis Lesions

Dedicated scan to search, map, and measure the DIE lesions.

Mapping of the Disease

Anatomical division of the pelvis into anterior and posterior part by a plane passing through the endometrium and the vagina. Anterior pelvis area includes

the uterovesicle pouch containing bladder, ureter, and anterior serosa covering the uterus and cervix. This area is best assessed on ultrasound by placing the probe in the anterior vaginal fornix. Also, endometriosis of the bladder, especially dome region, is best assessed when the bladder should be moderately distended, but it should not be overdistended to increase the visibility of the bladder dome.

So, either the bladder is scanned at the end of examination of TVS or in the beginning. Ureteral involvement can be missed on scans; so, it is a good practice to screen.

Posterior compartment scanning is optimized by placing the probe in the posterior vaginal fornix. Structures of interest are the uterosacral space, uterosacral ligament (USL), bowel mainly rectum, and posterior sreosa covering uterus, cervix, and posterior vaginal vault. Bowel rectum and rectosigmoid are usually associated when endometriosis is severe. USL involvement changes the normally hyperechoic ligaments to hypoechoic with usually associated nodularity or thickening.

TVS is reported to have an accuracy of approximately 75–95% depending on the location of disease. The DIE nodules involve the fibromuscular tissue and usually spare the mucosa of bladder. They appear hypoechoic, linear, or round lesions with smooth or irregular borders with minimal or nil vascularity. The report should describe the number, location, shape, and size. These nodules should be measured in three planes.[3,4]

Clinical Significance

DIE nodules correlate clinically with pain, dyspareunia, bladder, and bowel complaints. The extraperitoneal nodules are missed on laparoscopy.

So, special areas to be focused on scans are bladder bowel, rectovaginal area, and USL.

COMPONENT 3

Sliding sign assesses the obliteration of pouch of Douglas (POD) as a consequence to adhesions resulting from DIE. POD obliteration results from fixity of rectum or rectosigmoid with cervix with or without USL fusion. It is elicited in real time in cine mode.[5] Sliding sign is done in the sagittal plane. First, we have to press with the probe pressing the cervix and assess the movement of anterior rectum relative to the cervix and vagina. The second assessment is done by the free-hand pressing the abdominal wall against the fundus of the uterus and the probe is held against the cervix. The movement of bowel relative to the posterior uterine fundus is assessed.

A positive sign is when the relative movement is preserved, thus, excluding the adhesions. A negative sign connotes adhesions and obliterated respective spaces.

COMPONENT 4

Ultrasound soft markers are reported by seeing specific probe tenderness and decreased ovarian and/or uterine mobility. They connote the presence of superficial endometriosis or adhesions. Compared to the earlier hard markers –endometriomas, DIE, hematosalpinx, hysdrosalpinx, addition of these soft markers increased the diagnostic sensitivity of pelvic endometriosis. Okaro et al. report that 51 out of 73 patients with only soft markers on USG had pelvic endometriosis on laparoscopy. Guerriero et al. recommend site-specific tenderness as a reliable soft marker for endometriosis of rectovaginal area. To scan for ovarian mobility, probe pressure is applied between the uterus and the ovary to see if ovary is fixed to the uterus or pelvic side wall.

In the presence of severe adhesions, the ovaries become fixed to each other within the cul de sac - the kissing ovaries sign. This is a severe grade of endometriosis and is associated with the high incidence of associated bowel and fallopian tube endometriosis.

MODIFICATIONS IN USG TECHNIQUE

Transrectal ultrasonography (TRUS): Recommended by the ESHRE to diagnose endometriomas, especially in unmarried females and for rectal endometriosis. They report a high sensitivity and specificity in diagnosing, but add that it requires training.

Rectal water contrast: It means TVS scanning after installation of saline into the rectum through a catheter.

Sonovaginagraphy with saline or gel: For gel contrast vaginography around 50 mL of vaginal gel is inserted into the posterior vaginal fornix. The gel creates an acoustic window to optimize evaluation of vaginal wall and vaginal fornix.

LIMITATIONS OF ULTRASOUND

Limited field of view. Dedicated scans as recommended by the IDEA consensus group requires training. In the presence of pain, previous surgeries, there is limited maneuverability and restricted scans. Also, distorted anatomy due to adhesions and associated fibroids also compromise the scans.

Magnetic resonance imaging (MRI) is another noninvasive diagnostic modality of indispensable role in endometriosis. The advantage of

MRI - its ability to characterize hemorrhage and its age lends advantage in imaging. Also, MRI offers a larger field of view, and the effect of adhesions on surrounding structures can be imaged. In MRI pulse sequences, plane of imaging are important in MRI and contrast enhancement is not required. The ESHRE does not recommend MRI for diagnosing /excluding peritoneal endometriosis. Also, it

is not cost-effective modality, MRI advised to diagnose DIE. Limitations of MRI are that - small superficial implants less than 5 mm cannot be picked.

The main differential hemorrhagic cyst shows lower T1 and higher T2 in endo due to the higher protein concentration and viscosity. Teratoma shows loss of signal intensity on T1 fat sat sequence of a lesion hyperintense on T1 sequence. Deep pelvic endometriosis involves endometrial implants in anterior or posterior cul de sac, or pelvic side wall. Involved structures can be USL, rectum, rectovaginal septum, and vagina bladder. They present diagnostic limitations on physical examination, USG (TVS or TRUS). Deep endometriosis has limited access because of adhesions on laparoscopy. MRI scores over USG and laparoscopy by providing panoramic view and tissue characterization.[6,7] On MRI, these solid deep lesions show low signal on T1w and T2w sequences with punctate hyperintensities on T1w sequences.

Good practice point (GPP) recommends that MRI is not the recommended modality for endometriosis-associated infertility. There are specific indications of recommending MRI in endometriosis are - when malignancy is suspected, when diagnosis is in doubt, deep endometriosis and in virgins when TVS scan cannot be done.

Conclusion

TVS remains the prime screening imaging mortality in endometriosis. Standardization requires dedicate protocol - the IDEA protocol accurately assesses the location, extent, and severity of pelvic endometriosis. The dedicated scans are required to decide the management. The dynamic TVS is one advantage which improves the diagnostic accuracy and is not available with other diagnostic modalities.

References

1. Indrielle-Kelly T, Frühauf F, Fanta M, et al. Diagnostic accuracy of ultrasound and MRI in the mapping of deep pelvic endometriosis using the International Deep Endometriosis Analysis (IDEA) Consensus. Biomed Res Int. 2020;2020:3583989.
2. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698-704.
3. Gonçalves MO, Dias JA Jr, Podgaec S, et al. Transvaginal ultrasound for diagnosis of deeply infiltrating endometriosis. Int J Gynaecol Obstet. 2009;104(2):156-60.
4. Scioscia M, Virgilio BA, Laganà AS, et al. Differential diagnosis of endometriosis by ultrasound: a rising challenge. Diagnostics (Basel). 2020;10(10):848.
5. Hudelist G, Fritzer N, Staettner S, et al. Uterine sliding sign: a simple sonographic predictor for presence of deep infiltrating endometriosis of the rectum. Ultrasound Obstet Gynecol. 2013;41(6):692-5.
6. Kinkel K, Chapron C, Balleyguier C, et al. Magnetic resonance imaging characteristics of deep endometriosis. Hum Reprod. 1999;14(4):1080-6.
7. Chapron C, Vieira M, Chopin N, et al. Accuracy of rectal endoscopic ultrasonography and magnetic resonance imaging in the diagnosis of rectal involvement for patients presenting with deeply infiltrating endometriosis. Ultrasound Obstet Gynecol. 2004;24 (2):175-9.

Chapter 5

Sonographic Diagnosis of Adenomyosis

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Asha R Rao

INTRODUCTION

Adenomyosis is defined as the presence of ectopic endometrial tissue within the myometrium. The prevalence was higher in women with a history of recurrent pregnancy loss (38.2%; p <0.005) and prior in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) failure (34.7%; p <0.0001).[1] Adenomyosis was coexisting with endometriosis in 35.1% and with deeply infiltrating endometriosis (DIE) in 49%. Rise in prevalence of adenomyosis was seen in infertile women.

Detection to differentiate women with adenomyosis and without adenomyosis before assisted reproductive technology (ART) using standardized ultrasound protocol is important to reduce miscarriage rate.[2]

The number of women in reproductive age with ultrasound (US) or magnetic resonance imaging (MRI) diagnosis of adenomyosis are on the rise. Adenomyosis is correlated with a variety of symptoms such as pelvic pain, abnormal uterine bleeding (AUB) and/or infertility, but could be also asymptomatic. Adenomyosis often coexists with other gynecological comorbidities, such as endometriosis and uterine fibroids, and the diagnostic criteria are still not universal. Hence, the diagnosis of adenomyosis is challenging. Transvaginal ultrasonography (TVS) is offered as the first- line noninvasive imaging technique for the diagnosis of uterine adenomyosis as it is cost effective, with less discomfort, and high accuracy.

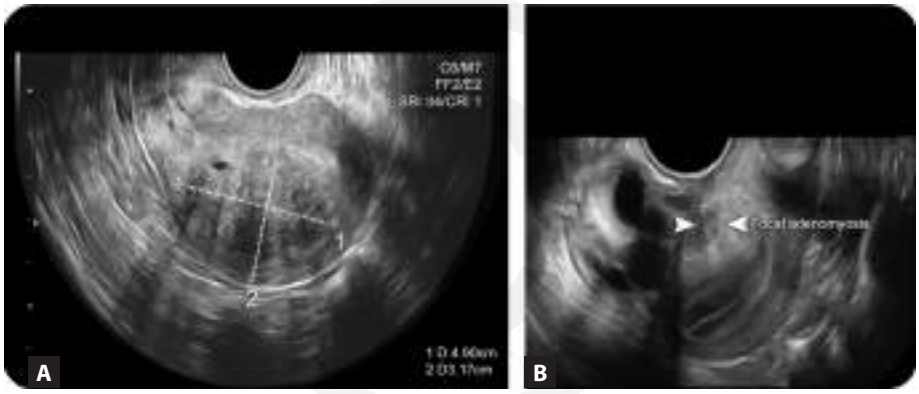
A standardized reporting system of ultrasound findings of adenomyosis was developed using the *Morphological Uterus Sonographic Assessment (MUSA)* criteria **(Table 1)**.

Women with 5 or more sonographic features of adenomyosis showed more than 3-fold risk of infertility [odds ratio (OR): 3.19, $p = 0.015$, 95% confidence interval (CI): 1.25–8.17], a highly significant association[3]

- Adenomyosis may be diffuse or focal **(Figs. 1A and B)**. When diffuse, myometrium shows in homogeneous, irregular myometrial echotexure in an indistinctly defined myometrial area with alternate hyperechoic and hypoechoic linear striations because of endometrial infiltration giving a

Table 1 Ultrasound criteria for adenomyosis

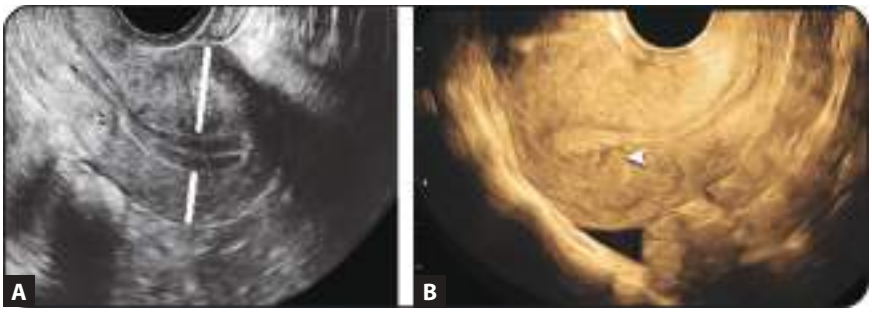
Asymmetric or globular uterine configuration
Asymmetry of anteroposterior myometrium
Myometrial cysts
Echogenic endometrial lines and buds
Hyperechogenic islands
Fan-shaped shadowing
Color Doppler showing translesional vascularity
Irregular or interrupted junctional zone



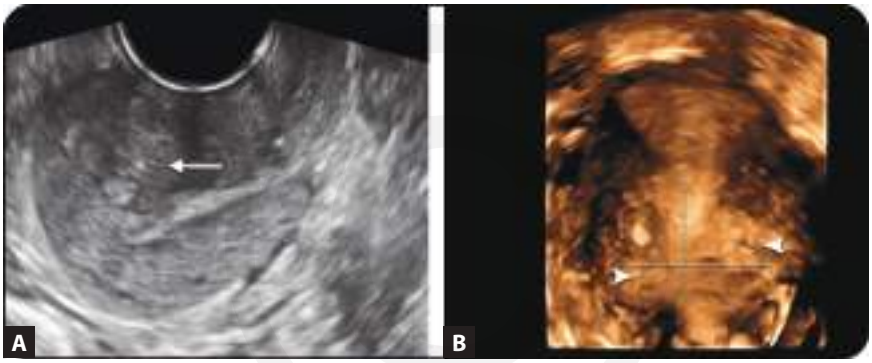
Figs. 1A and B: (A) Diffuse adenomyosis—hyperechoic irregular myometrial echoes; (B) Focal adenomyosis (arrowheads). Localized heterogeneous myometrial echoes

Swiss cheese or rain in forest appearance. Heterogeneous echogenicity has a sensitivity of 88 % for diagnosis of adenomyosis.[3]

- Diffuse adenomyosis is suspected if <25% of the lesion is surrounded by normal myometrium.
- Focal adenomyosis is suspected if >25% of the lesion is surrounded by normal myometrium. Focal adenomyosis shows the presence of solitary finding detected only in one part of the myometrium or at multiple sites forming a circumscribed lesion.
- Significant association exists between extent of diffuse adenomyosis and dysmenorrhea ($p = 0.005$), and AUB ($p = 0.03$).[4]
- *Eccentrically placed endometrial cavity:* It is seen when only one wall is involved in diffuse adenomyosis. Asymmetric myometrial thickening is the most common sonographic feature **(Fig. 2A)**.



Figs. 2A and B: (A) Asymmetry of the uterine wall; (B) Echogenic lines at endomyometrial junction (arrowhead)

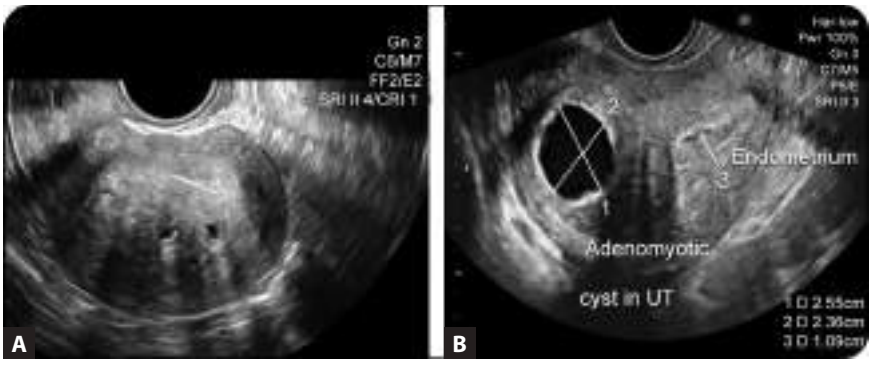


Figs. 3A and B: (A) 2D US image of echogenic islands (arrow); (B) 3D US image of echogenic islands (arrowhead)

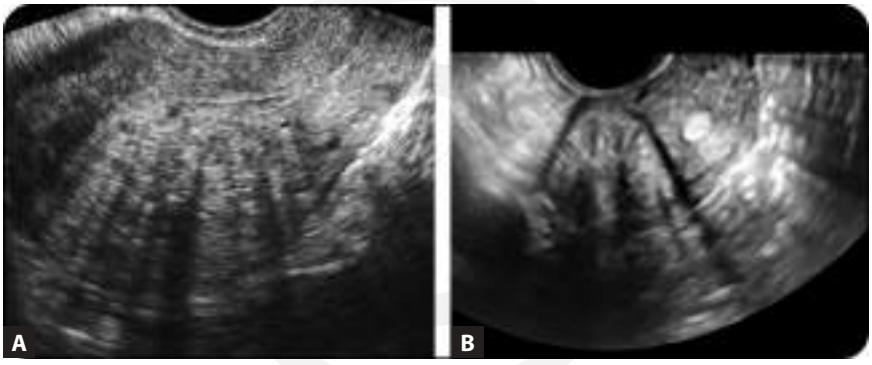
ECTOPIC ENDOMETRIAL GLANDS

Typically, adenomyosis occurs if the glands and stroma from the endometrium invade the inner myometrium in an "inside-out "sequence. The primary finding of echogenic striations and nodules are due to direct extension of endometrial tissue infiltrating the myometrium**.**

- *Subendometrial lines or buds:* They are perpendicular to endometrial cavity disrupting the junctional zone (JZ). They should be discriminated from small echogenic spots seen in subendometrium **(Fig. 2B)**.
- *Hyperechogenic islands:* They are seen as echogenic areas within the myometrium. May be regular or irregular. The number of hyperechogenic islands **(Figs. 3A and B)** and the maximum diameter of the largest may be noted.[5]
- *Myometrial cysts:* These result when ectopic endometrial glands fill with fluid. Cystic contents may be anechoic or with low-level echoes representing blood.



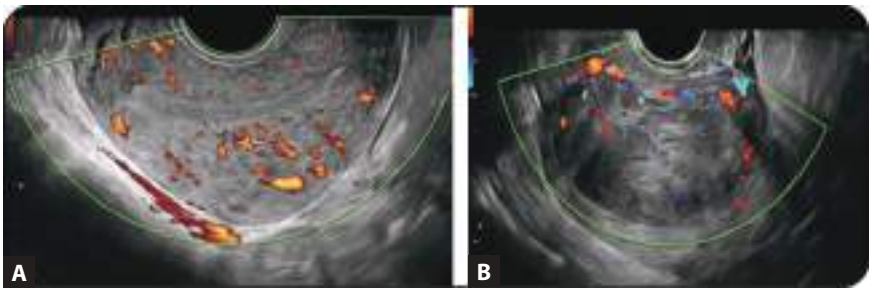
Figs. 4A and B: (A) Myometrial cyst—anechoic space with echogenic rim; (B) Adenomyotic cyst. Large anechoic space the myometrium



Figs. 5A and B: (A) Diffuse adenomyosis—linear striations—fan-shaped shadowing; (B) Fibroid—edge shadowing

Cysts have characteristically echogenic rim. Typically of 1–5 mm. It is sufficient to measure the largest diameter of the largest cyst only. Visualization of cysts can be improved by decreasing the field of view and zooming in on the image. Myometrial cysts **(Figs. 4A and B)** are highly characteristic of adenomyosis with 98% specificity.[6]

- *Fan-shaped shadowing:* It is caused by overlying cystic structures. It is defined by the presence of hypoechoic linear stripes alternating with echogenic stripes, whereas in fibroid, there will be edge shadowing[7] **(Figs. 5A and B)**.
- *Vascularity pattern:* Translesional vascularity is seen in adenomyosis. The vessels are perpendicular to the cavity/serosa, whereas fibroid shows circumferential flow along the myoma capsule **(Figs. 6A and B)**.
- *Question mark form of uterus:* It is a simple sonographic sign associated with the presence of adenomyosis.[8] The sign was present when the uterine corpus was retroflexed, the fundus of the uterus facing is pulled back because



Figs. 6A and B: (A) Color Doppler showing diffuse adenomyosis translesional vascularity; (B) Circumferential vascularity in myoma

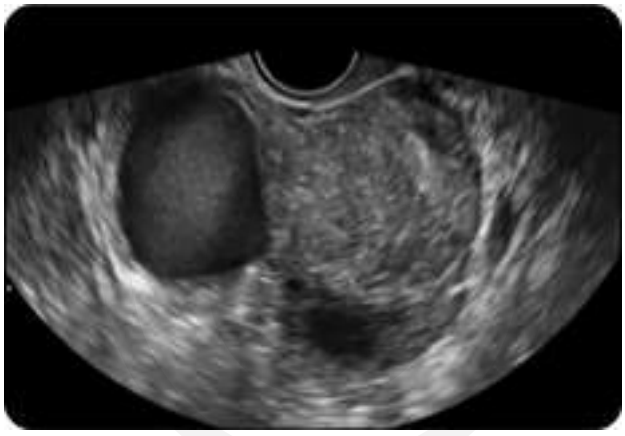


Fig. 7: Question mark sign—fundus of uterus pulled by adhesions

of adhesions and the cervix directed anteriorly **(Fig. 7)**. Question mark sign of uterus alone had a specificity of 93% and sensitivity of 75% for diagnosis. Number of ultrasonographic features were considered as an index of severity. It is essential to differentiate between adenomyosis and fibroid with regard to decision making in medical or surgical treatment **(Table 2)**.

SYSTEMATIC REPORTING OF ULTRASOUND FINDINGS OF ADENOMYOSIS

Uniform reporting system of ultrasound (US) findings of adenomyosis has been proposed recently, so that it can be used in future studies on prevalence, symptoms, effectiveness of medical/surgical treatment, impact on fertility and obstetric outcome.[5] According to this, adenomyosis was reported in its location (anterior, posterior, lateral left, lateral right, or fundal), differentiating between the focal and diffuse types.

Table 2 Differentiating criteria for adenomyosis and fibroid

Adenomyosis	*Fibroid*
Ill-defined margin	Well-defined margin
Heterogeneous echogenicity	Homogeneous
No calcification	Calcification - common
Tiny cysts	Solid occasionally macrocystic degeneration
Vessels traversing	Circumferential flow
Amid myometrium	Pushes away the myometrium
Resection results in loss of myometrial tissue	No loss of myometrium after myomectomy
Endometrium - Indistinct borders	Borders may be obscured or distorted

In case of focal lesion completely surrounded by hypertrophic myometrium, it can be called as 'adenomyoma'. When the same uterus can show the presence of both focal and diffuse lesions within the same uterus, it can be described as 'mixed type adenomyosis'.

Adenomyosis could be 'cystic' or 'non-cystic'. Intramyometrial cysts are reported as measurable if the largest diameter is more than 2 mm.[5]

Adenomyosis may infiltrate one or more of the three layers of uterus.

Type 1 adenomyosis involves only the JZ, type 2 involves middle layer of myometrium (the layer between the JZ and the vascular arcade), and type 3 if adenomyotic lesions are seen in the outer layer of myometrium. If the outer myometrium is involved, the serosal layer may be intact or interrupted. To help identify serosal involvement of adenomyosis, the presence of sliding of or fixed viscera (bowels) against the uterus should always be elicited.

Adenomyosis may be classified according to the severity and extent with regard to percentage of affected myometrium (mild adenomyosis <25%, moderate adenomyosis 25–50%, severe adenomyosis >50%). This is the first reporting system and classification of US of adenomyosis formed by a panel of expert sonographers **(Table 3)**. Further validation is needed in future prospective studies.

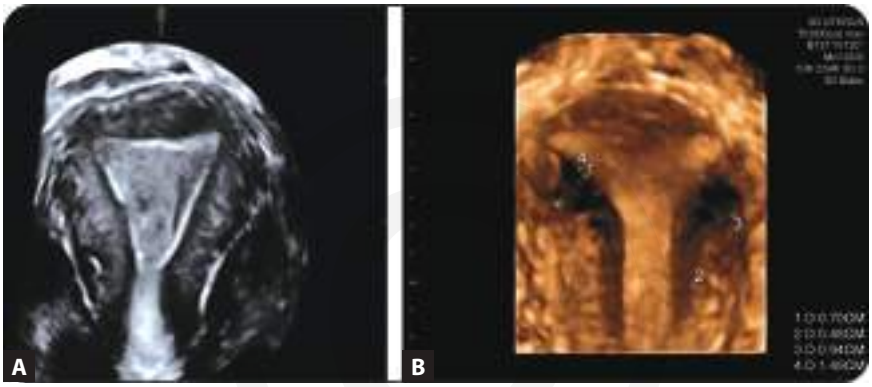
ROLE OF THREE-DIMENSIONAL ULTRASOUND

Junctional Zone

Junctional zone is a hormone-dependent compartment at the endomyometrial interface. Earlier, TVS was not considered reliable for the assessment of JZ. With high-frequency three-dimensional ultrasound (3D-US) probes, JZ, which critically governs many reproductive functions, can be evaluated reliably.[9] JZ

Table 3 Criteria in classification

Criteria	*Morphology of Adenomyosis*
Involved area	Inner myometrium or outer myometrium
Location	Anterior or posterior or fundus
Distribution	Diffuse or focal
Type of adenomyosis	Muscular or cystic
Extent	Expressed as 1/3, <2/3 or >2/3 or in cm



Figs. 8A and B: (A) 3D US with VCI-coronal view hypoechoic halo (junctional zone) around endometrium; (B) Increased junctional zone thickness

is nothing but a distinct layer of the inner myometrium, surrounding the entire endometrial cavity.

On the coronal view, JZ **(Fig. 8A)** appears as a hypoechoic zone around the endometrium. Coronal reconstruction of the uterus by 3D-US is a useful adjunct to conventional imaging. It allows delineation of the entire lateral and fundal aspects of the JZ, which is rarely visualized on two-dimensional (2D)-US. In addition, the hypoechoic features of the JZ often appear more prominent on 3D- versus 2D- US, especially with the application of certain rendering techniques, such as volume contrast imaging (VCI), by increasing the contrast of images and can better depict JZ.

JZ thickness was measured as distance from the basal endometrium to the internal layer of outer myometrium using VCI. JZ Max of >8 mm and JZ Max-JZ Min of >4 mm were significantly associated with adenomyosis than 2D features.[10]

Abnormality of JZ is characterized by thickening or hyperplasia **(Fig. 8B)**.[10] JZ may be reported as irregular, interrupted, not visible or not measurable **(Figs. 9A to C)**.[5] Hyperechogenic subendometrial lines or buds refer to structures which are perpendicular to endometrial cavity, but in continuation with the endometrium.

Figs. 9A to C: (A) Ill-defined junctional zone; (B) Interrupted junctional zone; (C) 3D US. HD live infiltration of junctional zone

Table 4 3D-US features of junctional zone (JZ) in adenomyosis

Features of JZ	***Adenomyosis***
JZ Thickness	Thickened – Max JZ Thickness (JZ Max) ≥8 mm – Ratio of JZ (JZ max/Total myometrial wall thickness) ≥-50% – Difference (JZ Max - JZ Min) JZ Diff ≥4 mm
JZ Regularity	Irregular/Ill-defined Distorted
JZ Boundary	Interrupted Infiltration of JZ by hyperechoic endometrial tissue

Endometrial glands infiltrate the subendometrial tissue resulting in a hyperplastic reaction which appear as echogenic linear striations arising from the endometrial layer. This is considered as a sign of JZ disruption.[5] Thus, 3D-US can be used to detect early adenomyosis and considered in the treatment and counseling.[11].

Andres et al. did a systematic review on the accuracy of 2D- and 3D-transvaginal ultrasound (TVUS), screening the literature from the last 10 years that included 8 studies. For 2D-US, pooled sensitivity and specificity in diagnosing adenomyosis for all combined imaging characteristics was 83.8% and 63.9%, respectively.[12] The maximum sensitivity (86.0%) for a single 2D-US feature was heterogeneous myometrium.

For 3D-US pooled sensitivity and specificity for all combined characteristics were 88.9% and 56.0%, respectively. The maximum pooled sensitivity (86%) and specificity (56.0%) for a single imaging feature is the poor definition of JZ. For an operator-dependent diagnostic method, such as TVS,[13] interobserver variability is an essential aspect for all diagnostic techniques **(Table 4)**.

Women with diffuse adenomyosis have a thicker junctional zone: JZ maximum (6.38 ± 2.30 mm, p <0.001) and JZ difference (4.33 ± 1.99 mm, p <0.001).

JUNCTIONAL ZONE IN TISSUE INJURY AND REPAIR (TIAR)

Persistent peristaltic myometrial movements can result in continuous microtrauma to the JZ, evoking inflammation thus promoting increased estrogen production locally.

Cyclical autotraumatization leads to altered JZ thereby affecting implantation, There exists an association between thickening of the JZ and impaired fertility.

JUNCTIONAL ZONE IN REPRODUCTIVE AND MAJOR OBSTETRICAL DISORDERS

A thickened JZ could be an independent indicator of the risk of miscarriage and may represent an important contributing factor to some causes of recurrent miscarriage (Lazzerin et al). These observations may offer new perspectives for screening and treatment of recurrent miscarriage. Abnormality of the JZ can result in impaired uterine peristalsis, altering the vascular plasticity involving the spiral arteries thereby activating inflammatory pathways, all relating to adverse obstetric outcomes. A recent study which includes pre- pregnancy ultrasound images and/or MRI showed a 1.83-fold rise in risk of preterm delivery in patients with adenomyosis and a 1.98-fold risk for preterm premature rupture of membranes (PPROMs).

ADENOMYOTIC CYST

Adenomyotic cyst is a rare variation. Endometrioma like intramyometrial hemorrhagic cystic mass is surrounded by adenomyotic tissue. Synchronous motion of cystic mass and uterus is suggestive of adenomyotic cyst thereby differentiating from ovarian cyst **(Fig. 3B)**.

UTERINE VOLUME ASSESSMENT

Ultralong Suppression Before Embryo Transfer

Uterine volume assessment can be used as a guide to plan ultralong suppression before embryo transfer.

In a study by Zhou et al.,[14] the average uterine volume reduction from 180 (± 73) cm to 86 (± 67) cm ($p < 0.05$) after 2–6 cycles of gonadotropin-releasing hormone agonists (GnRHa) showed similar in vitro fertilization and embryo transfer (IVF-ET) outcomes when compared to tubal controls. In a retrospective study, Li Xiaoxue et al.[15] showed that after GnRHa suppression, uterine volume greater than 98.81 cc was found to be associated with higher miscarriage and lower live birth rates with no difference in implantation rates. So, US can reliably be used in follow-up of medical therapy in adenomyosis.

Transabdominal Ultrasonography

Transabdominal ultrasonography has limited value but can be used when transvaginal route is not possible or when the uterus is grossly enlarged.[6] The transabdominal ultrasound features for diagnosing adenomyosis are a large uterus, with regular or irregular external contour, asymmetrical myometrial wall thickening and a heterogeneous myometrium, with intramyometrial cysts (Levy et al., 2013).

ULTRASOUND TECHNIQUES TO IMPROVE DIAGNOSTIC CONFIDENCE

The best way to visualize shadowing and heterogeneity of the myometrium is with high-frequency transvaginal imaging. However, it can be difficult to adequately penetrate through the entire posterior myometrium at high frequencies. In such cases, it is helpful to use penetration mode or low-frequency transabdominal US probes which can also improve visualization of endometrial borders. By using cineloops, myometrial echogenicity and Venetian blind shadows become apparent and is easier to demonstrate continuity of echogenic striations with endomyometrial interface.[7]

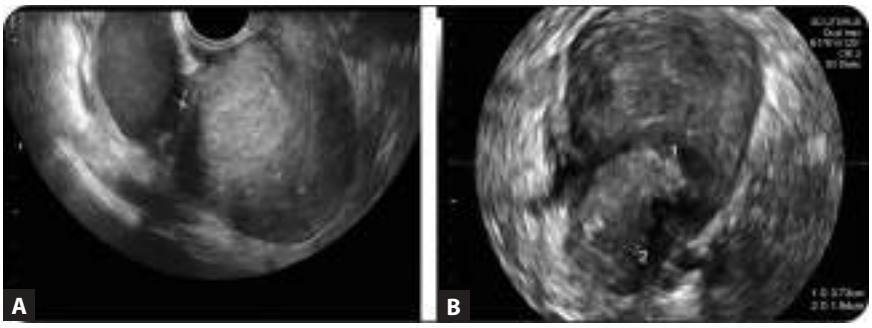
SALINE INFUSION SONOGRAPHY

Saline infusion sonography (SIS) is not a primary diagnostic tool for adenomyosis. The instillation of saline allows for the visualization of endometrium when it is otherwise obscured by adenomyosis. SIS can help confirm the presence of adenomyosis by directly filling the endometrial glands in continuity with endometrial cavity with anechoic fluid similar to hysterosalpingography (HSG).

TRANSVAGINAL SONOGRAPHY AND SUBMUCOSAL ADENOMYOMAS

Sometimes, TVS suggests a submucosal adenomyoma in case of an ill-defined endometrial lesion consisting of cystic spaces protruding into the endometrial cavity. The differentiating criteria with a leiomyoma, are ill-defined margins and a cystic component.

A new scoring system was developed by Lazzori et al. to accurately and schematically assess the type (diffuse, focal, and adenomyoma) and extent (external and internal myometrium) of uterine adenomyosis. Focal and diffuse forms of adenomyosis have well documented differences with regard to reproductive outcome. In fact, negative impact of diffuse adenomyosis was more pronounced when compared with the focal forms (Park et al., 2016).



Figs. 10A and B: (A) Focal outer adenomyosis—FOAM (Focal adenomyosis of the outer myometrium); (B) External adenomyosis

TRANSVAGINAL SONOGRAPHY AND EXTERNAL ADENOMYOSIS

External adenomyosis is particularly difficult to identify and the diagnosis should always be contemplated, especially in the presence of posterior deep endometriotic lesions. The posterior myometrium appears heterogeneous and on power Doppler shows radial vessels and myometrial cysts. Adenomyosis was seen in 21.8% of women with endometriosis. Focal adenomyosis of the outer myometrium (FOAM) **(Figs. 10A and B)** was associated with DIE in 33 % of women.

MRI AND TVS

MRI was considered as the gold standard in the diagnosis of adenomyosis. However, recent studies show TVUS imaging with higher accuracy and comparable detection rates. MRI can give additional information in difficult cases, especially with coexistence of other lesions like fibroids (Vnadenbosch et al., 2018).

Conclusion

Our understanding on adenomyosis has significantly improved and the awareness among clinicians has increased. The development of noninvasive diagnostic modalities has tremendous impact in giving an accurate diagnosis of adenomyosis, without any surgical procedure. Visualization of typical sonographic signs will lead to lesion detection. Imaging is essential not only for diagnostic purpose but also for a tailored management including medical or surgical conservative treatment. The 2D and 3D TVUS are the first-line investigating modalities for identifying adenomyosis, while expensive techniques, such as MRI, have a complementary role.

References

1. Van den Bosch T, Schoubroeck DV. Ultrasound diagnosis of endometriosis and adenomyosis: state of the art. Best Pract Res Clin Obstet Gynaecol. 2018;51:16-24.
2. Vercellini P, Consonni D, Dridi D, et al. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Human Reprod. 2014;29(5):964–77.
3. Eisenberg VH, Arbib N, Schiff E, et al. Sonographic signs of adenomyosis are prevalent in women undergoing surgery for endometriosis and may suggest a higher risk of infertility. Biomed Res Int. 2017;2017:8967803.
4. Pinzauti S, Lazzeri L, Tosti C, et al. Transvaginal sonographic features of diffuse adenomyosis in 18-30-year-old nulligravid women without endometriosis: association with symptoms. Ultrasound Obstet Gynecol. 2015;46(6):730-6.
5. Van den Bosch T, Dueholm M, Leone FPG, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284-98.
6. Bazot M, Cortez A, Darai E, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod. 2001;16(11):2427–33.
7. Cunningham RK, Horrow MM, Smith RJ, et al. Adenomyosis: a sonographic diagnosis. Radiographics. 2018;38(5):1576-89.
8. Di Donato N, Bertoldo V, Montanari G, et al. Question mark form of uterus: a simple sonographic sign associated with the presence of adenomyosis. Ultrasound Obstet Gynecol. 2015;46(1):126–7.
9. Fusi L, Cloke B, Brosens JJ. The uterine junctional zone. Best Pract Res Clin Obstet Gynaecol. 2006;20(4):479–91.
10. Exacoustos C, Brienza L, Di Giovanni A, et al. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011;37(4):471–9.
11. Larsen SB, Lundorf E, Forman A, et al. Adenomyosis and junctional zone changes in patients with endometriosis. Eur J Obstet Gynecol Reprod Biol. 2011;157(2):206–11.
12. Andres MP, Borrelli GM, Ribeiro J, et al. Transvaginal ultrasound for the diagnosis of adenomyosis: systematic review and meta-analysis. J Minim Invasive Gynecol. 2018;25(2):257–64.
13. Lazzeri L, Morosetti G, Centini G, et al. A sonographic classification of adenomyosis: interobserver reproducibility in the evaluation of type and degree of the myometrial involvement. Fertil Steril. 2018;110(6):1154-61.
14. Zhou L-M, Zheng J, Sun Y-T, et al. Study on leuprorelin acetate in treatment of uterine adenomyosis with infertility. Zhonghua Fu Chan Ke Za Zhi. 2013;48(5):334-7.
15. Li X, Pan N, Zhang W, et al. Association between uterine volume and pregnancy outcomes in adenomyosis patients undergoing frozen-thawed embryo transfer. Reprod Biomed Online. 2021;42(2):384-9.

Chapter 6

Current Trends in Medical Management of Endometriosis

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Mrinmayi Dharmadhikari

INTRODUCTION

Endometriosis, a benign gynecological disease, is characterized by the presence of endometriotic lesions consisting of functional endometrial glands and stroma outside the uterine cavity. It is a chronic, recurrent disease with a wide spectrum of presentation. Endometriosis affects 1 in 10 women of reproductive-age[1] and presents a challenge not only in treatment but also in the diagnosis itself. Pain, manifested as dysmenorrhea, noncyclic pelvic pain, and dyspareunia, represents the major clinical problem of this disease. The major goal of the current medical treatment of women with endometriosis is to create an acyclic, hypoestrogenic environment either by blocking ovarian estrogen secretion [gonadotropin-releasing hormone (GnRH)-agonists or GnRH-antagonists] or by locally inhibiting estrogenic stimulation of the ectopic endometrium (progestins, androgenic progestins). The treatment options available and widely used today, such as combined contraceptive pills, nonsteroidal anti-inflammatory drugs, and GnRH agonists, have their own drawbacks including risk of recurrence, side effects, cost, and contraceptive effect in women desirous of pregnancy. In addition, the risk associated with surgical management of deep infiltrating endometriosis and endometriomas like injury to vital structures, bleeding, and so on, have made treatment of endometriosis a challenging task.

Newer treatment options are being studied extensively given the burden of the disease and associated morbidity.

Although there is no optimal medical treatment for endometriosis and its symptoms partly due to lack of understanding of the pathogenesis and natural history of the disease, extensive work on dydrogesterone looks promising.

Consequently, the search continues for newer approaches in the medical treatment.

NEWER TRENDS IN MEDICAL MANAGEMENT

Hormonal

Progestins

Progestins are compounds with varied actions on progesterone receptors including decreased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), hypoestrogenic state, and amenorrhea that help in controlling endometriosis and associated symptoms. They also have antiestrogenic effect causing endometrial pseudodecidualization and provoke apoptosis of endometriotic cells. Progestins are recommended as the first-line hormonal therapy for the treatment of endometriosis-related pain and may compare favorably with other treatment choices.[2] The progestins most commonly used for the treatment of endometriosis include dienogest (DNG), norethindrone acetate (NETA), medroxyprogesterone acetate (MPA), and dydrogesterone. There are certain side effects associated with progestin treatment such as irregular bleeding, weight gain, mood changes and bone loss, especially with depot MPA. Generally speaking, however, progestins are safe and play a possible role in the treatment of endometriosis.

Norethindrone Acetate

Norethindrone acetate (NETA), a 19-nortestosterone derivative, helps in pain relief in women with endometriosis. Its residual androgenic activity can lead to weight gain, acne, and seborrhea. The administration of NETA in a dose of 5 mg/day given continuously for endometriosis is approved by the United States Food and Drug Administration (US FDA).

Medroxyprogesterone Acetate

Medroxyprogesterone acetate (MPA) is a 17-OH progesterone derivative, with both oral and parenteral formulations. MPA is used in endometriosis treatment, but loss in bone mineral density (BMD) on long-term use of depot MPA is a cause for concern.

Dienogest

Dienogest 2 mg daily is a fourth-generation progestin that binds to the progesterone receptor and inhibits gonadotropin secretion when taken continuously. It also exerts antiproliferative and anti-inflammatory effects on endometriotic lesions, thus differentiating dienogest from other progestins.

In pooled analysis of dienogest 2 mg, it was found to be well tolerated. The reported adverse effects seen were headache, breast discomfort, depression, and acne, each occurring in <10% of patients, mild to moderate in intensity.[3]

Administration of dienogest for up to 5 years has also demonstrated a favorable safety and tolerability profile.[4] Medical treatments, such as dienogest, can be used post-surgery to prevent recurrence of endometriosis unless the patient desires pregnancy.

Small decreases in BMD have been seen with dienogest treatment of up to 52 weeks; however, there does not appear to be a cumulative decrease in BMD. Changes in BMD should not prevent the use of dienogest when indicated, but patients should be counseled appropriately, particularly if predisposed to osteoporosis.

Dienogest 2 mg offers an effective and tolerable alternative to surgical intervention for the long-term management of endometriosis, providing several important advantages over combined oral contraceptive pills (COCs).

Dydrogesterone

Dydrogesterone is a selective progesterone receptor agonist with good oral bioavailability. Dydrogesterone has been shown to help in symptom relief as well as regression of endometriosis with an improvement in conception rates in subfertile patients.[5]

Dydrogesterone acts by causing atrophy of ectopic endometrium with no effect on the normal endometrium along with inhibiting the development of new endometriotic lesions. It does not interfere with ovulation and menstruation and neither does it cause weight gain and edema.

Prolonged cyclical and continuous regimen of dydrogesterone are effective for reducing chronic pelvic pain in women with endometriosis. Results of the ORCHIDEA study[6] revealed 356 women were treated with 10 mg dydrogesterone 2–3/day either from day 5 to day 25 or continuous for 6 months. A marked reduction in chronic pelvic pain and dysmenorrhea with both groups was observed without any difference in either group. Improvements in other parameters related to quality of life and sexual well-being were also noted.

A meta-analysis of dydrogesterone as treatment in endometriosis published in 2021[7] compared to gestrinone showed that dydrogesterone relieved dysmenorrhea, increased pregnancy rates, and reduced the risk of certain adverse effects. As compared to GnRH-agonist, dydrogesterone also lowered the risk of endometriosis recurrence.

There are studies showing the combined use of dydrogesterone with letrozole[8] reduced the levels of vascular endothelial growth factor (VEGF), cancer antigen 125 (CA125), interleukin (IL)-6, and tumor necrosis factor (TNF)-α, as compared to control groups.

Use of levonorgestrel-releasing intrauterine device (IUD) in women with endometriosis accompanied with adenomyosis for chronic pelvic pain, dysmenorrhea showed promising response at least for 1–2 years.[9]

GnRH Antagonists

GnRH antagonists immediately reduce gonadal steroid levels by suppressing pituitary gonadotropin secretion, avoiding the initial stimulatory phase of the agonists. GnRH antagonists have a rapid onset and reversibility of action as compared to GnRH agonists. GnRH antagonists, such as cetrorelix and ganirelix, are synthetic peptides, requiring subcutaneous administration or implantation of long-acting depots. The peptide structure is responsible for histamine-related hypersensitivity reactions. The newer antagonists are now available for oral administration with a more favorable safety profile as they are non-peptide forms (Elagolix, Abarelix, Ozarelix, TAK-385).

These produce a hypoestrogenic milieu in a dose-dependent manner by direct pituitary gonadotropin suppression. Thus, endometriotic cell proliferation and invasion is inhibited, but sufficient circulating estrogen levels are maintained to avoid the adverse effects of estrogen deficiency such as vasomotor symptoms, vaginal atrophy, and bone demineralization.

There have been several studies evaluating the use of the novel GnRH antagonist, elagolix, for medical management of endometriosis-associated pain.

Diamond et al.[10] in a phase 2 study in women with laparoscopically confirmed endometriosis and associated pain, demonstrated that elagolix had an acceptable efficacy and safety profile. Dysmenorrhea and nonmenstrual pelvic pain scores were reduced with elagolix as compared to placebo.

Elagolix demonstrated efficacy in the management of endometriosis-associated pain in phase 1 and 2 trials.[11]

In a study by Carr et al.,[12] elagolix demonstrated efficacy similar to subcutaneous depot medroxyprogesterone acetate for endometriosis-associated pain.

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs) can have variable effects on progesterone receptors from different tissues, ranging from being a pure agonist or a mixed agonist/antagonist to a pure antagonist.

Ulipristal acetate and asoprisnil belong to this category of drugs. Ulipristal acetate with its proapoptotic effects has been shown to cause regression and atrophy of endometriotic lesions in rats, reduced cellular proliferation, as indicated by a decrease in Ki-67 expression, and has an anti-inflammatory effect, as shown by a decrease in cyclooxygenase-2 expression.[13] Its feasibility, however, is yet to be determined.

Asoprisnil, the first SPRM to reach an advanced stage of clinical development, was shown to induce a reversible amenorrhea and suppress endometriosis-associated pain without estrogen deprivation.

The role of asoprisnil to reduce nonmenstrual pelvic pain/dysmenorrhea scores was shown to be statistically significant in a study by K Chwalisz et al.,[14] but due to endometrial changes in patients, the phase 3 trials were discontinued.

Tanaproget is another SPRM which has been seen to cause regression of experimentally induced endometriosis in vivo. However, its feasibility in humans is yet to be evaluated.[15]

Selective Estrogen Receptor Modulators

Raloxifene is a selective estrogen receptor modulator (SERM) compound which has pre-clinically demonstrated its estrogen antagonist effect on uterine tissue in rats. In a study by Z Yao et al.,[16] raloxifene in a dose of 10.0 mg/kg produced statistically significant endometriotic implant regression in rat models. Another study was, however, terminated prematurely when it was seen that chronic pelvic pain from endometriosis returned sooner in those treated with raloxifene as compared to placebo.[17]

Bazedoxifene (BZA), a third-generation SERM, effectively antagonises estrogen-induced uterine endometrial stimulation without countering estrogenic effects in bone or the central nervous system. BZA induced regression of endometriosis implants probably due to decreased estrogen-mediated cell proliferation.[18] A similar effect was observed when BZA was combined with conjugated estrogen as seen in murine models.[19] This novel therapy in which BZA is combined with one or more estrogens called as tissue-selective estrogen complex (TSEC) therapy aims towards better tolerability.

Aromatase Inhibitors

Aromatase inhibitors including letrozole and anastrozole inhibit the conversion of testosterone and androstenedione to estradiol and estrone, respectively thereby reducing the production of estrogen in the endometriosis implants. Endometriotic implants do express the enzyme aromatase and can sustain their own growth and viability by estrogen production. Animal studies have shown that aromatase inhibitors can effectively eradicate endometriotic implants.[20]

Aromatase inhibitors are usually reserved for women with severe, intractable endometriosis-associated pain. They are generally administered as a combination therapy with oral contraceptive pills, progestins, and GnRH analogues.[21] These agents suppress the hypothalamic-pituitary-ovarian axis thereby preventing superovulation and consequent ovarian cyst formation which may result from aromatase inhibitor monotherapy. Other concerns about prolonged aromatase inhibitor therapy are associated bone loss due to hypoestrogenism. A systematic review of eight studies with a total of 137 patients demonstrated that aromatase inhibitors combined with progestogens, COCs, GnRH agonists reduced the

mean pain scores and size of the endometriosis lesion with improvement in quality of life.[22] Despite these results, the use of aromatase inhibitor for treatment of endometriosis remains an off-label use of the drug and patients should be counseled with respect to the same.

NON-HORMONAL TREATMENTS

Immunomodulators

Endometriosis is a chronic inflammatory condition and targeting proinflammatory markers can result in regression of the lesions as shown in a number of studies with various immunomodulators. Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine playing a vital role in initiating inflammatory cascades. It is found to be increased in the peritoneal fluid and serum of women with endometriosis implicating its role in the pathogenesis of the disease process.[23] Etanercept, a TNF-α blocker, was evaluated in a randomized controlled trial (RCT) in an animal study. It led to a statistically significant decrease in the surface area as well as absolute number of endometriotic red lesions in the treatment group.[24] In another study using a rat model, long-term treatment with human interferon-α2b (IFN-α2b) resulted in a reduction in surgically induced endometriosis implant size when compared with placebo.[25] Another immunomodulator (loxoribine) caused a reduction in natural killer cells and endometriotic lesions in a rat model.[26] Other immunomodulators, such as lipoxin,[27,28] rapamycin,[29] and pentoxifylline,[30] also showed a similar reduction of endometriotic lesions.

On the other hand, a small RCT clinically evaluating infliximab, another TNF-α blocker, was shown to have no effect on endometriosis-related pain.[31]

A Cochrane Database systematic review (2013) of the effectiveness and safety of anti-TNF-α treatment in the management of endometriosis which included only one trial studying infliximab concluded that there is not enough evidence to support the use of anti-TNF-α drugs in the management of endometriosis-related pelvic pain.[32]

Anti-angiogenic Agents

Neoangiogenesis or formation of new blood vessels from pre-existing ones, is important for the growth, initiation, spread, invasion as well as recurrence of endometriosis. Survival of endometriotic lesions is crucially dependent on the establishment of an adequate blood supply as mentioned in a number of studies.[33,34] The peritoneal fluid from patients with endometriosis contains increased amounts of angiogenic growth factors and low levels of anti-angiogenic compounds.[35] Finally, the eutopic endometrium from patients with endometriosis has been shown to exhibit an increased angiogenic potential when compared with healthy women. This may contribute to formation of endometriosis

lesions by retrograde menstruation of highly angiogenic endometrial fragments into the peritoneal cavity lending more credibility to the theory of retrograde menstruation causing endometriosis. Endometriosis has been, therefore, classified as a typical angiogenic disease, similar to cancer, psoriasis or diabetic retinopathy. Keeping this in mind, antiangiogenic agents were thought to be able to inhibit these processes and contain endometriosis. Thus, many antiangiogenic agents have been evaluated in vitro for treating endometriosis such as growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclooxygenase-2 inhibitors, phytochemical compounds, and so on. However, clinic evidence is still lacking.

Different members of the statin family have been shown to be effective in vitro in reducing angiogenesis and endometriotic implant size in in vitro and animal studies.[36]

The angiogenesis inhibitor lodamin, an oral nontoxic formulation of TNP-470, statistically significantly decreased endothelial progenitor cell levels while suppressing lesion growth.[37]

Romidepsin is a histone deacetylase (HDAC) inhibitor. It targets VEGF at the transcriptional level, which subsequently leads to the reduction of the secreted active form of VEGF from human immortalized epithelial cells. Thus, romidepsin may be a potential therapeutic candidate against angiogenesis in endometriosis.[38]

In a nude mouse model of endometriosis, Icon romidepsin, the immunoconjugate molecule of romidepsin, destroyed endometriotic implants by vascular disruption without apparent toxicity, reduced fertility, or subsequent teratogenic effects. Consequently, Icon romidepsin could serve as a novel nontoxic, fertility-preserving, and effective treatment for endometriosis.[39]

Dopaminergic agonists, such as cabergoline, quinagolide, and bromocriptine also exhibit antiangiogenic activities. Cabergoline was shown to decrease vascular endothelial growth factor (VEGF) and VEGFR-2 protein expression in mice.[40] Cabergoline and bromocriptine reduced endometriotic lesion size in a human study as well and were comparable to GnRH agonists.[41]

Bentamapimod is a c-Jun NH2-terminal kinase inhibitor (JNKI). A prospective randomized, placebo-controlled study in baboons was conducted to evaluate its feasibility in treating induced endometriosis. It also has fewer side effects and less effect on cycle length or serum reproductive hormones.[42]

There is a need for controlled clinical trials to transfer the experimental findings from studies involving anti-angiogenic agents from bench to bedside. Anti-angiogenic agents which exhibit an acceptable side effect without effect on fertility or pregnancy in young women need to be identified and studied further. In the event of successful research in this field, anti-angiogenic treatment holds great potential in treatment of endometriosis.

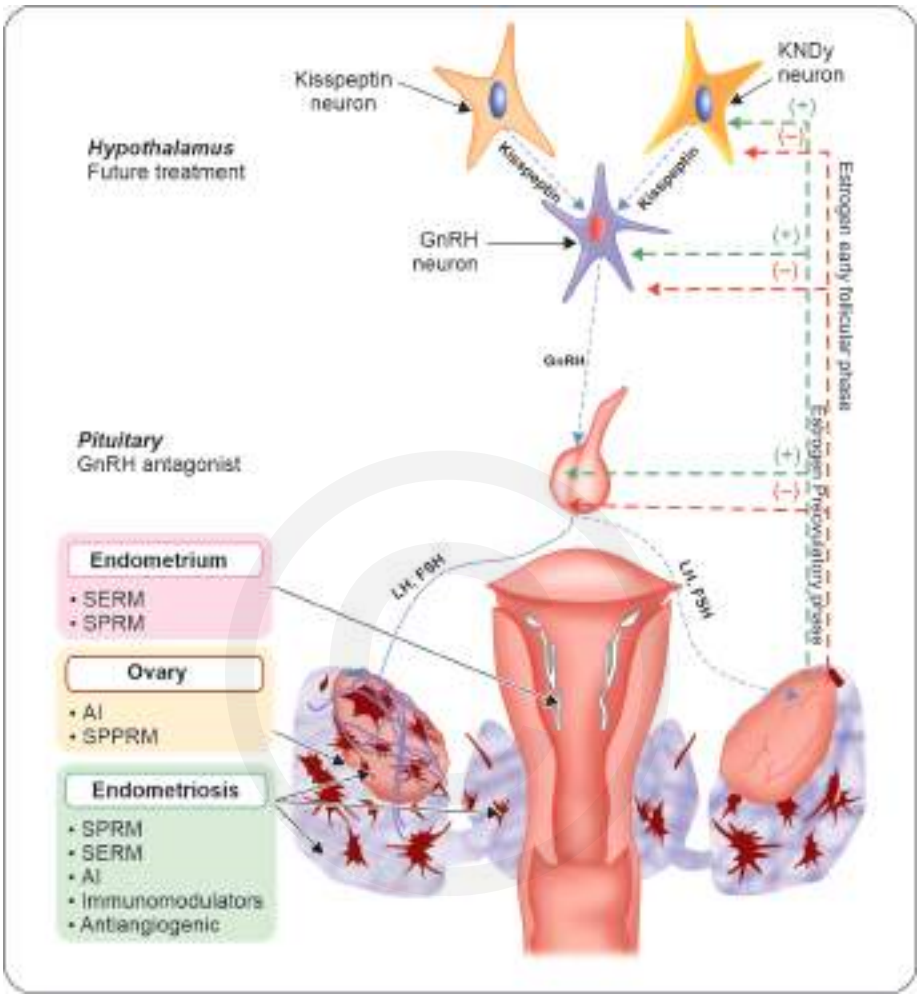

Fig. 1: Schematic representation of the different investigational approaches and trends in the treatment of endometriosis with their target sites[1]

FUTURE

Recent novel discoveries in neuroendocrinology, tumorigenesis, neurogenesis, and genomics have the potential to transform the management approaches for endometriosis.

The kisspeptin/neurokinin B/dynorphin (KNDy) hypothesis suggests that KNDy neurons in the arcuate nucleus may interact to control the release and pulsatility of GnRH which may in turn have a role in control of endometriosis.[43]

In patients with endometriosis-associated pain, central sensitization is thought to play a role and, therefore, other treatment strategies that could be

offered include neuromodulators or myofascial trigger point injections. In these patients, physiotherapy and cognitive treatment have been suggested, although more clinical trials specifically in endometriosis are required.

Nerve growth factor, a major neurotrophic factor in endometriosis,[44] may be responsible for increased nerve density and this can be a potential future target for the treatment of endometriosis though more research is needed in this area.

In order to translate these findings to clinical practice, additional work is required to identify the genes associated with the disease process **(Fig. 1)**.

Conclusion

Endometriosis is an enigmatic entity causing substantial morbidity and reduced quality of life due to its various manifestations such as chronic pelvic pain, severe dysmenorrhea, and infertility. Recent research involving the possible role of genetics, the environment, and the immune system have shed more light on the pathogenesis of this disorder and opened up several new potential targets for newer treatment options. Medical management options available and commonly used today have a number of limitations including risk of recurrence, contraceptive effect in women desiring pregnancy as well as a number of side effects. This further highlights the need for new research in this field and emphasizes the need for newer trends in the medical management of endometriosis.

References

1. Bedaiwy MA, Alfaraj S, Yong P, et al. New developments in the medical treatment of endometriosis. Fertil Steril. 2017;107(3);555-65.
2. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril. 2017;107(3):533-6.
3. Strowitzki T, Faustmann T, Gerlinger C, et al. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. Int J Womens Health. 2015;7:393-401.
4. Lee SR, Yi KW, Song JY, et al. Efficacy and safety of long-term use of dienogest in women with ovarian endometrioma. Reprod Sci. 2018;25(3):341-6.
5. Taylor PJ, Kredentser JV. Nonsurgical management of minimal and moderate endometriosis to enhance fertility. Int J Fertil. 1992;37(3):138-43.
6. Sukhikh GT, Adamyal LV, Dubrovina SO, et al. Prolonged cyclical and continuous regimens of dydrogesterone are effective for reducing chronic pelvic pain in women with endometriosis: results of the ORCHIDEA study. Fertil Steril. 2021;116(6):1568-77.
7. Peng C, Huang Y, Zhou Y, et al. Dydrogesterone in the treatment of endometriosis: evidence mapping and meta-analysis. Arch Gynaecol Obstet. 2021;304(1):231-52.
8. Sun S, Zhang H, Zhong P, et al. The effect of letrozole combined with dydrogesterone for endometriosis in China: a meta-analysis. Biomed Res Int. 2021;2021:9946060.
9. Batamondes L, Petta CA, Fernandes A, et al. Use of levonorgestrel-releasing intrauterine system in women with endometriosis, chronic pelvic pain and dysmenorrhea. Contraception. 2007;75(6 Suppl):S134-9.
10. Diamond MP, Carr B, Dmowski WP, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. Reprod Sci. 2014;21(3):363-71.

11. Melis GB, Neri M, Corda V, et al. Overview of elagolix for the treatment of endometriosis. Expert Opin Drug Metab Toxicol. 2016;12(5):581-8.
12. Carr B, Dmowski WP, O'Brien C, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. Reprod Sci. 2014;21(11):1341-51.
13. Huniadi CA, Pop OL, Antal TA, et al. The effects of ulipristal on Bax/Bcl-2, cytochrome c, Ki-67 and cyclooxygenase-2 expression in a rat model with surgically induced endometriosis. Eur J Obstet Gynecol Reprod Biol. 2013;169(2):360-5.
14. Chwalisz K, Perez MC, DeManno D, et al. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev. 2005;26(3):423-38.
15. Bruner-Tran KL, Zhang Z, Eisenberg E, et al. Down-regulation of endometrial matrix metalloproteinase-3 and -7 expression in vitro and therapeutic regression of experimental endometriosis in vivo by a novel nonsteroidal progesterone receptor agonist, tanaproget. J Clin Endocrinol Metab. 2006;91(4):1554-60.
16. Yao Z, Shen X, Capodanno I, et al. Validation of rat endometriosis model by using raloxifene as a positive control for the evaluation of novel SERM compounds. J Invest Surg. 2005;18(4):177-83.
17. Stratton P, Sinaii N, Segars J, et al. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstet Gynecol. 2008;111(1):88-96.
18. Kulak J Jr, Fischer C, Komm B, et al. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology. 2011;152(8):3226-32.
19. Naqvi H, Sakr S, Presti T, et al. Treatment with bazedoxifene and conjugated estrogens results in regression of endometriosis in a murine model. Biol Reprod. 2014;90(6):121.
20. Bilotas M, Meresman G, Stella I, et al. Effect of aromatase inhibitors on ectopic endometrial growth and peritoneal environment in a mouse model of endometriosis. Fertil Steril. 2010;93(8):2513-8.
21. Committee opinion no. 663 summary: aromatase inhibitors in gynecologic practice. Obstet Gynecol. 2016;127(6):1187-8.
22. Nawathe A, Patwardhan S, Yates D, et al. Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis. BJOG. 2008;115(7):818-22.
23. Bedaiwy MA, Falcone T, Sharma RK, et al. Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. Hum Reprod. 2002;17(2):426-31.
24. Barrier BF, Bates GW, Leland MM, et al. Efficacy of anti-tumor necrosis factor therapy in the treatment of spontaneous endometriosis in baboons. Fertil Steril. 2004;81(Suppl 1):775-9.
25. Ingelmo JMR, Quereda F, Acien P. Effect of human interferon-α-2b on experimental endometriosis in rats: comparison between short and long series of treatment. Eur J Obstet Gynecol Reprod Biol. 2013;167(2):190-3.
26. Keenan JA, Williams-Boyce PK, Massey PJ, et al. Regression of endometrial explants in a rat model of endometriosis treated with the immune modulators loxoribine and levamisole. Fertil Steril. 1999;72(1):135-41.
27. Xu Z, Zhao F, Lin F, et al. Lipoxin A4 inhibits the development of endometriosis in mice: the role of anti-inflammation and anti-angiogenesis. Am J Reprod Immunol. 2012;67(6):491-7.
28. Kumar R, Clerc A-C, Gori I, et al. Lipoxin A4 prevents the progression of de novo and established endometriosis in a mouse model by attenuating prostaglandin E2 production and estrogen signaling. PLoS One. 2014;9(2):e89742.
29. Laschke MW, Elitzsch A, Scheuer C, et al. Rapamycin induces regression of endometriotic lesions by inhibiting neovascularization and cell proliferation. Br J Pharmacol. 2006;149(2):137-44.

30. Vlahos NF, Gregoriou O, Deliveliotou A, et al. Effect of pentoxifylline on vascular endothelial growth factor C and flk-1 expression on endometrial implants in the rat endometriosis model. Fertil Steril. 2010;93(4):1316-23.
31. Koninckx PR, Craessaerts M, Timmerman D, et al. Anti-TNF-α treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. Hum Reprod. 2008;23(9):2017-23.
32. Lu D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. Cochrane Database Syst Rev. 2013;(3):CD008088.
33. Laschke MW, Menger MD. Anti-angiogenic treatment strategies for the therapy of endometriosis. Hum Reprod Update. 2012;18(6):682-702.
34. Groothuis PG, Nap AW, Winterhager E, et al. Vascular development in endometriosis. Angiogenesis. 2005;8(2):147-56.
35. Becker CM, D'Amato RJ. Angiogenesis and antiangiogenic therapy in endometriosis. Microvasc Res. 2007;74(2-3):121-30.
36. Oktem M, Esinler I, Eroglu D, et al. High-dose atorvastatin causes regression of endometriotic implants: a rat model. Hum Reprod. 2007;22(5):1474-80.
37. Becker CM, Beaudry P, Funakoshi T, et al. Circulating endothelial progenitor cells are up-regulated in a mouse model of endometriosis. Am J Pathol. 2011;178(4):1782-91.
38. Imesch P, Samartzis EP, Schneider M, et al. Inhibition of transcription, expression, and secretion of the vascular epithelial growth factor in human epithelial endometriotic cells by romidepsin. Fertil Steril. 2011;95(5):1579-83.
39. Krikun G, Hu Z, Osteen K, et al. The immunoconjugate "icon" targets aberrantly expressed endothelial tissue factor causing regression of endometriosis. Am J Pathol. 2010;176(2):1050-6.
40. Novella-Maestre E, Carda C, Ruiz-Sauri A, et al. Identification and quantification of dopamine receptor 2 in human eutopic and ectopic endometrium: a novel molecular target for endometriosis therapy. Biol Reprod. 2010;83(5):866-73.
41. Ercan CM, Kayaalp O, Cengiz M, et al. Comparison of efficacy of bromocriptine and cabergoline to GnRH agonist in a rat endometriosis model. Arch Gynecol Obstet. 2015;291(5):1103-11.
42. Hussein M, Chai DC, Kyama CM, et al. c-Jun NH 2-terminal kinase inhibitor bentamapimod reduces induced endometriosis in baboons: an assessor-blind placebo-controlled randomized study. Fertil Steril. 2016;105(3):815-24.e5.
43. Navarro VM, Gottsch ML, Chavkin C, et al. Regulation of gonadotropin-releasing hormone secretion by kisspeptin/dynorphin/neurokinin B neurons in the arcuate nucleus of the mouse. J Neurosci. 2009;29(38):11859-66.
44. de Arellano MLB, Arnold J, Vercellino F, et al. Overexpression of nerve growth factor in peritoneal fluid from women with endometriosis may promote neurite outgrowth in endometriotic lesions. Fertil Steril. 2011;95(3):1123-6.

Chapter 7

Stimulation Protocols Most Suited for IVF in Endometriosis

Kundan Ingale

INTRODUCTION

Endometriosis is an enigmatic disease which is defined as development of endometrial tissue outside uterus and associated with chronic inflammatory reaction. Carl Rokintanski discovered endometriosis as disease for the first time. Its incidence is 70–80% in the group of patients with chronic pelvic pain and 40% in the group of patients with infertility. It is associated with inflammatory reaction surrounding ectopic endometrial implants which leads to severe dysmenorrhea, dyspareunia, and chronic pelvic pain. It involves all pelvic reproductive organs which leads to infertility. Endometriosis affects not only ovarian reserve but also oocyte quality. In this chapter, we will discuss about ovarian stimulation protocols to optimize the number of oocytes as well as the quality of oocyte.

OVARIAN FACTORS: OVARIAN DYSFUNCTION

An altered follicular environment, represented by elevated concentrations of progesterone and interleukin-6 (IL-6) and decreased concentration of vascular endothelial growth factor, may be responsible for alterations within the oocyte, leading to impaired fertilization capacity of the oocytes, and reduced embryo quality with low implantation potential. The presence of ovarian endometriomas, especially if bilateral, can affect the ovarian reserve, impacting the ovarian response to gonadotropins during assisted reproductive technologies (ART). A histological study reported a significant reduction in the primordial follicle cohort in affected ovaries. Follicle depletion may be secondary to damage induced by the endometriosis-associated inflammatory reaction and by increased tissue oxidative stress leading to fibrosis. A group of potentially toxic agents, such as free iron, that can diffuse through the cyst wall of the endometrioma, as well as long-lasting mechanical stretching of ovarian cortex, can all have a detrimental impact on the ovarian reserve. Due to detrimental impact of endometriosis on oocyte qualitatively and quantitatively, we need to follow proper ovarian stimulation protocols so that we get optimum number of good quality oocytes to achieve maximum clinical and ongoing pregnancy rate.

DIFFICULTIES DURING OVARIAN STIMULATION

Endometriosis is known to affect reproductive outcome of IVF treatment. The cumulative pregnancy rate is lower in moderate-to-severe endometriosis than in those with tubal factor infertility.

As per meta-analysis by Barnhatt and collegues in 2002, significantly fewer number of oocytes were retrieved from women with endometriosis than in tubal factor controls [odds ratio (OR):0.92; confidence interval (CI):0.85–0.99].[1] They also demonstrated that mean number of oocytes obtained and peak serum estradiol levels achieved during stimulation were significantly lower in those with stage III-IV as opposed to stages I-II disease.[1] In a systematic review and meta-analysis from 2013, Harb and colleagues included 27 observational studies and a total of 8,984 women and reported significantly lower fertilization rates [relative risk (RR):0.93; 95%CI: 0.87–0.99; 7 studies; 2044 patients], with no significant reduction in implantation, clinical pregnancy, or live birth rates in women with American Society for Reproductive Medicine (ASRM) stage I/II endometriosis compared to women without endometriosis.[2]

Camille Robin et al. in 2021 demonstrated in their single center comparative retrospective study that there is no difference in average oocyte quality index (AOQI) and metaphase II oocyte morphological score (MOMS) in endometriosis and control women(adjusted p = 0.084 & 0.053 respectively).[3] In case of endometriosis, there were significantly fewer metaphase II oocytes retrieved, embryos obtained, grade 1 embryos, and number of cumulative clinical pregnancies compared to controls. In the endometriosis group, endometriosis surgery was associated with a reduced number of mature oocytes retrieved, and the presence of endometrioma(s) was associated with some abnormal oocyte shapes.

Decrease in ovarian response that required higher doses of gonadotropins is usually seen in patients with endometriomas. This effect is prominently seen in women with larger as well as with multiple endometriomas.

Significant decrease in ovarian reserve with lower antral follicle count (AFC), fewer oocytes, embryos, and top-quality embryos were observed in patients with ovarian endometriomas of size ≥ 6 cm ($p < 0.05$).[4]

OVARIAN STIMULATION PROTOCOLS

Different ovarian stimulation protocols, such as ultra-long GnRH agonist, long GnRH agonist, and GnRH antagonist are useful in IVF treatments in women with endometriosis. Since the last two decades, literature supported the use of ultra-long GnRH agonist protocols for ovarian stimulation in endometriosis.

In prospective randomized trial by Recai Pabuccu et al., they showed that outcome of controlled ovarian hyperstimulation (COH) with both GnRH antagonist and GnRH agonist were similar in patients with mild-to-moderate

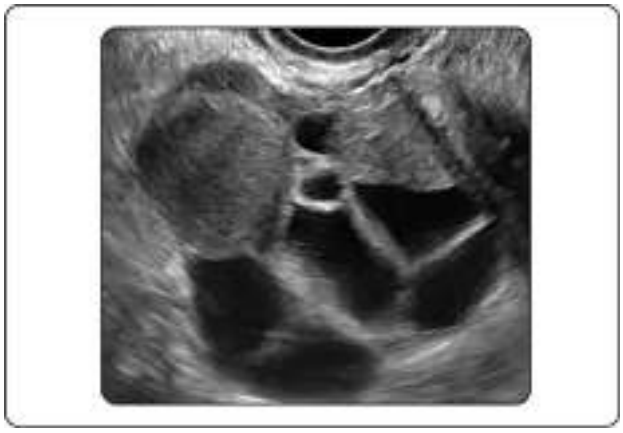

Fig. 1: Controlled ovarian hyperstimulation in presence of endometrioma

Table 1 Patients undergone ovarian surgery for endometrioma

	GnRH antagonist	*GnRH agonist*
Implantation rate	15.9%	22.6%
Clinical Pregnancy rate	27.5%	39%

Table 2 Patients with endometrioma and no history of ovarian surgery

	GnRH antagonist	*GnRH agonist*
Implantation rate	12.5%	14.8%
Clinical pregnancy rate	20.5%	24.2%

endometriosis. They concluded that considering the implantation and clinical pregnancy rates **(Fig. 1)**, COH with both GnRH antagonist and GnRH-agonist protocols may be equally effective in patients with mild-to-moderate endometriosis and endometrioma who did and did not undergo ovarian surgery **(Tables 1 and 2)**.[5]

Ercan Bastu et al. in their comparative study of GnRH agonist and GnRH antagonist protocols in endometriosis patients who have undergone laparoscopic endometrioma resection surgery showed that the number of follicles on human chorionic gonadotropin injection day, duration of hyperstimulation, number of retrieved metaphase II oocytes, and total number of grade 1 embryos were statistically significantly higher in the long GnRH-agonist protocol **(Fig. 2)**.[6]

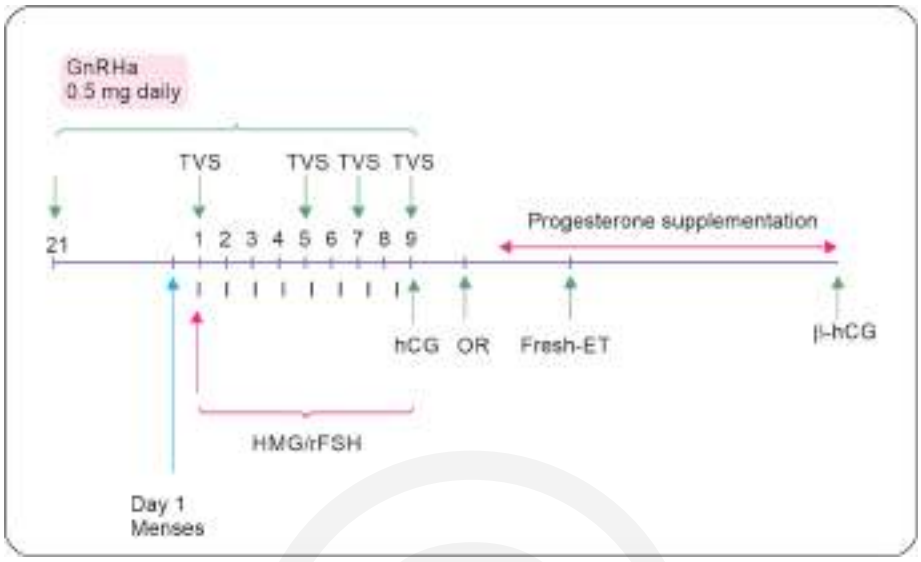

Fig. 2: Long GnRH-agonist protocol

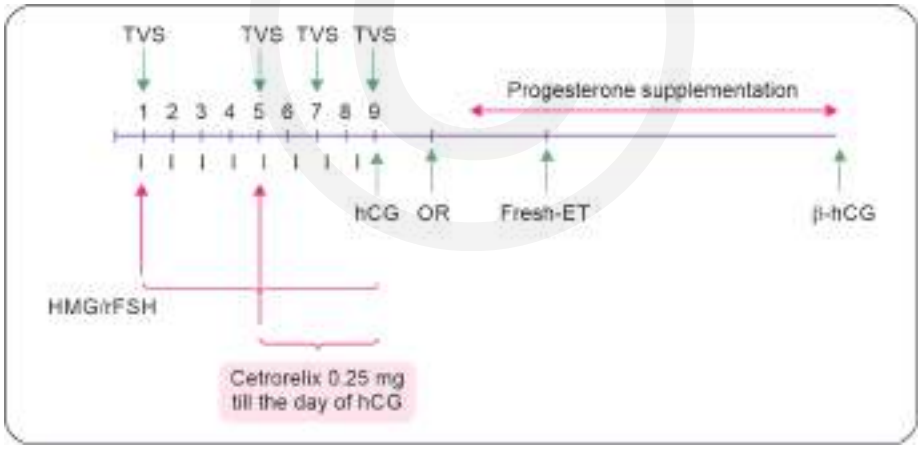

Fig. 3: GnRH-antagonist protocol

Kolanska et al. performed a retrospective analysis of 284 IVF cycles, and reported that women with endometriosis experienced higher pregnancy and live birth rates after fresh embryo transfer but not after frozen cycle when long GnRH agonist protocols were compared to GnRH antagonist protocols **(Fig. 3)**.[7] When comparing the GnRH agonist and antagonist groups, patients with endometriosis stage I-II, had a tendency toward higher β-human chorionic gonadotropin (hCG) positive, clinical pregnancy, and live birth rates (42.8% vs. 26.7%; p = 0.07) in favor of GnRH agonist use.[8]

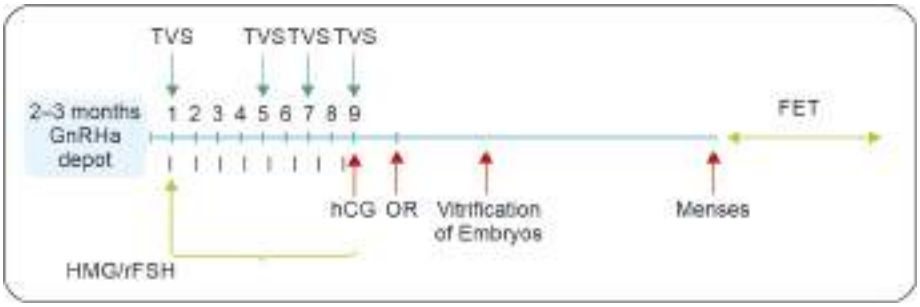

Fig. 4: Prolonged GnRH-agonist protocol

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A specific protocol for ART in women with endometriosis cannot be recommended. Both GnRH antagonist and agonist protocols can be offered based on patients' and physicians' preferences as no difference in pregnancy or live birth rate has been demonstrated.

ULTRA-LONG GNRH-AGONIST PROTOCOL

Retrospective study by Feiyan Zhao et al. compared all three ovarian stimulation protocols (ultra-long GnRH agonists, GnRH antagonist, long GnRH agonist) for women with endometriosis. They concluded that no significant differences were found in the implantation rate and clinical pregnancy rate among the groups. For those DOR patients, who had undergone ovarian endometriosis cystectomy, the prolonged GnRH-agonist protocol **(Fig. 4)** may achieve better clinical in vitro fertilization and embryo transfer (IVF-ET) outcomes, but there were no significant differences from the other groups. In addition, no significant differences were present in the number of retrieved oocytes, oocyte fertilization rate, embryo utilization rate, live birth rate, abortion rate, ectopic pregnancy rate, or multiple pregnancy rate in the three groups ($p>0.05$). The GnRH-antagonist protocol may reduce the cost and time of drug treatment.[9]

The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis is not recommended, as the benefit is uncertain.

Conclusion

IVF is an effective means of overcoming the abnormal pelvic environment in endometriosis. Though it is recommended only for stage III and stage IV endometriosis patients, overall pregnancy rates are on higher side in patients with endometriosis than in those who do not have endometriosis irrespective of stage of disease. To achieve the

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primary objective of ovarian stimulation in IVF, GnRH agonist protocol (Fresh cycle) is recommended, especially in revised ASRM (rASRM) stage I and II endometriosis patients. Either GnRH agonist or GnRH antagonist both are equally good protocols for stage III-IV endometriosis patients, decision should be individualized based on stage of disease, ovarian reserve, and other fertility factors. Prolonged GnRH agonist before IVF stimulation is now not recommended as there are no advantages over other protocols like GnRH agonist and GnRH antagonist.

References

1. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril. 2002;77(6):1148-55.
2. Harb HM, Gallos ID, Chu J, et al. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. BJOG. 2013;120(1):1308-20.
3. Robin C, Uk A, Decanter C, et al. Impact of endometriosis on oocyte morphology in IVF-ICSI: retrospective study of a cohort of more than 6000 mature oocytes. Reprod Biol Endocrinol. 2021;19(1):160.
4. Zeng C, Lu R, Li X, et al. The presence of ovarian endometrioma adversely affects ovarian reserve and response to stimulation but not oocyte quality or IVF/ICSI outcomes: aretrospective cohort study. J Ovarian Res. 2022;15(1):116.
5. Pabuccu R, Onalan G, Kaya C. GnRH agonist and antagonist protocols for stage I-II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril. 2007;88(4):832-9.
6. Bastu E, Yasa C, Dural O, et al. Comparison of ovulation induction protocols after endometrioma resection. JSLS. 2014;18(3):e2014.00128.
7. Kolanska K, Cohen J, Bendifallah S, et al. Pregnancy outcomes after controlled ovarian hyperstimulation in women with endometriosis-associated infertility: GnRH-agonist versus GnRH-antagonist. J Gynecol Obstet Hum Reprod. 2017;46(9):681-6.
8. Drakopoulos P, Rosetti J, Pluchino N, et al. Does the type of GnRH analogue used, affect live birth rates in women with endometriosis undergoing IVF/ICSI treatment, according to the rAFS stage? Gynecol Endocrinol. 2018;34(10):884-9.
9. Zhao F, Lan Y, Chen T, et al. Live birth rate comparison of three controlled ovarian stimulation protocols for in vitro fertilization-embryo transfer in patients with diminished ovarian reserve after endometrioma cystectomy: a retrospective study. J Ovarian Res. 2020;13(1):23.

Chapter 8

Tips and Tricks to Improve ART Outcomes in Endometriosis

Jatin Shah

INTRODUCTION

Endometriosis is a heterogeneous disease whose pathogenesis is complex and often affects fertility. From an IVF point of view, the main concerns are a reduced yield of oocytes, impaired endometrial receptivity and a lower cumulative clinical pregnancy rate. Tips and tricks will focus on controlled ovarian stimulation protocols, the nuances of surgery prior to IVF, fresh or frozen embryo transfer, medical pretreatment with analogs or dienogest and the importance of fertility preservation in endometriosis patients undergoing complex surgeries. The future lies in developing therapeutic alternatives targeting oxidative stress, inflammation, aberrant angiogenesis, oocyte quality and endometrial receptivity for improving IVF outcomes.

PREVALENCE

The prevalence of endometriosis in subfertile women ranges from 20% to 50%;[1] and in one large study, it was found that the risk of infertility was increased 2-fold in women <35 years with endometriosis compared to women without endometriosis.[2] More than a third of women undergoing IVF have endometriosis.

ETIOLOGY OF INFERTILITY IN ENDOMETRIOSIS

The possible causes of impaired fertility in endometriosis are adhesions, chronic intraperitoneal inflammation, luteinized unruptured follicle (LUF), luteal phase defects, disturbed folliculogenesis, progesterone resistance, detrimental effects on sperm, anti-endometrial antibodies, and dysfunctional uterotubal motility.[3-7]

Among women with mild endometriosis, approximately 50% will be able to conceive without treatment, whereas in women with moderate disease, only 25% will conceive spontaneously. Surprisingly, superficial peritoneal lesions are more closely associated with infertility than solitary endometriomas or deep infiltrating endometriosis.[5]

INTRAUTERINE INSEMINATION OR IN VITRO FERTILIZATION

Intrauterine insemination (IUI) is typically not offered to women with moderate/severe endometriosis, because of probable adhesionsaround the fallopian tubes, whereas in vitro fertilization (IVF) is a successful treatment option with results comparable to other causes of infertility. Moreover, there is evidence that the risk of recurrence of endometriosis is increased with IUI and not with IVF.[8-10]

INDICATIONS FOR IN VITRO FERTILIZATION IN ENDOMETRIOSIS

IVF is indicated for endometriosis with diminished ovarian reserve, advanced age, infertility duration of more than 5 years, failed IUI cycles, recurrent endometriomas, bilateral large endometriomas, and presence of adenomyosis, bilateral tubal factor, and presence of male factor.

SURGERY BEFORE IN VITRO FERTILIZATION TO IMPROVE OUTCOMES

Laparoscopic surgery prior to and solely for improving IVF outcomes is not beneficial and in fact can do harm by reducing an already depleted ovarian reserve. There is also a strong case for freezing oocytes/embryos prior to laparoscopic surgery for endometriosis, especially in young or nulliparous women as surgery is likely to cause a depletion of the ovarian reserve. Muzii in 2018 showed that anti-Müllerian hormone (AMH) levels are reduced in patients with ovarian endometriomas compared to patients with other benign ovarian cysts. He also showed that during stripping of the cyst wall, the ovarian tissue pulled from around the ovarian hilum showed presence of primordial, primary, and secondary follicles in 69% of cases thereby confirming the loss of ovarian reserve and precious oocytes.

ENDOMETRIOMAS:INDICATIONS FOR SURGERY

Garcia and Velasco have clearly mentioned the indications for resection of endometrioma before an IVF cycle. These include rapid growth, suspicious features on ultrasonography (USG), pain attributed to the mass, and potential for rupture during pregnancy, inability to access follicles in normal ovarian tissue, and very large or bilateral endometriomas.

EFFECTS OF ENDOMETRIOSIS ON OOCYTE AND EMBRYO QUALITY

Sanchez in 2017 showed that endometriosis is associated with decreased number of follicles (with increased incidence of atresia), increased intracellular reactive oxygen species (ROS) generation which hinders oocyte maturation, oocytes with altered morphology and lower cytoplasmic mitochondrial content, and higher incidence of meiotic abnormalities.[11] However, in a subsequent study by the same

author in 2020, it was found that there was no difference in fertilization, cleavage or blastulation rates, when oocytes and embryos from endometriosis patients were compared with normal women. The reduction in ongoing pregnancy rates was attributed to a possible alteration of endometrial receptivity.[12]

DOES ENDOMETRIOSIS AFFECT OOCYTE QUALITY OR ENDOMETRIAL RECEPTIVITY?

A recent review of oocyte donation studies found that patients receiving oocytes from donors with endometriosis achieve lower implantation and pregnancy rates, whereas the status of the recipient does not influence treatment outcome. This suggests that a reduced fertility potential in women with endometriosis may be the result of poor oocyte quality rather than a defective endometrium.[13]

To further address the issue, Kamath et al. did an analysis of 13,614 donor oocyte recipient and autologous IVF cycles in women with endometriosis. There was no difference in live birth rates in oocyte recipients with endometriosis as compared to oocyte recipients without endometriosis indicating that endometrial receptivity might not be altered as thought earlier.[14]

On the other hand, the presence of an endometrioma is not correlated with oocyte quality. Numerous studies have shown that ovarian responsiveness and oocyte quality does not significantly differ between the affected and intact ovaries if the endometrioma is <5cm. Also, the presence of an endometrioma does not affect oocyte developmental competence. Caution has to be exercised to avoid inadvertent puncturing of the endometrioma during oocyte retrieval as contamination of the retrieved oocytes with endometrioma fluid could affect IVF outcomes. On a practical note, these oocytes should be washed repeatedly and cultured separately from the uncontaminated ones. On the other hand, the presence of large endometriomas (>5cm) at the time of IVF significantly decreases the number of oocytes retrieved from the affected ovary. However, oocyte quality and competence were not affected.[15]

PRE-TREATMENT FOR IN VITRO FERTILIZATION IN ENDOMETRIOSIS

As regards pre-treatment for IVF in endometriosis, a recent study showed that 3 months of Dienogest 2 mg/day had the same results as 3 months of gonadotropin-releasing hormone (GnRH) agonist suppression with a significantly lower cost of treatment and reduced side effects.[16]

However, the need for pre-treatment itself is under doubt. A Cochrane meta-analysis in 2019 clearly showed that: "Contrary to previous findings, it was uncertain as to whether long-term GnRH agonist therapy impacts the live birth rate, clinical pregnancy rate, early pregnancy losses, mean number of oocytes, and embryos in women with endometriosis."

CONTROLLED OVARIAN STIMULATION FOR ENDOMETRIOSIS

- Young patients with endometriosis and normal AMH levels should undergo controlled ovarian stimulation (COS) using recombinant follicle-stimulating hormone (rFSH) with the short antagonist protocol. The choice of trigger would depend upon the number of follicles [Agonist vs human chorionic gonadotropin (hCG)].
- However, most patients of endometriosis would categorize as Poseidon 3 or 4 (if AMH <2) and would require targeted management as is done with poor responders. The choice would be:
  - Coenzyme Q, Vitamin D, dehydroepiandrosterone (DHEA) or testosterone, and other nutritional supplements can be given for 1–2 months before the IVF cycle.
  - Long agonist protocol with standard downregulation from the mid-luteal phase. Stimulation with 300–450 IU human menopausal gonadotropin (hMG), rather than follicle-stimulating hormone (FSH) alone, from the beginning is preferred. The agonist will ensure better follicular synchrony thereby giving more oocytes, more metaphase II (MII) oocytes and more top quality embryos.
  - *Short antagonist protocol:* Begins with antagonist pre-treatment on days 2, 3, and 4 (to ensure follicular synchrony) followed by a combination of rFSH and hMG from day 5. Optionally, luteal estradiol or short term oral contraceptive pills (10–12 days only) could be used as pre-treatment to ensure follicular synchrony. The antagonist is restarted when the lead follicle is 14 mm in mean diameter. A dual trigger with HCG and an agonist is preferred.

EMBRYO TRANSFER: FRESH OR FROZEN?

Fresh embryo transfer is associated with lower pregnancy rates in women with endometriosis owing to dysfunctional embryo attachment and defective signaling. Also, markers of endometrial receptivity, such as HOXA10 and HOXA11, were found to be altered in the luteal phase endometrium of women with endometriosis. Furthermore, abnormal endometrial pinopod formation, an embryo-toxic milieu, and progesterone resistance in women with endometriosis might lead to defective implantation. These aberrations are easily corrected with ovarian suppression using the agonist downregulation protocol with exogenous estrogen/progesterone and frozen embryo transfer (FET). Studies have shown that FET helps improve clinical pregnancy and cumulative pregnancy rates by virtue of improved endometrial receptivity and pregnancy outcomes as a result of the combined effect of the agonist on the endometrium and low level of ovarian steroids.[17-18]

CLINICAL PREGNANY RATES, CUMULATIVE LIVE BIRTH RATES AND PREGNANCY OUTCOMES IN ENDOMETRIOSIS

A recent study analyzedwomen with advanced endometriosis with regards to whether the presence of an endometrioma and whether endometrioma excision or aspiration prior to IVF affects pregnancy outcomes. Clearly, the group with endometriosis had lower number of oocytes retrieved (8 vs 11), lower number of MII (6 vs 9), lower number of Day 3 high-quality embryos (2.6 vs 3.98), and lower number of viable embryos (2.9 vs 4.5) as compared to the non-endometriosis group. Furthermore, on comparing the endometrioma group with the peritoneal endometriosis groups, the study found that the mature oocyte rate, fertilization rate, viable embryo rate per oocyte retrieved, and high-quality embryo rate per oocyte retrieved were all significantly lower in the group with peritoneal endometriosis. Also, when they compared outcomes in the endometrioma cystectomy with the endometrioma aspiration group, they found that the cystectomy group had significantly lower number of oocytes retrieved, MII oocytes, and viable embryos. However, when FET outcomes between all the groups were compared, the clinical pregnancy rates per transfer were identical in all. The only difference was a lower cumulative pregnancy rate in the endometriosis group when compared to non-endometriosis controls owing to lower total number of oocytes and embryos obtained. The study concluded that the only negative effect of advanced endometriosis on IVF outcomes was a lower cumulative clinical pregnancy rate per oocyte retrieval cycle as fewer embryos were available for transfer. This negative effect is mainly caused by the diminished ovarian reserve associated with endometriomas per se or surgery and to a small extent by the damaging effects of endometrial endometriosis on oocyte maturation. The study clearly concluded that surgical excision of endometriomas prior to IVF would not improve FET outcomes.[19]

ASSOCIATED ADENOMYOSIS

Adenomyosis is often associated with endometriosis and many studies report that adenomyosis has a detrimental effect on IVF outcomes with decreased clinical pregnancy rates (50% lower than control), higher rates of miscarriage (3x), and generally poorer obstetric outcomes.[20,21] However, in a recent large study by Higgins, it was found that after correction for age and ovarian reserve, adenomyosis does not have the detrimental impact on IVF that has previously been suggested.[22]

Conclusion

- ART in women with endometriosis may be challenging due to reduced ovarian reserve.
- ART in women with endometriosis results in fewer oocytes, and possibly lower fertilization and implantation rates.

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- The detrimental effects of endometriosis on oocyte quality, fertilization, and cleavage rates are debatable and are more often seen with peritoneal endometriosis rather than with a solitary endometrioma.
- Clinical pregnancy rates may not be different than other causes of infertility.
- Live birth rates are the same as for other causes of infertility.
- Cumulative live birth rate might be lower in severe endometriosis/large endometriomas because of fewer oocytes and embryos obtained.
- The presence of an endometrioma does not impair oocyte or embryo quality and surgery for endometriomas prior to ART reduces ovarian reserve without improving pregnancy rates.
- Prophylactic oocyte/embryo freezing prior to laparoscopic surgery for endometriosis is strongly recommended, especially in young, nulliparous women.
- 3 months of Agonist/Dienogest pre-treatment does not improve IVF outcomes.
- Long agonist protocol with hMG could be the first-choice protocol for women with endometriosis having a diminished ovarian reserve. Antagonist protocol is recommended for women with endometriosis having a normal ovarian reserve.
- Frozen embryo transfer after downregulation is preferred to fresh embryo transfer for better IVF outcomes.
- Adenomyosis per se does not reduce IVF pregnancy rates or outcomes unless very severe.

References

1. Mahmood TA, Templeton A. Prevalence and genesis of endometriosis. Hum Reprod. 1991;6(4):544-9.
2. Prescott J, Farland LV, Tobias DK, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod. 2016;31(17):1475-82.
3. Taylor RN, Lebovic DI. Endometriosis. In: JF Strauss, RL Barbieri, (Eds). Yen & Jaffe's Reproductive Endocrinology. 7th Edition. Philadelphia: Elsevier Saunders. 2014;565-85.
4. Koninckx PR, Meuleman C, Demeyere S, et al. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril. 1991;55(4):759-65.
5. Olive DL, Stohs GF, Metzger DA, et al. Expectant management and hydrotubations in the treatment of endometriosis-associated infertility. Fertil Steril. 1985;44(1):35-41.
6. Bérubé S, Marcoux S, Langevin M, et al. Fecundity of infertile women with minimal or mild endometriosis and women with unexplained infertility. The Canadian Collaborative Group on Endometriosis. Fertil Steril. 1998;69(6):1034-41.
7. Santulli P, Lamau MC, Marcellin L, et al. Endometriosis-related infertility: ovarian endometrioma per se is not associated with presentation for infertility. Hum Reprod. 2016;31(8):1765-75.
8. Werbrouck E, Spiessens C, Meuleman C, et al. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril. 2006;86(3):566-71.
9. Omland AK, Tanbo T, Dale PO, et al. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod. 1998;13(9):2602-5.
10. Singh M, Goldberg J, Falcone T, et al. Superovulation and intrauterine insemination in cases of treated mild pelvic disease. J Assist Reprod Genet. 2001;18(1):26-9.

11. Sanchez AM, Vanni VS, Bartiromo L, et al. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res. 2017;10(1):43.
12. Sanchez AM, Pagliardini L, Cermisoni GC, et al. Does endometriosis influence the embryo quality and/or development? Insights from a large retrospective matched cohort study. Diagnostics (Basel). 2020;10(2):83.
13. Hauzman EE, Garcia-Velasco JA, Pellicer A. Oocyte donation and endometriosis: what are the lessons? Semin Reprod Med. 2013;31(2):173-7.
14. Kamath MS, Subramanian V, Antonisamy B, et al. Endometriosis and oocyte quality: an analysis of 13,614 donor oocyte recipient and autologous IVF cycles. Hum Reprod Open. 2022;2022(3):hoac025.
15. Li A, Zhang J, Kuang Y, et al. Analysis of IVF/ICSI-FET outcomes in women with advanced endometriosis: influence on ovarian response and oocyte competence. Front Endocrinol (Lausanne). 2020;11:427.
16. Khalifa E, Mohammad H, Abdullah A, et al. Role of suppression of endometriosis with progestins before IVF-ET: a non-inferiority randomized controlled trial. BMC Pregnancy Childbirth. 2021;21(1):264.
17. Chang Y, Shen M, Wang S, et al. Association of embryo transfer type with infertility in endometriosis: a systematic review and meta-analysis. J Assist Reprod Genet. 2022;39(5):1033-43.
18. Mohamed AMF, Chouliaras S, Jones CJP, et al. Live birth rate in fresh and frozen embryo transfer cycles in women with endometriosis. Eur J Obstet Gynecol Reprod Biol. 2011;156(2):177-80.
19. Wu Y, Yang R, Lan J, et al. Ovarian endometrioma negatively impacts oocyte quality and quantity but not pregnancy outcomes in women undergoing IVF/ICSI treatment: a retrospective cohort study. Front Endocrinol (Lausanne). 2021;12:739228.
20. Mijatovic V, Florijn E, Halim N, et al. Adenomyosis has no adverse effects on IVF/ICSI outcomes in women with endometriosis treated with long-term pituitary down-regulation before IVF/ICSI. Eur J Obstet Gynecol. 2010;151(1):62-5.
21. Salim R, Riris S, Saab W, et al. Adenomyosis reduces pregnancy rates in infertile women undergoing IVF. Reprod Biomed Online. 2012;25(3):273-7.
22. Higgins C, Fernandes H, Da Silva Costa F, et al. The impact of adenomyosis on IVF outcomes: a prospective cohort study. Hum Reprod Open. 2021;2021(2):hoab015.

Chapter 9

Surgery for Endometrioma with Infertility

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INTRODUCTION

Endometriosis is benign, but potentially metastatic, estrogen-dependent chronic inflammatory condition characterized by histological presence of ectopic endometrial tissue outside the uterine cavity.[1] Endometriomas are the most common manifestation of endometriosis of ovaries. Their presence indicates more severe disease in patients with endometriosis and leads to decreased ovarian reserve.[2]

EVALUATION

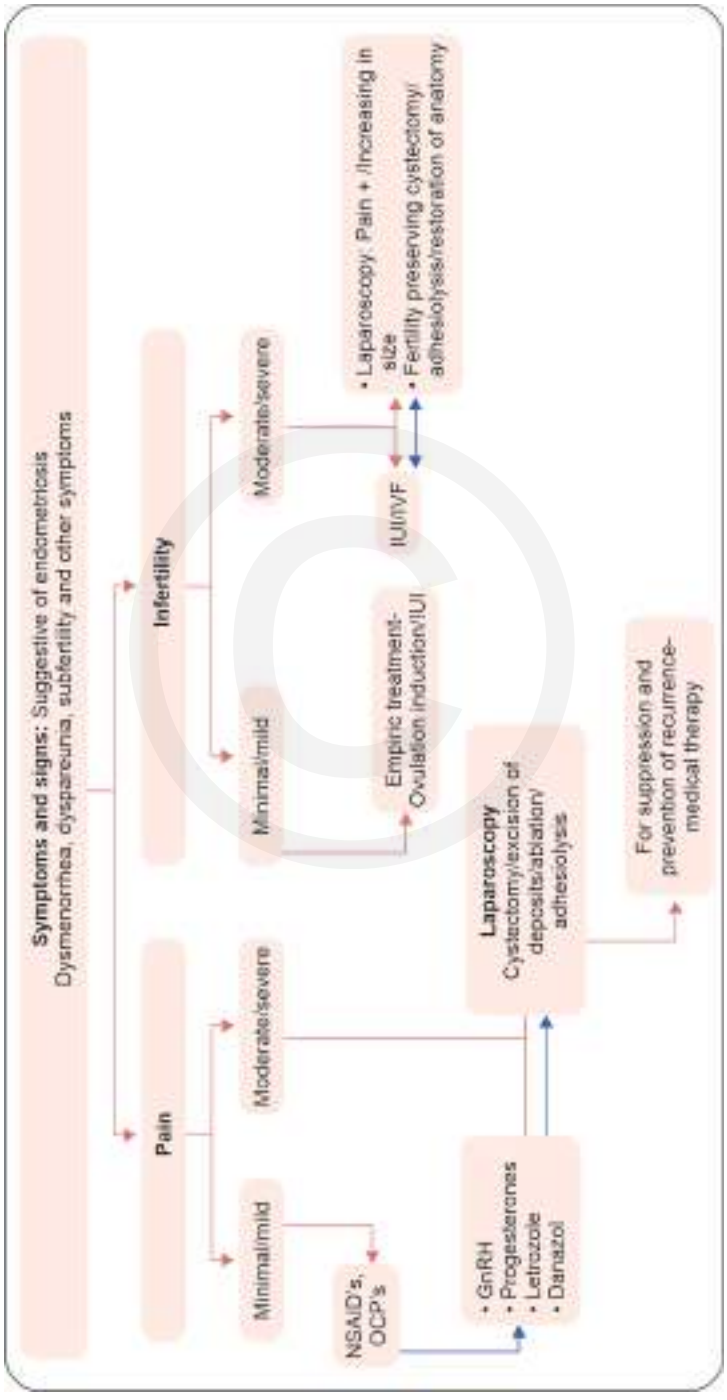
Endometriomas are often visualized on ultrasonography imaging. They appear as low-level homogeneous echos, also described as ground-glass appearance. If the findings are not visualized on imaging, the diagnosis becomes more elusive. However, definitive diagnosis of endometriosis is made through surgical (Laparoscopic) visualization of the lesions.[3] Laboratory investigations, such as CA-125, may be elevated in women with endometriosis. It is a nonspecific marker and should not be ordered routinely.[1]

TREATMENT OF ENDOMETRIOMAS

Treatment for endometriosis consists of hormonal medications or surgical management. Milder forms of endometriosis are treated with oral contraceptives, progesterone therapy, gonadotropin-releasing hormones (GnRH) agonists.[4] If the endometriosis is severe enough to have a presence of endometriomas, surgical management is always a preferred method of choice **(Flowchart 1)**.[5]

Medical Management

The treatment of endometriosis depends on the severity of the symptoms and the patient's desire to become pregnant. They act by suppressing the ovarian activity and menstrual cycle and decreases the endometrial atrophy. Recurrence of symptoms after 6 months of medication may occur in about 50% of patients. This may be due to the poor response of the large nodules to the medical treatment. In



Flowchart 1: Endometriosis treatment algorithm

Courtesy: Dr Manjula Anagani and Dr Sindura Ganga

minimal-to-mild endometriosis, suppression of ovarian function is not effective to improve fertility. There is no evidence that medical therapy improves fecundity; and, in severe disease, there is no evidence of its effectiveness.

Expectant management in a case of endometriomas to be reserved only for asymptomatic cases and sub-fertile woman with size of endometrioma less than 4 cm. But risks associated during oocyte retrieval are cyst rupture (2.8%), contamination of retrieved embryos affecting their development and implantation, and chance of infection must be kept in mind.

Several recent studies promote a change in protocol, suggesting that surgical management of endometriomas does not seem to significantly improve in vitro fertilization (IVF) clinical pregnancy rates per cycles with no treatment.[6]

Surgical Management

Surgery is also indicated in stage I and II, i.e., for minimal and mild disease due to significant conception rates postsurgery.

The natural conception rate of infertile women with endometriosis during the first postoperative year was found to be 41.9% and women successfully conceived without antiretroviral therapy (ART) or hormonal therapy.[7]

Laparoscopy for Endometriomas

Management of endometrioma before IVF remains controversial. The recommended treatment for endometriosis is still a subject of debate. Medical management of endometrioma does not improve fertility. Surgical treatment is proved to be effective than medical management in the treatment of pain and fertility, particularly for women with more severe endometriosis.[8]

The treatment approaches are as follows:
Conservative:

- Transvaginal ultrasonography-guided aspiration (TUGA)
- Laparoscopic aspiration with sclerotherapy
- Laparoscopic fenestration and ablation (fulguration or vaporization)
- Total cystectomy (vasopressin technique/ Gelatin-thrombin matrix seal)
- Cystectomy with combined technique.

Radical: Salpingo-ophorectomy.

General consensus suggests that ovarian endometriomas larger than 4 cm should be removed to reduce pain and to improve spontaneous conception rates. Small endometriomas (2–4 cm) does not reduce the success of IVF treatment.[8] Surgeons should bear in mind that if all healthy follicles grow without damaging the endometrioma, a cyst of 2–3 cm does not require surgery in asymptomatic patients; however, smaller cysts that hide growing follicles, when the ovary is fixed, may require intervention.

Goals of Surgical Treatment

- To remove all implants
- Resect adhesions
- Relieve chronic pelvic pain
- Reduce the risk of recurrence
- Prevent postoperative adhesions
- Restore the involved organs to a normal anatomic and physiologic condition.

Surgical Techniques

Three-stage Technique:[9] Three-stage technique included laparoscopic drainage of the cyst followed by Inj GnRH agonists for 3 months to reduce the diameter of the cyst followed by second look laparoscopy and vaporization of cyst wall with CO_2. This technique was beneficial than cystectomy because the normal ovarian tissue is not removed and is associated with less thermal damage. Drawbacks of this method was that it needs surgery twice with prolonged duration of time before the IVF cycle is started.

Combined Ablation and Cystectomy:[10] Combined ablation and cystectomy combined both ovarian endometriotic cystectomy, where 80–90% of the disease is eliminated and is coupled with CO_2 laser to ablate the rest of the cyst wall. A GnRH agonist is given for 3 months postsurgery. Advantages of this procedure are that recurrence rates are lesser as compared to any single procedure alone. Studies proved that 6 months after the surgery, the ovarian volume and antral follicle count (AFC) in the operated ovary and contralateral ovary were not statistically significant. Potential disadvantages are that there is a chance of loss of healthy cortex and thermal damage.

For both the above techniques, more research is needed on the use of potassium-titanyl-phosphate (KTP) laser or plasma laser to maximize the fertility outcomes.

Laparoscopic Cystectomy with Vasopressin: Diluted vasopressin [20 units in 100 mL of normal saline (NS)] that is injected into the cyst wall helps in reducing the amount of bipolar energy needed for hemostasis following cystectomy. It also reduces the accidental removal of the healthy ovarian tissue as it causes hydrodissection and separation of the endometriotic cyst wall from the healthy ovarian tissue. The main goal of successful treatment in endometriosis is preservation of the vascular blood supply to the ovary and thus antral follicular counts.

In well experienced hands, laparoscopic stripping of endometriomas appears to be a technique that does not significantly damage the ovarian tissue.

Cystectomy with Gelatin-thrombin Matrix Seal: The use of Gelatin-thrombin matrix seal (FloSeal®, Baxter Inc., IL, USA) for hemostasis as a replacement for coagulation – first used in 2009 by two research groups. However, longitudinal studies and studies including IVF outcomes following the procedure are needed.

Aspiration with Sclerotherapy: Ultrasound-guided aspiration with a sclerosing agent such as 95% ethanol (EST) or methotrexate. It prevents recurrence by chemically destroying the wall of the cyst. It is a less invasive procedure and sclerosing agents are less likely to damage the healthy ovarian tissue and reduction of ovarian reserve. The risks associated are infection, bleeding, irritation from the sclerosing agent- can be reduced by removing the agent after 10 minutes and irrigating the area with saline. Commonly used sclerosing agent is Methotrexate 30 mg diluted with 3 mL of saline. It prevents deoxyribonucleic acid (DNA) synthesis and is believed to suppress cells in the endometrioma cyst wall.

Fertility Preservation: The role of fertility preservation prior to surgical interventions for ovarian endometriomasis what is also being considered many at times. Current methods of fertility preservation include:

- Combined surgical techniques.
- Autotransplantation of the cryopreserved or fresh, healthy ovarian tissue- done in cases of post-oophorectomy done for severe endometriosis and malignancy.
- Cryopreservation of oocytes or embryos.

Fertility preservation is recommended as a part of preoperative counseling for young patients with endometriosis and women should decide which option fits best with their plans for fertility in future.

OUTCOMES OF SURGERY FOR ENDOMETRIOMAS[11,12]

See **Table 1**.

Table 1 Outcomes of surgery for endometriomas[11,12]

Stage of disease	*Spontaneous pregnancy rates postsurgery for endometriosis*
I	35.7%
II	44.4%
III	53.3%
IV	20.0%

Conclusion

Ovarian endometriomas lead to infertility by mechanical stretching of the ovarian cortex, inflammatory reaction, cytotoxic oxidative stress and increased fibrosis in the ovary. Both the presence of endometriomas and surgical excision of endometriomas appear to be damaging to ovarian function and ovarian reserve.

Surgery is the predominant clinical practice for the treatment of endometriomas and the most common surgical technique is stripping of the endometrioma. Although this technique has several advantages including increasing spontaneous pregnancy rates,

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it has also been shown to further reduce ovarian reserve. Fertility preserving surgical techniques have evolved to decrease the loss of ovarian reserve and also decrease the chance of recurrence like total cystectomy using vasopressin.

Nevertheless, the presence of an endometrioma does not appear to adversely affect IVF outcomes and surgical excision of an endometrioma does not appear to improve IVF outcomes.

The most recent evidence suggests that asymptomatic infertile women, those that are older, having diminished ovarian reserve, having bilateral endometriomas, or have had prior surgical treatment, would benefit from proceeding directly to IVF. This treatment path would avoid the risks associated with surgery and reduce the time to achieve pregnancy for the patient.

In patients who have symptoms, intact ovarian reserve, unilateral cysts, or sonographic features suggestive of malignancy or who are not planning on pursuing IVF, surgery is indicated. These women need to be adequately counseled on the potential for decrease in ovarian reserve and only fertility preserving techniques should be utilized.

There is a lack of randomized controlled studies comparing nonintervention to surgical excision of an endometrioma before IVF in infertile women. Future research is needed to better identify surgical techniques, such as aspiration with sclerotherapy and drainage with endometrial ablation using plasma laser energy, which may cause less ovarian damage.

References

1. Vercellini P, Viganò P, Somigliana E, et al. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10(5):261-75.
2. Hwu Y-M, Wu FS-Y, Li S-H, et al. The impact of endometrioma and laparoscopic cystectomy on serum anti-Müllerian hormone levels. Reprod Biol Endocrinol. 2011;9:80.
3. Hoyle AT, Puckett Y. Endometrioma. Treasure Island (FL): StatPearls Publishing; 2022.
4. Guzick DS, Huang L-S, Broadman BA, et al. Randomized trial of leuprolide versus continuous oral contraceptives in the treatment of endometriosis-associated pelvic pain. Fertil Steril. 2011;95(5):1568-73.
5. Dunselman GAJ, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29(3):400-12.
6. Tsoumpou I, Kyrgiou M, Gelbaya TA, et al. The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis. Fertil Steril. 2009;92(1):75-87.
7. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698-704.
8. Tinkanen H, Kujansuu E. In vitro fertilization in patients with ovarian endometriosis. Acta Obstet Gynecol Scand.2000;79(2):119-22.
9. Donnez J, Nisolle M, Gillet N, et al. Large ovarian endometriomas. Hum Reprod. 1996;11(3):641-6.
10. Donnez J, Lousse J-C, Jadoul P, et al. Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. Fertil Steril.2010;94(1):28-32.
11. Lee HJ, Lee JE, Ku S-Y, et al. Natural conception rate following laparoscopic surgery in infertile women with endometriosis. Clin Exp Reprod Med. 2013;40(1):29-32.
12. Rizk B, Turki R, Lotfy H, et al. Surgery for endometriosis-associated infertility: do we exaggerate the magnitude of effect? Facts Views Vis Obgyn. 2015;7(2):109-18.

Chapter 10

Adenomyosis and Reproductive Outcomes

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INTRODUCTION

Adenomyosis, defined as an enigmatic disorder, is now being recognized for its effects on reproduction and seen under new light as more and more women seeking fertility treatment are recognized with the disease. Adenomyosis is characterized by the downward infiltration of endometrial glands and stroma into the myometrium causing surrounding myometrial hyperplasia and increase in uterine volume.

More women are now being diagnosed with adenomyosis because of better imaging with transvaginal ultrasonography and higher age of women seeking fertility treatment. The prevalence of adenomyosis was found to be 24.4% in women older than 40 years and 22% in women younger than 40 years seeking fertility treatment. The incidence was higher in women with history of recurrent pregnancy loss (38.2%) and recurrent implantation failure (34.7%).[1]

PATHOGENESIS

The pathogenesis for adenomyosis begins with defining the mechanisms for the endometrial glands and stroma to get relocated into the myometrium. The tissue injury and repair mechanism as suggested by Leyendecker et al.[2] states that micro-trauma is induced in the basal endometrium by estrogen driven increased peristalsis of the subendometrial myometrium. Trauma activates tissue injury and repair mechanism which once again increases estrogen. This estrogen fueled hyperperistalsis and trauma allows basal endometrium to enter myometrium and cause proliferation, fibrosis, inflammation and neuroangiogenesis, and myohyperplasia. External adenomyosis involving the outer myometrium is suggested to be invasion of endometriotic implants in the myometrium from outside.[3]

Another mechanism is the embryonic pluripotent müllerian remnants undergoing metaplasia.[4]

Risk factors for adenomyosis includes age, prolonged exposure to estrogen, multiparity, uterine trauma, such as dilatation and curettage (D&C), and

cesarean section, smoking, and presence of hyperestrogenic conditions such as myomas and endometriosis.

DIAGNOSIS

Diagnostic criteria for adenomyosis as described by the Morphological Uterus Sonographic Assessment (MUSA) includes direct features, such as cysts in the myometrium, hyperechogenic islands, echogenic subendometrial lines, or buds, and indirect features, such as globular uterus, asymmetrical myometrial thickening, fan-shaped shadowing, translesional vascularity, irregular junctional zone (JZ), and interrupted JZ **(Figs. 1 to 5)**.[5]

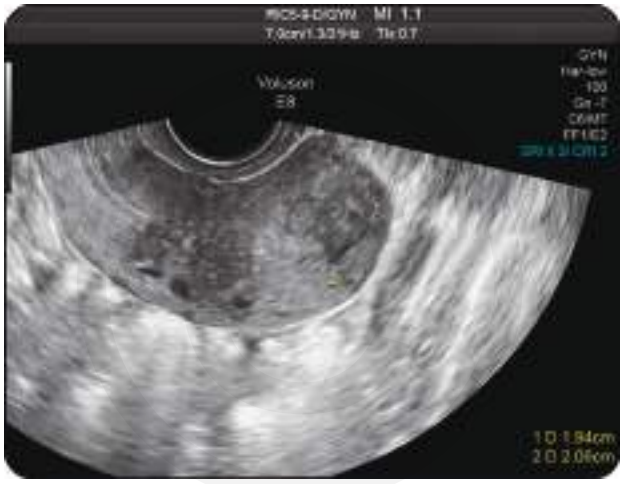


Fig. 1: Focal adenomyosis

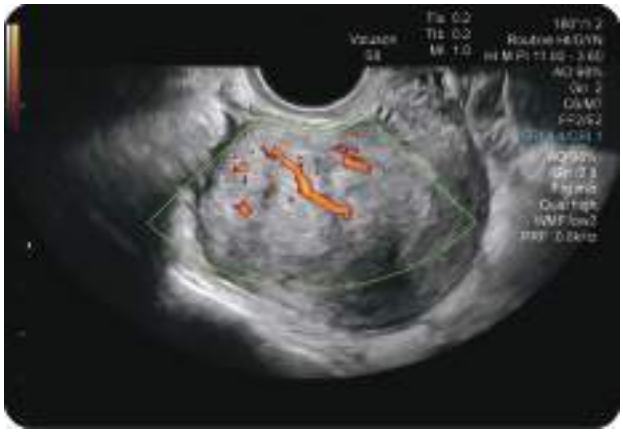
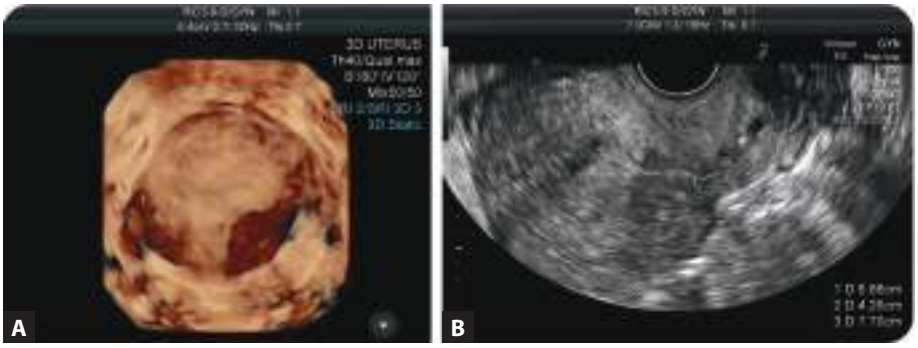


Fig. 2: Translesional blood flow



Figs. 3A and B: Diffuse adenomyosis

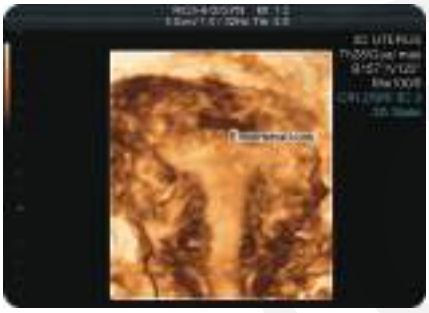


Fig. 4: Endometrial buds

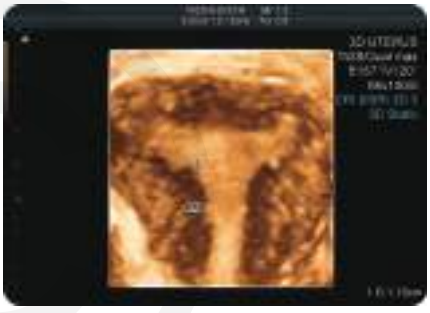


Fig. 5: Thickened junctional zone

The diagnosis of adenomyosis is more accurate with three-dimensional (3D) ultrasound than two-dimensional (2D) ultrasound. 3D ultrasound helps us to identify adenomyosis at a very early stage by the changes seen in the hypoechoeic area around the endometrium namely the JZ. The sensitivity for 2D and 3D transvaginal sonography (TVS) or diagnosis of adenomyosis were 83.8% and 88.9% and specificity were 63.9% and 56%, respectively.[6]

For 3D transvaginal ultrasound (TVUS), imaging should be done in the late follicular phase, pre-ovulatory with the help of transvaginal high-frequency transducer, with the woman in empty bladder.

Exacoustos et al.[7] suggested the following JZ features for the diagnosis of adenomyosis by 3D ultrasound:

- Thickening and disruption of the JZ with little or no endometrial invasion
- Maximum JZ thickness ≥8 mm
- JZ difference ≥4 mm.

A regular uninterrupted JZ is an indicator of the absence of adenomyosis.[5]

EFFECTS ON REPRODUCTIVE OUTCOMES

The mechanism by which adenomyosis causes infertility includes anatomical and physiopathological alterations. Submucosal and intramural adenomyoma altering the endometrial cavity causes infertility. The peristalsis of the archimyometrium[3] (myometrial part of JZ) which is responsible for sperm and embryo transport is markedly increased leading to increased endometrial pressure. This dysperistalsis affects the uterotubal sperm transport and embryo placement. Also, chronic inflammation causes increase in pro-inflammatory and chemotactic cytokines such as interleukin (IL)-6, IL-10, hypoxia-inducible factor (HIF)-alpha, vascular endothelial growth factor (VEGF), catalase which impairs implantation.[8,9] Increased cytochrome P450 activity, increased expression of estrogen receptors, and decreased expression of progesterone receptors alters estrogen/progesterone balance in luteal phase and causes adverse fertility outcomes. Also, expression of adhesive molecules and implantation markers, such as leukemia inhibitory factor (LIF), are altered in adenomyosis **(Fig. 6)**.[8]

Adenomyosis is found to be associated with reduced implantation rates, clinical pregnancy rates, and live birth rates with increased miscarriage rates.

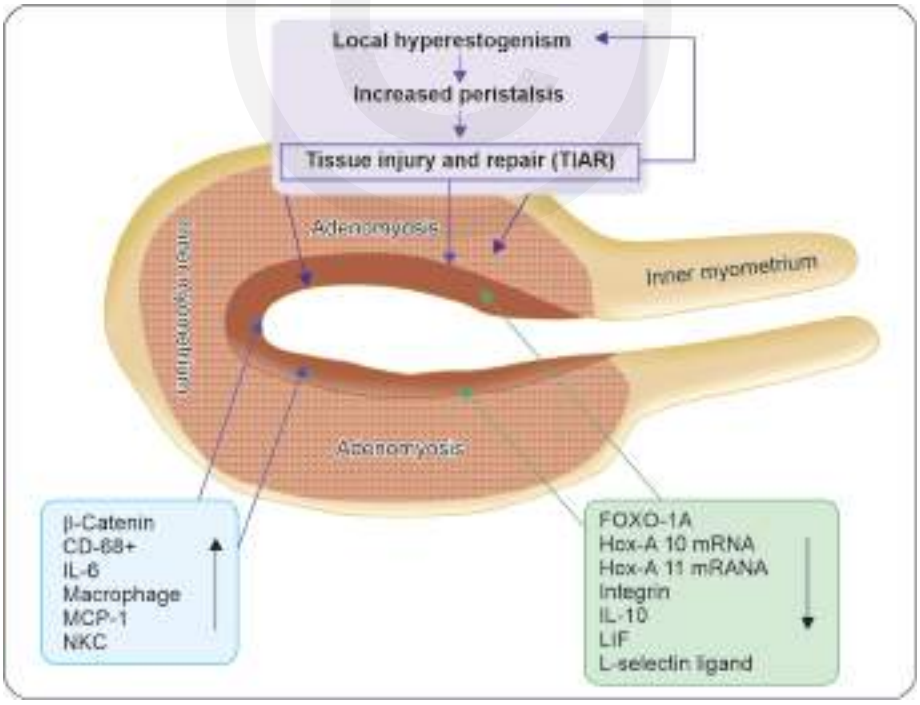


Fig. 6: Adenomyosis and negative impact on fertility
Reprinted from: Munro MG. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertil Steril. 2019;111(4):629-40[17]

This was demonstrated in many studies done by Brosens et al. 2010,[10] Sunkara and Khan, 2012,[11] Campo et al. 2012,[12] Younes and Tulandi, 2017,[13] Sharma et al. 2019,[14] and Nirgianakis et al. 2021.[15]

A meta-analysis by Deuholm M showed reduced pregnancy rate of 0.73 and live birth rate of 0.69 in women with adenomyosis undergoing ART. The miscarriage rate was 2.12 times higher when adenomyosis is present in these women.[16]

Although 70% of women with endometriosis are associated with adenomyosis, the reduced implantation and adverse pregnancy outcomes causing reduced live birth rates are independent of endometriosis as demonstrated by Sharma et al.[14]

As women diagnosed with adenomyosis are older compared to other women undergoing fertility treatment, the effect of embryo was to be considered in treatment failure. Hence, a selective evaluation of uterus was done by Stanekova et al.[18] and Martinez-Conejero et al.[19] by transferring quality euploid embryos and embryos made from oocytes of young donors in women with adenomyosis, respectively. Both studies demonstrated no difference in implantation rates but increased miscarriage rates leading to decreased pregnancy rates.

Nirgianakis et al. have demonstrated that even when the results were adjusted for age, adenomyosis resulted in increased miscarriage rates [six studies, odds ratio (OR): 2.50; 95% confidence interval (CI): 1.26–4.95] though clinical pregnancy rates were marginally nonsignificant (eight studies, OR: 0.78; 95% CI: 0.58–1.05).[15]

Ali A et al. in their study assessed the JZ at the time of oocyte retrieval and showed that the thickness of JZ in patients with history of unexplained repeated implantation failure (RIF) was higher (0.38 +/–0.11) than those with unexplained infertility (0.31 +/–0.09)($p < 0.001$).[20]

Maged AM et al. demonstrated that the implantation rate is inversely proportional to the JZ thickness on the day of oocyte pick-up (OPU).[21]

ASSISTED REPRODUCTIVE TECHNOLOGIES IN ADENOMYOSIS

The aim of treating adenomyosis in women undergoing assisted reproductive technologies (ART) is suppression of the adenomyotic lesions, reversing the estrogen/progesterone imbalance, achieving a favorable molecular profile, and reducing the uterine volume. Commonly, gonadotropin-releasing hormone (GnRH) agonists are used for downregulation of the disease. Other drugs of significance are progestins - levonorgestrel-releasing intrauterine system (LNG-IUS), aromatase inhibitors, danazol, and GnRH antagonists.

For the fear of increased obstetric adverse effects, it is recommended to promote single embryo transfers in women with adenomyosis.

In anticipation of difficult embryo transfers in women with enlarged and distorted uterus, mock embryo transfers should be done to assess uterine length and plan embryo transfer catheters.

GnRH Agonists

GnRH agonists have direct antiproliferative effects on the myometrium and also causes hypoestrogenic state which markedly reduces the inflammation and angiogenesis and induces apoptosis causing regression of the adenomyosis. GnRH agonists also reduce the expression of aromatase cytochrome P450 in the eutopic endometrium of women with endometriosis and adenomyosis.[8,22] This potentially therapeutic estrogen deficiency leads to uterine volume reduction, inactivation of the disease, and restores endometrial receptivity. Ultrasound helps us appreciate the regression of imaging features of adenomyosis after GnRH agonist treatment.

While using GnRH agonist, it is important to remember the severe hypoestrogenic adverse effect of the same on the bones and hence should be used with caution. Add-back therapy should be prescribed when appropriate.

Ultralong versus Short Protocols for Controlled Ovarian Stimulation

Ultralong protocol versus short protocols were compared by Nirgiankis et al.[15] in their meta-analysis and stated that ultralong protocols were better than the short protocols such as luteal agonist and antagonist protocols. The therapeutic hypoestrogenic state provided by ultralong protocol provides superior results.

J Lan et al. in a retrospective study showed that ultralong GnRH agonist protocol was associated with lesser miscarriage rate than women undergoing long protocol (12.0% vs 26.5%, p = 0.045). They also analyzed outcomes of both the protocols in women with diffuse and focal adenomyosis. Women with diffuse adenomyosis showed better outcomes after the ultralong protocol [clinical pregnancy rate (CPR) - 55.3% versus 37.9%, p = 0.025; live birth rate (LBR) - 43.4% versus 25.9%, p = 0.019, respectively in ultralong and long protocol], which was not demonstrated in women with focal adenomyosis.[23]

Thalluri and Tremellen have demonstrated that GnRH antagonist protocol for controlled ovarian stimulation (COS) in women with adenomyosis was associated with reduced implantation and viable clinical pregnancy rates (23.6%) compared to women undergoing COS with antagonist without adenomyosis (44.6%).[24]

Ultralong Protocol versus Downregulated Frozen Embryo Transfer

The administration of GnRH agonists before controlled ovarian stimulation is associated with profound suppression of ovary leading to higher dose and prolonged stimulation. In women with poor ovarian reserve, it is more difficult to stimulate the ovaries after long suppression. Also, the advantage of creating a hypoestrogenic state is compromised by the supraphysiological hormones during the COS. Hence, it is wise to opt for a short protocol (luteal agonist protocol/antagonist protocol), cryopreserve the embryos and plan for downregulated transfers. This advantage was demonstrated by Park et al. and Niu et al.

Park et al., in their retrospective study, showed higher clinical pregnancy rate following downregulated frozen embryo transfer (FET) (39.5%) rather than fresh embryo transfer (ET) following ultralong protocol (30.5%).[25] Similarly, Niu et al. showed clinical pregnancy, implantation, and ongoing pregnancy rates were 51.35%, 32.56%, and 48.91%, respectively, in women with adenomyosis undergoing GnRH agonist pre-treatment before FET, which is significantly higher than that of hormone replacement therapy (HRT) group (24.83%, 16.07%, and 21.38%), respectively.[26]

French et al. in their study have reported that adenomyosis is associated with adverse reproductive outcomes and treatment with GnRH analogues before FET may increase the pregnancy rates.[27] Medical management gives the additional benefit of avoiding the dreaded complication associated with surgery namely uterine rupture.

The duration of downregulation with GnRH agonist varies based on the severity of the adenomyosis and ultrasound features with uterine volume can be used as a guide for the same. Zhou et al. demonstrated that when the mean uterine volume reduction was done from (180 ± 73 cm) to (86 ± 67 cm) ($p < 0.05$), the embryo implantation rate, clinical pregnancy rate, and miscarriage rate were 39.1% , 54.2%, and 4.7% in comparison to 35.8%, 53.7%, and 4.2% in the control group with tubal factor infertility.[28]

Aromatase Inhibitors

Aromatase cytochrome P450 activity is increased in the ectopic endometrium and aromatase inhibitors help in controlling the same in the adenomyotic implants, thereby causing hypoestrogenic state and downregulates the adenomyosis. Badawy et al. compared letrozole 2.5 mg/day and goserelin 3.6 mg/month for 12 weeks and found similar efficacy in women with adenomyosis in both groups by a randomized controlled trial (RCT).[29] Combined efficacy of GnRH agonist and aromatase inhibitors can be tried in women with refractory and huge adenomtyosis. Sbracia et al. compared combination of GnRH agonist and aromatase inhibitor with dienogest before ART by an RCT and found the pregnancy rates to be 48.1% and 20.7 %, respectively.[30]

All the drugs causing hypoestrogenic state should be used with add-back therapy to prevent bone loss. Nor-ethisterone acetate can be used as add-back therapy.

GnRH Antagonists

GnRH antagonists competitively bind to the GnRH receptors in the pituitary and inhibit the secretion of gonadotropins in a dose-dependent manner. The advantages of GnRH antagonist is the oral administration, immediate onset of action without initial flare, rapidly reversible action, dose-dependent effects,

and possible reduced adverse effects on bone with reduced doses. Donnez et al. in their recent study administered women with adenomyosis oral linzagolix at a dose of 200 mg/day for 12 weeks followed by 100 mg/day for another 12 weeks, the mean uterine volume reduction was 159 +/–95 cc and 204 +/–126 cc at 12 weeks (55% mean decrease) and 24 weeks (32% mean decrease) respectively from 333+/–250 cc. Also, there was improvement in chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, and quality of life.[31]

Levonorgestrel-releasing Intrauterine System

The LNG-IUS provides satisfactory results to women suffering from symptomatic adenomyosis but appropriate duration is debatable. Also, the effect on uterine volume reduction is not promising. Cho et al. reported relief of pain with LNG-IUS by 6 weeks and volume reduction by 12 months but both the effects reduced by 2 years.[32] Recent retrospective study by Song et al. demonstrated that LNG-IUS is effective for relief of pain and abnormal uterine bleeding (AUB) for up to 6 years but no uterine volume reduction.[33]

SURGERY AS A LAST RESORT

Surgery for adenomyosis is being done from a long time back since 1952 and many techniques have been described. Focal adenomyosis can be done by laparoscopy, whereas laparotomy is preferred for diffuse adenomyosis as better tissue feel helps for excision and closure is better in laparotomy than laparoscopy.

The disadvantages of performing a surgery are offending tissue is not completely removed, risk of recurrence, distortion of pelvic anatomy/fallopian tubes, Asherman's syndrome, and risk of uterine rupture and placenta acreta during pregnancy. In a review by Osada et al., the pooled clinical pregnancy rate, miscarriage rate, and live birth rate was 38.8 %, 17.9 %, and 30.4%, respectively.[34] Overall, the risk of uterine rupture has been reported to be 2–11%.

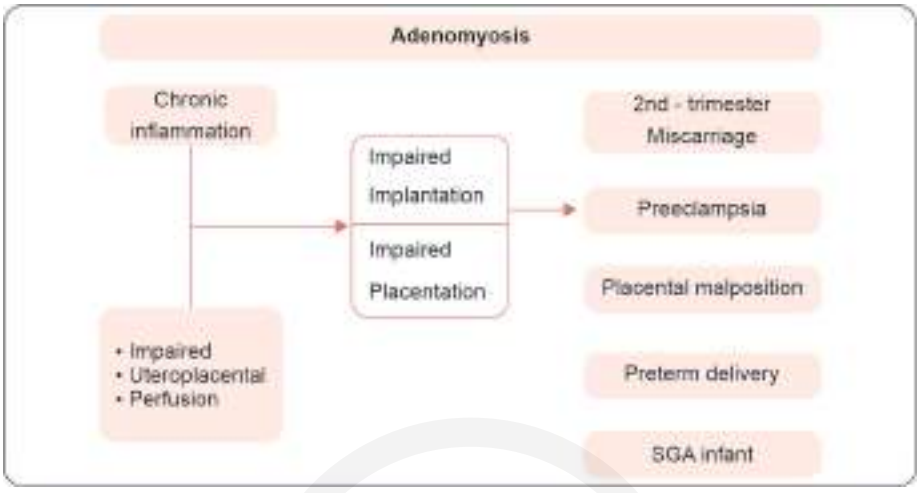
Justin Tan et al. did a systematic review to assess the reproductive outcomes following conservative uterine surgeries in focal and diffuse adenomyosis. The mean pregnancy outcomes after surgery in focal and diffuse adenomyosis were 52.7% and 34.1% with uterine rupture of 0% and 6.8%, respectively. They concluded that the option of surgical management should be chosen with caution on a case-to-case basis.[35]

Indications for surgery include repeated failed medical management in recurrent implantation failures, repeated abortions, and large focal adenomyosis >5 cm.

OBSTETRIC OUTCOME

Adenomyosis is associated with adverse pregnancy outcomes, such as increased incidence of preterm delivery, SGA infant, pre-eclampsia, abnormal placental

Flowchart 1: Adenomyosis: Pregnancy outcome



positioning, fetal malpresentation, and postpartum hemorrhage (PPH) **(Flowchart 1)**. Chronic inflammation causing defective spiral artery remodeling and improper placentation are responsible for most adverse effects of pregnancy.

The meta-analysis by Horton et al. on pregnancy outcomes showed higher risk of pre-term delivery, small for gestational age babies, cesarean section, and pre-eclampsia.[36]

In a comparative study by Hashimoto et al., 49 pregnant women with adenomyosis and 345 pregnant women without adenomyosis were included. They were evaluated by controlling some important confounding factors, such as age, primiparity, and ART use, and concluded that women with adenomyosis had increased risk of preterm delivery, small for gestational age (SGA) infants, cesarean section, late spontaneous abortion, abnormal placental positioning, and hypertensive disorders of pregnancy.[37] Similar results were reported by a meta-analysis by Nirgianakis et al,[15] when adjusted for maternal age.

Some strategies to avoid the complication of adenomyosis in pregnancy are to follow the concept of single embryo transfer and to start the women on Ecosprin to avoid hypertensive complications during pregnancy.

Conclusion

Adenomyosis in reproductive age group is a challenge that requires insight into its pathophysiology to guide us for the treatment. Medical management provides us promising results avoiding complications of surgery. So, medical management should be the first line of treatment for women seeking fertility treatment with surgery reserved for a select group.

References

1. Puente JM, Fabris A, Patel J, et al. Adenomyosis in infertile women: prevalence and the role of 3D ultrasound as a marker of severity of the disease. Reprod Biol Endocrinol. 2016:14:60.
2. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. Arch Gynecol Obstet. 2009;280(4):529-38.
3. Squillace ALA, Simonian DS, Allegro MC, et al. Adenomyosis and in vitro fertilization impacts - a literature review. JBRA Assist Reprod. 2021;25(2):303-9.
4. Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online. 2012;24(1):35-46.
5. Van den Bosch T, Dueholm M, Leone FPG, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284-98.
6. Andres MP, Borrelli GM, Ribeiro J, et al. Transvaginal ultrasound for the diagnosis of adenomyosis: systematic review and meta-analysis. J Minim Invasive Gynecol. 2018;25(2):257-64.
7. Exacoustos C, Brienza L, Di Giovanni A, et al. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet Gynecol. 2011;37(4):471-9.
8. Harada T, Khine YM, Kaponis A, et al. The impact of adenomyosis on women's fertility. Obstet Gynecol Surv. 2016;71(9):557-68.
9. Tomassetti C, Meuleman C, Timmerman D, et al. Adenomyosis and subfertility: evidence of association and causation. Semin Reprod Med. 2013;31(2):101-8.
10. Brosens I, Pijnenborg R, Benagiano G. Defective myometrial spiral artery remodelling as a cause of major obstetrical syndromes in endometriosis and adenomyosis. Placenta. 2013;34(2):100-5.
11. Sunkara SK, Khan KS. Adenomyosis and female fertility: a critical review of the evidence. J Obstet Gynaecol. 2012;32(2):113-6.
12. Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online. 2012;24(1):35-46.
13. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril. 2017;108(3):483-90.e3.
14. Sharma S, Bathwal S, Agarwal N, et al. Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. Reprod Biomed Online. 2019;38(1):13-21.
15. Nirgianakis K, Gasparri ML, Radan A-P, et al. Obstetric complications after laparoscopic excision of posterior deep infiltrating endometriosis: A case-control study. Fertil Steril. 2018;110(3):459-66.
16. Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. Acta Obstet Gynecol Scand. 2017;96(6):715-26.
17. Munro MG. Uterine polyps, adenomyosis, leiomyomas, and endometrial receptivity. Fertil Steril. 2019;111(4):629-40.
18. Stanekova V, Woodman RJ, Tremellen K. The rate of euploid miscarriage is increased in the setting of adenomyosis. Hum Reprod Open. 2018;2018(3):hoy011.
19. Martínez-Conejero JA, Morgan M, Montesinos M, et al. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril. 2011;96(4):943-50.
20. Ali A, Taha S, El-Ghany M, et al. Assessment of sub-endometrial junction zone by 3-dimensional transvaginal ultrasound in unexplained recurrent implantation failure and its effect on ICSI Outcomes. Open J Obstet Gynecol. 2019;9(1):54-61.

21. Maged AM, Ramzy A-M, Ghar MA, et al. 3D ultrasound assessment of endometrial junctional zone anatomy as a predictor of the outcome of ICSI cycles. Eur J Obstet Gynecol Reprod Biol. 2017;212:160-5.
22. Mahajan N, Kaur S, Alonso MR. Window of implantation is significantly displaced in patients with adenomyosis with previous implantation failure as determined by endometrial receptivity assay. J Hum Reprod Sci. 2018;11(4):353-8.
23. Lan J, Wu Y, Wu Z, et al. Ultra-long GnRH agonist protocol during IVF/ICSI improves pregnancy outcomes in women with adenomyosis: a retrospective cohort study. Front Endocrinol (Lausanne). 2021;12:609771.
24. Thalluri V, Tremellen KP .Ultrasound diagnosed adenomyosis has a negative impact on successful implantation following GnRH antagonist IVF treatment. Hum Reprod. 2012;27(12):3487-92.
25. Park CW, Choi MH, Yang KM, et al. Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med. 2016;43(3):169-73.
26. Niu Z, Chen Q, Sun Y, et al. Long-term pituitary downregulation before frozen embryo transfer could improve pregnancy outcomes in women with adenomyosis. Gynecol Endocrinol. 2013;29(12):1026-30.
27. French HM, Zhang W, Movilla PR, et al. Adenomyosis and fertility: does adenomyosis impact fertility and does treatment improve outcomes. Curr Opin Obstet Gynecol. 2022;34(4):227-36.
28. Zhou L-M, Zheng J, Sun Y-T, et al. Study on leuprorelin acetate in treatment of uterine adenomyosis with infertility. Zhonghua Fu Chan Ke Za Zhi. 2013;48(5):334-7.
29. Badawy AM, Elnashar AM, Mosbah AA. Aromatase inhibitors or gonadotropin-releasing hormone agonists for the management of uterine adenomyosis: a randomized controlled trial. Acta Obstet Gynecol Scand.. 2012;91(4):489-95.
30. Sbracia M, Scarpellini F. A controlled trial on uterine adenomyosis treatment comparing aromatase inhibitor plus GnRH analogue versus dienogest in women undergoing IVF. Fertil Steril. 2018;110(4):E83-4.
31. Donnez J, Donnez O, Brethous M, et al. Treatment of symptomatic uterine adenomyosis with linzagolix, an oral gonadotropin-releasing hormone receptor antagonist: a pilot study. Reprod. Biomed. Online. 2022;44(1):200-3.
32. Cho S, Nam A, Kim H, et al. Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. Am J Obstet Gynecol. 2008;198(4):373.e1-7.
33. Song SY, Lee SY, Kim HY, et al. Long-term efficacy and feasibility of levonorgestrel-releasing intrauterine device use in patients with adenomyosis. Medicine (Baltimore). 2020;99(22):e20421.
34. Osada H. Uterine adenomyosis and adenomyoma: the surgical approach. Fertil Steril. 2018;109(3):406-17.
35. Tan J, Moriarty S, Taskin O, et al. Reproductive outcomes after fertility-sparing surgery for focal and diffuse adenomyosis: a systematic review. J Minim Invasive Gynecol. 2018;25(4):608-21.
36. Horton J, Sterrenburg M, Lane S, et al. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2019;25(5):592-632.
37. Hashimoto A, Iriyama T, Sayama S, et al. Adenomyosis and adverse perinatal outcomes: increased risk of second trimester miscarriage, preeclampsia, and placental malposition. J Matern Fetal Neonatal Med. 2018;31(3):364-9.

Chapter 11

Endometriosis and Cancer: What Exactly is the Equation?

Sarita Kumari,
Neerja Bhatla

INTRODUCTION

Pelvic endometriosis is a chronic and debilitating condition which affects around 10% of women in the reproductive age group. However, its prevalence may be as high as 20–30% in women with infertility, and 40–60% in women with chronic pelvic pain.[1] True prevalence remains unknown as it requires laparoscopy or laparotomy for the diagnosis.[2] Histologically, the disease is characterized by chronic inflammation and presence of endometrial tissue outside the uterus, most commonly on the pelvic peritoneum and ovaries.[3]

Presenting symptoms, such as dysmenorrhea, pelvic pain, dysuria, dyschezia, and chronic fatigue, have a considerable negative impact on the quality of life. Endometriotic lesions are identified mainly at laparoscopy, located in the ovaries and the pouch of Douglas;[4] rare extraperitoneal sites have also been reported.[5]

Endometriosis is uncommon before the onset of menses and it usually regresses after menopause. Among the five proposed theories of endometriosis, i.e., retrograde menstruation (Sampson's theory), celomic metaplasia, origin from embryonic cell rests, induction theory, and lymphatic and vascular dissemination; Sampson's theory is accepted most widely.[6] Sampson was the first to report a case of ovarian cancer arising from the endometrial tissue in that organ in 1925.[7] Since then, the hypothesis of a possible etiological association between endometriosis and ovarian cancer has been studied extensively. Currently, there is no doubt whatsoever that ovarian endometriosis can give rise to malignant epithelial ovarian tumors and both epithelial and nonepithelial malignancies have been documented in literature. A knowledge about risk quantification is crucial as it might have implications in long-term management of women with endometriosis.

POTENTIAL UNDERLYING MECHANISM

Although endometriosis is a nonmalignant condition, it shares a few features which are similar to cancer, e.g. lesion development at distant foci and deep invasion of organs.

Endometriosis and ovarian cancer share some common predisposing factors, including early age at menarche, late age of menopause, and nulliparity and they are both inversely associated with tubal ligation, hysterectomy, use of oral contraceptives, and pregnancy.[8] Trabert et al. suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) usage for >10 years is associated with risk of ovarian cancer and this drug is used as the first-line agent in women with endometriosis.[9] Genome wide studies have reported loci common to endometriosis and ovarian cancer, especially in clear cell, endometrioid, and serous histotypes but without taking any clinical data into account.[10] Endometriosis leads to a state of chronic inflammation, altered immune response, and an aberrant hormonal milieu. Vercellini et al. suggested that ovarian endometriomas harboring alterations in the microenvironment have potential for neoplastic transformation.[11] Activation of oncogenic KRAS and PI3K pathways and inactivation of tumor suppressor genes, PTEN, and ARID1A have been suggested as a mechanism for the transformation of endometriosis particularly ovarian endometriosis to malignancy.[12]

OVERALL CANCER RISK

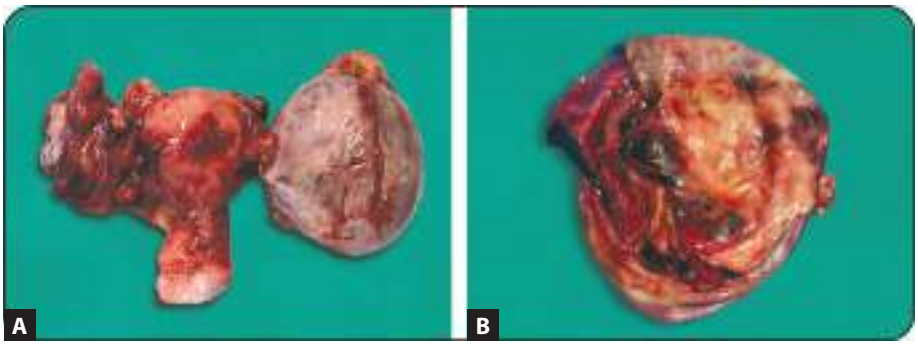
In the systematic review and meta-analysis by Kvaskoff M et al., the authors suggested a small and statistically insignificant risk of development of cancer in women with endometriosis based on five cohort studies [Standardized rate ratio (SRR) 1.07, 95% confidence interval (CI) = 0.98–1.16] and there was a substantial heterogeneity between studies.[13]

Ovarian Cancer

Among published literature, the most recent high-level evidence calculates a 93% greater risk of ovarian cancer among women with endometriosis compared to controls. In this systematic review and meta-analysis, the authors included 24 studies evaluating the association between endometriosis and ovarian cancer. There was a 4-fold increased risk in the Asian women. Overall risk was 1.93 (95% CI = 1.68–2.22) but the studies were heterogenous. Studies which assessed the temporality had a stronger association (N = 11, SRR = 2.19, 95% CI = 1.64–2.92). Studies having a low or moderate risk of bias also had a stronger association (N = 13, SRR = 2.09, 95% CI = 1.69–2.59).[13]

Histotype having the strongest association was clear cell carcinoma (N = 5, SRR 3.44, 95% CI = 2.82–4.20), followed by endometrioid (N = 5, SRR = 2.33, 95% CI = 1.82–2.98). No association was seen with the mucinous variety and among serous tumors, an association was seen with low-grade serous tumors (N = 3, SRR = 2.33, 95% CI 1.64–3.31).

When we discuss about the phenotype of endometriosis and cancer risk, based on published evidence, endometrioma is the one associated with the development of ovarian cancer (N = 4, SRR 5.41, 95% CI 2.25–13.00). However,



Figs. 1A and B: (A) Panhysterectomy specimen depicting a thick walled endometrioma along with endometriotic deposits on uterus and fallopian tubes; (B) Thick walled, multiseptated, solid cystic mass in a background of endometrioma

the authors did not report on exclusion of superficial and deep endometriosis occurring along with endometrioma, so the causation cannot be attributed to endometriomas alone. Furthermore, in the light of nonovarian origin of ovarian cancers, the possibility of origin from superficial and deep peritoneal implants cannot be safely excluded. Saavalainen et al. distributed the macrophenotypes and in their study the association with endometrioma was significantly stronger [p = 0.03, relative risk (RR) = 2.56, 95% CI = 1.98–3.27).[14] **Figures 1A and B** depict a solid cystic thick walled, multiseptated mass, i.e. carcinoma ovary arising in a background of endometrioma. They also demonstrated that ovarian endometrioma had a positive association with clear cell [standardized incidence ratio (SIR) = 10.1], endometrioid (SIR 4.7), and serous (SIR 1.62) histotypes. More targeted studies in future might provide a better answer to the process of neoplastic transformation. **Figure 2** depicts the risk association between endometriosis and ovarian cancer.

Breast Cancer

Reported literature has a small borderline risk of breast cancer in women with endometriosis [N = 20, SRR 1.04, (95% CI = 1.00–1.09)][13] Gandini et al. reported similar findings.[15] Risk was independent of any specific histology as well as menopausal status. Farland et al. reported a positive association between endometriosis and estrogen receptor positive/progesterone receptor-negative subtype.[16]

Endometrial Cancer

No significant risk of endometrial cancer is seen in women with endometriosis (N = 17, SRR of 1.23 (95% CI = 0.97–1.57).[13] Li et al. also reported a nonsignificant association, but Gandini et al. reported a 38% higher and statistically significant

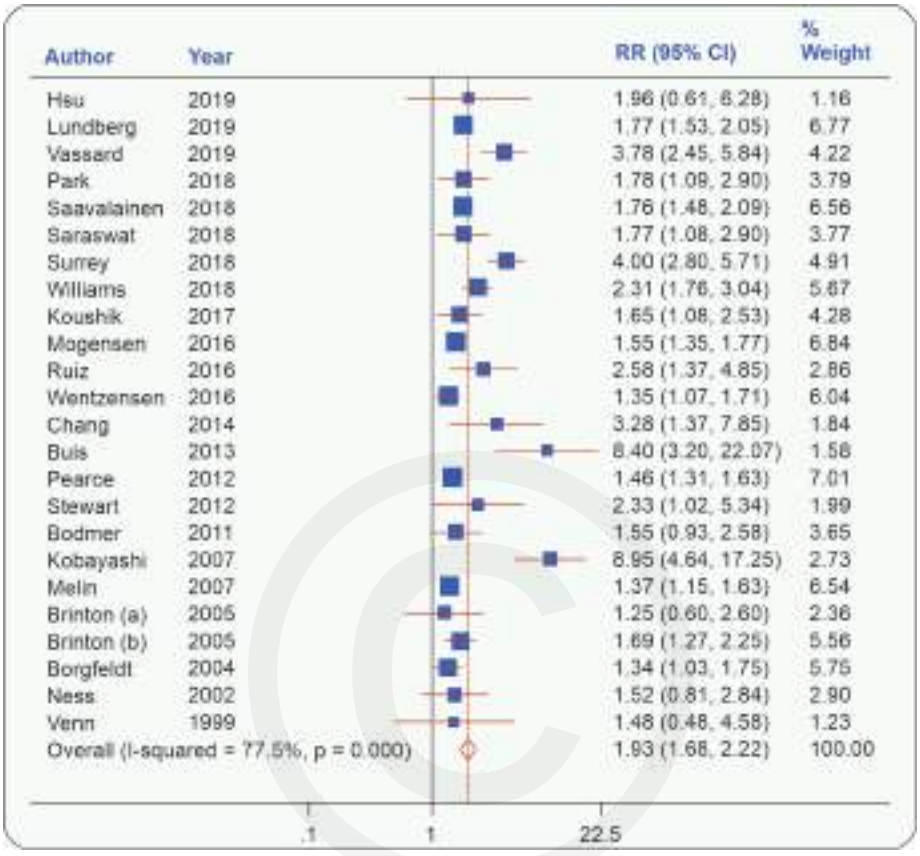


Fig. 2: Association between endometriosis and ovarian cancer risk among 24 studies published through 2019

Adapted from: Kvaskoff M, Mahamat-Saleh Y, Farland LV, et al. Endometriosis and cancer: a systematic review and meta-analysis. Hum Reprod Update. 2021;27(2):393-420.

risk in their meta-analysis.[15,17] Higher body mass index (BMI) might be a confounding factor in these studies.

Cervical Cancer

There is a strong risk reduction seen in women with endometriosis based on four studies (SRR 0.68, 95% CI 0.56–0.82).[13] Authors found a risk reduction of 32% and it is similar to prior studies by Li et al., 33% and Gandini et al., 22%.[15,17] Women who are diagnosed with endometriosis are more likely than women without endometriosis to have a better access to healthcare, undergo frequent gynecologic examination henceforth routine screening. Also, dyspareunia and chronic pelvic pain can have a potential negative impact on sexual relationships and prevalence of human papillomavirus (HPV) infection in these women.

Skin Cancer

Studies report modest nonsignificant risk of cutaneous melanoma (N = 7, SRR 1.17, 95% CI = 0.97–1.41). Similar findings have been reported by Gandini et al.[13,15] For basal cell carcinoma, the calculated risk was 1.18 (N = 2, 95% CI = 1.11–1.25). Future studies with low/moderate bias is needed.

Thyroid Cancer

A positive association is seen based on published studies (N = 5, SRR 1.39, 95% CI = 1.24–1.57).[13]

Colorectal Cancer

A positive association of borderline clinical significance has been shown although with a wide confidence interval (SRR 2.29, 95% CI = 1.00–5.26) necessitating more future studies.[13]

Other Cancers

Studies do not report any significant association with hematopoietic, lung, gastric, liver, pancreatic, urinary tract, buccal or renal cancers.

PROGNOSIS

Endometriosis-associated epithelial ovarian cancer appears to develop in younger women and has a better prognosis than non-endometrioid epithelial ovarian cancers. Mean age is 49 years versus 59 years and has a better median overall survival than patients without endometriosis.[18]

INFORMING WOMEN WITH ENDOMETRIOSIS ABOUT CANCER RISK AND PREVENTION

Gynecologists managing women with endometriosis should inform and reassure women regarding their long-time cancer risk. Ovarian cancer is rare and its absolute risk is 1.3% and its calculated absolute risk in women with endometriosis is 2.5%, i.e. a 1.2% difference from women without endometriosis which is still low. For breast cancer, the lifetime absolute risk in general population is 12.8% which increases to 13.3% in women with endometriosis. Similarly, for thyroid cancer, a lifetime absolute risk of 1.3% increases to 1.8% in these women. Hence, it is important to stress that based on the currently available evidence, the increase in risk for women with endometriosis in terms of absolute cancer risk is very small. Routine screening for ovarian cancer is not recommended in low-risk women and neither bilateral salpingo-oophorectomy has a positive impact on quality-adjusted life years and is not cost effective. Clinicians should reassure

women with endometriosis with regards to cancer risk and address their concern to reduce their risk by recommending general cancer prevention measures (avoiding smoking, maintaining healthy weight, exercise regularly, having a balanced diet with high intake of fruits and vegetables and low intake of alcohol, and using sun protection).

Conclusion

Endometriosis is associated with almost 2-fold increased risk of ovarian cancer particularly clear cell (3.4 fold) and endometrioid (2.4 fold) histologies. Risk is potentially increased in women with endometrioma. Endometriosis also leads to a small increase in breast cancer risk of borderline significance. It also increases the risk of thyroid cancer by almost 40%. Endometrial cancer risk is doubtful; however, there is a robust almost 30% reduction in risk of cervical cancer. However, the absolute risk of any cancer remains small. Women should be informed about general prevention measures to reduce cancer risk, e.g. avoid smoking, maintain healthy weight, exercise regularly, have a balanced diet rich in fruits and vegetable, low intake of alcohol, and use of sun protection. Use of oral contraceptive pills decreases the risk of ovarian cancer in all users.

References

1. Sayasneh A, Tsivos D, Crawford R. Endometriosis and ovarian cancer: a systematic review. ISRN Obstet Gynecol. 2011;2011:140310.
2. Somigliana E, Vigano' P, Parazzini F, et al. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol. 2006;101(2):331-41.
3. Munksgaard PS, Blaakaer J. The association between endometriosis and gynecological cancers and breast cancer: a review of epidemiological data. Gynecol Oncol. 2011;123(1):157-63.
4. Nezhat F, Datta MS, Hanson V, et al. The relationship of endometriosis and ovarian malignancy: a review. Fertil Steril. 2008;90(5):1559-70.
5. Pados G, Tympanidis J, Zafrakas M, et al. Ultrasound and MR-imaging in preoperative evaluation of two rare cases of scar endometriosis. Cases J. 2008;1:97.
6. Gazvani R, Templeton A. New considerations for the pathogenesis of endometriosis. Int J Gynaecol Obstet. 2002;76(2):117-26.
7. Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. Arch Surg. 1925;10(1):1-72.
8. Van Gorp T, Amant F, Neven P, et al. Endometriosis and the development of malignant tumours of the pelvis. a review of literature. Best Pract Res Clin Obstet Gynaecol. 2004;18(2):349-71.
9. Trabert B, Poole EM, White E, et al. Analgesic use and ovarian cancer risk: an analysis in the ovarian cancer cohort consortium. J Natl Cancer Inst. 2019;111(2):137-45.
10. Anglesio MS, Bashashati A, Wang YK, et al. Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. J Pathol. 2015;236(2):201-9.
11. Vercellini P, Viganò P, Buggio L, et al. Perimenopausal management of ovarian endometriosis and associated cancer risk: When is medical or surgical treatment indicated? Best Pract Res Clin Obstet Gynaecol. 2018;51:151-68.

12. Grandi G, Toss A, Cortesi L, et al. The association between endometriomas and ovarian cancer: preventive effect of inhibiting ovulation and menstruation during reproductive life. Biomed Res Int. 2015;2015:751571.
13. Kvaskoff M, Mahamat-Saleh Y, Farland LV, et al. Endometriosis and cancer: a systematic review and meta-analysis. Hum Reprod Update. 2021;27(2):393-420.
14. Saavalainen L, Lassus H, But A, et al. Risk of gynecologic cancer according to the type of endometriosis. Obstet Gynecol. 2018;131(6):1095-102.
15. Gandini S, Lazzeroni M, Peccatori FA, et al. The risk of extra-ovarian malignancies among women with endometriosis: a systematic literature review and meta-analysis. Crit Rev Oncol Hematol. 2019;134:72-81.
16. Farland LV, Tamimi RM, Eliassen AH, et al. Laparoscopically confirmed endometriosis and breast cancer in the Nurses' Health Study II. Obstet Gynecol. 2016;128(5):1025-31.
17. Li J, Liu R, Tang S, et al. Impact of endometriosis on risk of ovarian, endometrial and cervical cancers: a meta-analysis. Arch Gynecol Obstet. 2019;299(1):35-46.
18. Orezzoli JP, Russell AH, Oliva E, et al. Prognostic implication of endometriosis in clear cell carcinoma of the ovary. Gynecol Oncol. 2008;110(3):336-44.

Chapter 12

DIE (Deeply Infiltrating Endometriosis)

T Ramanidevi,
Sripriya Pragasam

INTRODUCTION

Endometriosis is a chronic gynecological disorder caused by the presence of ectopic endometrial tissue, which responds to hormones estrogen and progesterone by proliferation, differentiation, and bleeding.[1]

Endometriosis can present as three distinct phenotypes:

- Peritoneal or superficial endometriosis
- Ovarian endometrioma (OMA)
- DIE (deeply infiltrating endometriosis).

DIE is the most aggressive of the three phenotypes and can affect the whole pelvis, altering the anatomy and physiology of all the pelvic organs, thus causing a negative impact on the patient's quality of life and fertility.[2]

DEFINITION

- The common definition is the presence of endometriotic lesions > 5mm in depth under the peritoneal surface.
- Others define it as *"Adenomyosis Externa"*
  Type I lesions: Slightly deeper, with classic lesions greater than 5 mm in depth.
  Type II and III lesions: Unique lesions (infrequently two or three) that are large (>1 cm in diameter).
- DIE can also be defined as the infiltration of fibrous and muscular tissue in anatomic structures affected by endometriosis, including endometrial tissue, with no reference to the extent of lesion depth underneath the peritoneum according to a recent Cochrane meta-analysis.[3]

PREVALENCE

- Estimating the exact prevalence of endometriosis is a challenge, as many women are asymptomatic while others report nonspecific symptoms.
- The prevalence of endometriosis in women of reproductive age is 7–10% and in women with subfertility – 50%.[4]

- The prevalence varies between 2% and 74 % in women suffering from chronic pelvic pain and it exceeds 33% in women presenting with acute pelvic pain.

PATHOGENESIS

- The growth and development of endometriosis is multifactorial:
  - Genetic, hormonal, immunological factors, and even intestinal permeability play a role.[5]
  - The pathophysiology of DIE can be explained by the role of endometrial stem/progenitor cells, celomic epithelial and mesenchymal cells, which could be the origin of premenarcheal pelvic endometriosis. In the adolescent, it is characterized by angiogenic, hemorrhagic, peritoneal, and ovarian lesions.[6]
  - DIE is a delayed stage of endometriosis developing at a later age.
  - The role of genetic and epigenetic changes could explain the mechanisms of disease progression.
  - The hereditary predisposition is compatible with the clonality of deep and cystic ovarian endometriosis and also the eventual causal effect of dioxin or radiation.[7]

DIAGNOSIS

As there are neither specific signs and symptoms nor diagnostic tests for the clinical diagnosis of DIE, there can be a great delay between the onset of symptoms and diagnosis. The delay averages from 5 to 11 years **(Table 1)**.

Structured evaluation, with detailed history taking, physical examination and appropriate use of imaging techniques might be as accurate as laparoscopy.

Vaginal Examination

Vaginal examination, though having a low sensitivity and specificity, cannot be omitted as a basic diagnostic tool.

Table 1 Main localizations and associated symptoms of deep infiltrating endometriosis (DIE)

Localization	*Symptoms*
Uterosacral and cardinal ligaments, pouch of Douglas, posterior vaginal fornix	Dyspareunia, dysmenorrhea, chronic pelvic pain, pelvic tenderness
Bladder, bladder-uterine septum	Urinary symptoms (frequency, urgency, dysuria, hematuria)
Ureter	Asymptomatic, colicky flank pain, hematuria
Bowel and rectovaginal septum	Dyschezia, diarrhea, constipation, intestinal cramping, painful defecation, abdominal bloating

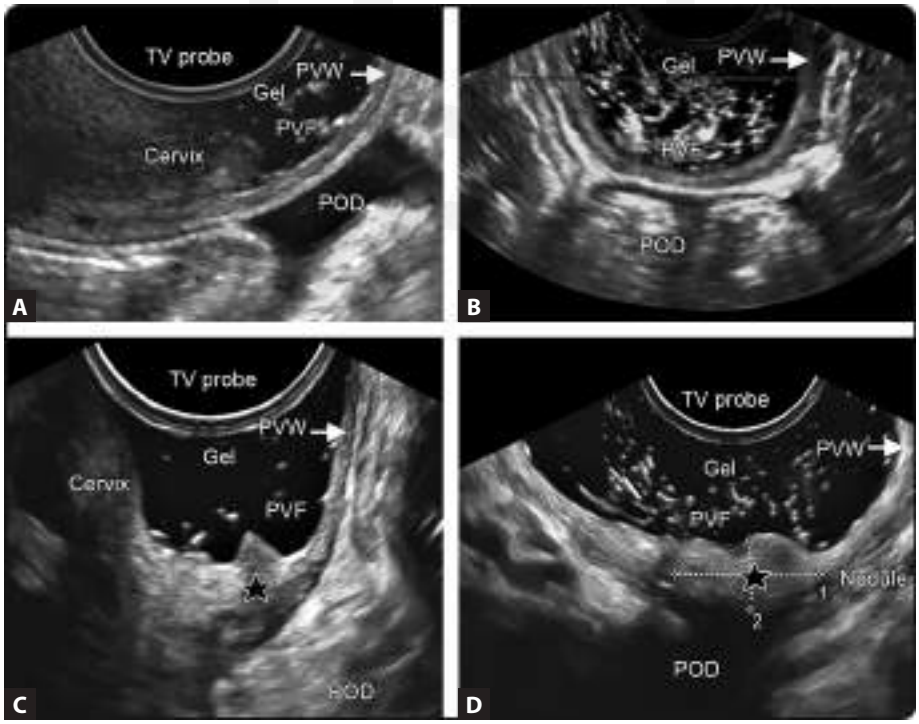
Uterosacral ligament scarring, nodularity or pain, painful or fixed adnexal masses, fixed retroverted uterus or pain on movement of uterus, nodularity or pain in POD, vaginal endometriotic lesions cannot be ignored.

Transvaginal Ultrasound

The experience of the examiner can have a profound influence on the results; and so, he has to be extensively trained. Transvaginal ultrasound (TVUSG) can be an effective tool to both confirm and exclude a diagnosis of endometrioma with good accuracy. It can also be the first strategic tool for preoperative mapping of lesions **(Figs. 1A to D)**.

The examiner should systematically visualize the bladder wall, the pouch of Douglas, the rectovaginal septum, the rectosigmoid, the retrocervical (uterosacral ligaments andtorus uterinus) and paracervical areas (ureteric involvement).

DIE can be identified as hypoechoic, sometimes poorly delimited areas, roughly round, infiltrating the organ wall. When the transducer is pressed against the endometriotic focus, the patient can complain of deep pain.[8]



Figs. 1A to D: TV USG of deep infiltrating endometriosis
(Stars) Deep infiltrative nodules in the anterior rectal wall

Prior bowel preparation with laxatives, rectal aqueous contrast, and vaginal injection of ultrasound gel have improved the detection rates of intestinal and vaginal lesions.

DIE: IMPACT ON FERTILITY

By the time, the patient seeks medical treatment, they have already developed chronic pain disorders and the uterine function is already significantly impaired. So, infertility and sterility are the cardinal symptoms. So, subfertility and sterility are the common presentations

- Enlarged uterus, anatomical distortion, intramural adenomyoma may have a *negative impact on sperm migration.*
- Altered myometrial contractility *impairs sperm progression towards the tubes.*
- The molecular and histological phenomenon *affects the endometrial receptivity and disrupts the implantation window* (progesterone receptor downregulation and local hyperestrogenism).
- *Impaired decidualization* due to altered levels of *HOXA 10*, leukemia inhibitory factor (LIF), interleukins (IL-6, IL-10), and autoimmune process.
- *Thickening of the* junctional zone (JZ) was correlated with higher *implantation failure even by in vitro fertilization (IVF).*
- Abnormal expression of both integrin βV-3 and OPN mRNA (osteopontin) and an *abnormal high level of free radicals* such as nitric oxide released by the activated macrophages leading to *early miscarriage.*

  DIE and adenomyosis (AM) can cause pain and sterility in young women.

THE PHENOMENON OF "ARCHIMETROSIS"

Archimetrosis phenomenon is explained as uterine hyperperistalsis causing microtraumatization within the *JZ* of uterus.[9] This hyperperistalsis, during repetitive cycles without conception, over time becomes destructive. The tissue injury and repair *(TIAR)* sets up a vicious cycle of chronic traumatization and healing. Because of the mechanical alteration and repetitive regeneration processes, stem cells are activated, they migrate and promote disease progression. Increased local estrogen levels induce proliferation and angiogenesis. Over expression of oxytocin and vasopressin receptors leads to structural and functional changes.[9] Pro-inflammatory mediators are released.

DIE: IMPLICATION ON PREGNANCY AND OUTCOME[10]

If pregnancy is achieved spontaneously or through assisted reproductive technologies (ART), there is an increased risk for the pregnant women and the unborn child. The high miscarriage rate even after achieving a good quality embryo at IVF is well documented. Uterine hyper-and dys-peristalsis (concept of archimetrosis) may compromise blastocyst implantation, leading to increased

rates of placenta previa. Chronic inflammatory processes in the endometrium and peritoneal space could increase the risk of preterm premature rupture of membranes (PPROM). Pro-inflammatory, prostaglandin-dependent process may be involved in early cervical maturation, rupture of membranes, and in the onset of preterm labor.

The disturbed architecture of JZ could disrupt trophoblastic invasion, spiral artery transformation,and thus abnormal placentation. In consequence, preterm birth, intrauterine growth restriction (IUGR), hypertensive disorders of pregnancy, and placental abruption can occur.

In women with DIE, due to intestinal adhesions, spontaneous hemoperitoneum or intestinal perforations can occur. Previous surgical treatment and the resultant scarring can weaken tissues. Injuries to the birth canal and uterine ruptures can be anticipated.

Lower segment cesarean section (LSCS) rates are high [labor dystocia, pathological cardiotocography (CTG), advanced age, IVF pregnancy] and difficulties in approach and increased blood loss due to peripartal hemorrhages should be anticipated.

MEDICAL MANAGEMENT

Medical treatments are generally safe, well tolerated, inexpensive,and are effective in long-term management of complex disease.[11] More than 50% women can be managed medically to control their symptoms.[12]

The aim is to stop the growth of lesions, induce their regression, encourage apoptosis, and decrease the densities of nerve fibers. Women who have undergone previous complex excisional surgery and now have recurrent or intractable symptoms can be managed medically. Medical management in DIE can be continued as long as obstructive uropathy or bowel stenosis symptoms do not occur.

They need constant follow-up to check if their symptoms are deteriorating or need serial imaging to document either improvement or stable disease. Unfortunately, early symptom recurrence is common once treatment is stopped. So, medical treatment is not of benefit in short-term usage.

Those who need to optimize their fertility prospects or those with symptomatic DIE and colorectal extension may need minimally invasive surgical excision from centers of excellence in this procedure.

CURRENTLY AVAILABLE TREATMENTS[12]

Progestogens

Norethisterone acetate (NETA) 5 mg/day and dienogest (2 mg/day) improve intestinal symptoms and reduce the volume of the nodule.

The European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend progestogens as the first-line medical therapy.

Combined Oral Contraceptives (COCs)

Combined oral contraceptives (COCs) have a higher dose of estrogen than what occurs physiologically. So, they may have additional side effects and contraindications.

Danazol

Newer administrative routes (vaginal ring, gel, or capsule) have helped to reduce the hyperandrogenic side effects such as hirsutism, acne, weight gain, and deepening of voice.

Gonadotropin-releasing Hormone Analogues

Leuprolide acetate depot 3.75 mg monthly for 6 months can be used for treatment. Beyond 6 months,add-back treatment is needed. The gonadotropin-releasing hormone (GnRH) antagonists, such as elagolix, relugolix, and linzagolix, can be taken orally. Its shorter half-life and rapid elimination lower the adverse effects. There is no initial flare up like agonist.

Aromatase Inhibitors (AI)

Letrozole (2.5 mg/day) has been used in combination with COCs, progestins, and GnRH analogues in the treatment of pain. This is the second-line management for endometriosis-associated pelvic pain (EAPP).

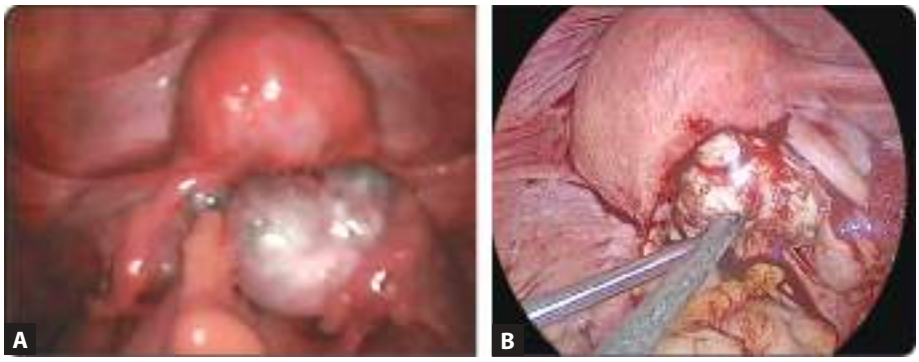
Adverse reactions, such as menopausal symptoms and loss of bone mineral density (BMD), should be looked for and appropriately treated with add-back therapy.

Selective Progesterone Receptor Modulators and Selective Estrogen Receptor Modulators

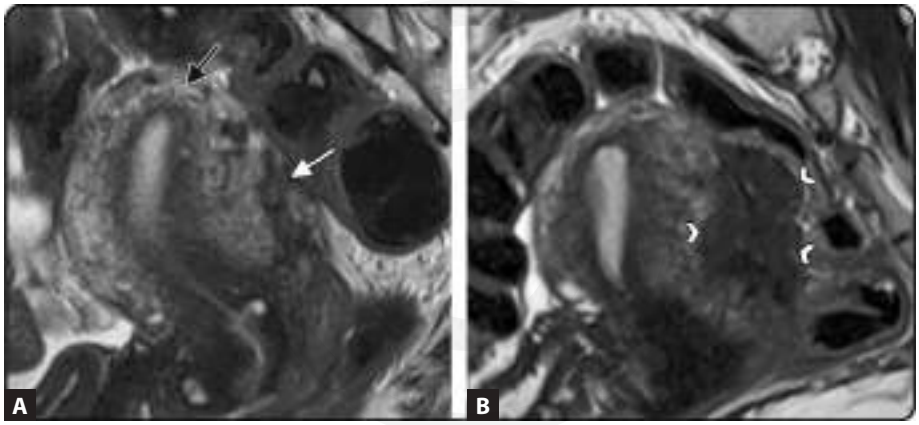
The effectiveness of both selective progesterone receptor modulators (SPRMs) and selective estrogen receptor modulators (SERMs) for management is yet to be established in humans.

Surgical Treatment

It is indicated in patients who do not respond to medical therapy or those who have severe symptoms (e.g. hydronephrosis caused by ureteral stenosis or intestinal obstruction). The decision to do surgery should be dictated by the patients' medical history, age, disease stage, symptoms, severity, future child bearing, and personal choice.



Figs. 2A and B: Laparoscopic view of deep infiltrating endometriosis



Figs. 3A and B: MRI of deep infiltrating endometriosis (A) (black arrow)- Nodule in the bowel, (white arrow)- Nodule in the pouch of Douglas (B) (arrowheads)- Nodule in the pouch of Douglas

The goal of surgery would be complete eradication of endometriosis, achieving good long-term outcomes in pain relief, prevention of recurrences, and regaining functional anatomy of the involved organs **(Figs. 2A and B)**.

Preoperative Planning

Preoperative suspicion of DIE calls for extensive preoperative planning.

Preoperative Imaging and Mapping

The role of magnetic resonance imaging (MRI), use of T1-and T2-weighted sequences, adding vaginal and rectal contrast or opacification of the vagina and rectum with ultrasound gel have improved the pick-up rates of various morphological abnormalities **(Figs. 3A and B)**. A radiologist who has specialized

in MRI for DIE is very crucial to the multidisciplinary team approach **(Table 2)**. He has to prepare his reports in a standardized fashion.

His reporting should include the number of lesions, the multifocality, lesion size (small or >3 cm), extent of bowel surface improvement, the lesion depth, and also specify if the lesion is coming from outside or developing inside the lumen. All these information, preoperatively would be critical for surgical planning.

MULTIDISCIPLINARY APPROACH

Referral to specialized center, where multispecialty providers, such as colorectal surgeons and urologists, are available is very important. The creation of specialized endometriosis care center is being debated. In such centres, subspecialty surgeon can work in conjunction, to coordinate patient care, have extensive surgical planning, and avoid incomplete surgical debulking. The previous surgical history would be reviewed in detail with reference to previous rectal surgery or colpotomy.

The present surgery could be planned according to the age and fertility requirements of the patient, risk factors,such as diabetes and body mass index (BMI), help to evaluate and plan surgery. Individualized comprehensive work-up would be done that would help not only in diagnosis and clinical care of patient but also in improving pregnancy rates and for research purpose.

Pathological review of all surgical specimens should be done to have histological evidence of endometriosis. With advances in surgical techniques, specialization and centralization of care, the operative time, the postoperative complications, and the pregnancy rates have definitely improved.

Preoperative Counseling

Extensive counseling has to be done. All therapeutic possibilities have to be explained by the physician, they have to help the patients make the right choice, and minimize the impact of disease on their lives.

The complexity of surgery and the need for extensive surgery necessitating adhesiolysis with associated urological or gastrointestinal intervention, prolonged operative time, need for blood transfusion, and postoperative complications should be explained.

Laparoscopy would be the preferred route, but the conversion possibility to a laparotomy in case of technical difficulty should be emphasized. Discussion should be regarding conservative or radical surgery (depending on the age of patient, her pregnancy desire or ovarian conservation to avoid premature menopause). Need for colostomy has to be discussed.

Preoperative Cystoscopy

There is a role when the patient has persistent urinary symptoms [dysuria, bladder irritations, frequent visits for urinary tract infection (UTI) symptoms

Table 2 Summary of MRI findings in deep infiltrating endometriosis[13]

Finding	*MRI findings*	*Comments*
Posterior cul-de-sac obliteration	Endometrial plaques: • ↑T1 • T2 variability Dense adhesions between uterosacral ligaments, uterine serosa, ovaries, rectum and vagina: • ↓T1 and ↓T2	Responsible for majority of symptomatic endometriosis A feature of severe disease May limit surgical visualization
Hematosalpinx	↑T1 within dilated fallopian tube	Highly specific feature of endometriosis Strong association with infertility
Ovarian endometrioma	Large, often multilocular, thick-walled, cystic lesion ↓T2 ('shading sign') and ↑T1 is pathognomonic for endometriomas ± medialized ovaries	Most common site for endometriosis and endometriomas High association with severity of disease Differential diagnosis: hemorrhagicadnexal cyst, ovarian dermoid cyst, peritoneal inclusion cyst
Uterine serosal plaque	↑T1 due to hemorrhagic/proteinaceous content Elevated vaginal fornices ↑T2 suggests cystic areas with active glandular deposits ↓T1 ↓T2 suggests predominantly fibrous component Enhancement post-gadolinium administration	Differential diagnosis: uterine leiomyoma

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Finding	***MRI findings***	***Comments***
Elevated vaginal fornices	Upper level of fornix superior to angle of the uterine isthmus Acute angulation of fornix Fornix pulled in superior direction with stretching of vaginal wall Thickening of superior 1/3 of posterior vaginal wall ± nodularity • Nodules: ↓T2 ± ↑T1 (if active hemorrhagicdeposits)	Due to regional tethering secondary to adhesions
Fixed anteversion or retroflexion	Anteversion: • ↓T1 ↓T2 nodules/bands on anterior uterine wall • Anterior cul-de-sac obliteration (if severe) Retroversion: • Torus uterinusthickening • Distorted/shortened of posterior lower uterine surface • Irregular configuration/shortening of posterior uterine surface (tethering) Anterior/posterior cul-de-sac obliteration (if severe) • Effacement, distortion of fat planes and loss of interface between organs	Due to regional tethering secondary to adhesions
Upper rectal distortion	Obliteration of fat planes Poor interface visualization Stranding between rectum and adjacent organs 'Mushroom cap sign' • ↓T2 at 'base' and ↑T2 at 'cap'	Due to regional tethering secondary to adhesions Rectosigmoid is most commonly affected part of intestine 'Mushroom cap sign' is specific to severe, invasive rectal involvement May indicate need for colorectal surgical input Common symptoms: abdominal pain, constipation/diarrhea, dyschezia and hematochezia
Thickened uterosacral ligament	Bilateral asymmetrical thickening and ↓T2 ± ↑T1 within ligament (glandular material)	A feature of severe disease

with negative urine cultures], to rule out stone or diverticula and to visualize the ureteric orifices. Preoperative ureteric stenting in case of hydronephrosis, hydroureter, or to reduce the rate of ureteric injuries during surgery in extensive disease is mandatory.

Preoperative Colonoscopy

Preoperative colonoscopy has a role when the bowel involvement is larger than 4 cm or extensive.

Per Operative Special Surgical Techniques[14]

The goal would be to do a complete, successful surgical resection of nodules from all sites with adequate margins. Ovarian endometriomas should be removed. Frozen pelvis could be faced. A retroperitoneal or lateral wall approach could be planned. Dense pelvic adhesions with obliteration of pouch of Douglas (POD) can be treated with extensive adhesiolysis and appendicectomy.

In preparation for IVF, some may require drainage, ablation and/or excision of large (>5 cm) endometriomas, ovariolysis, salphingectomy, and tubal clipping.

In women who have completed the family hysterectomy with bilateral salpingo-oophorectomy (BSO)and partial posterior vaginectomy should be planned even if vagina is apparently disease free.

If radical surgery is planned, nerve-sparing approach conserving the inferior hypogastric nerve plexus helps to reduce bladder, rectal, and sexual dysfunction.

SURGERY FOR RECTOVAGINAL AND BOWEL ENDOMETRIOSIS[15]

Excision of the nodule

Excision of nodules on utero sacral, pouch of douglas with adequate margins can be done.

Shaving of Lesion

Rectal nodules which infiltrate the muscle layer but does not cross it and that does not involve the rectal lumen can be treated by this method. The advantage is that, we are able to treat bowel infiltration without opening or suturing the rectal wall.

Discoid Excision

Small rectal nodules that cross the muscular layer but involving less than one-third of the lumen circumference can be treated with this method. Closure can be done with circular or linear staplers introduced trans-anally.

Rouen Technique[16]

Using the contour transtar stapler, large DIE nodules (5–6 cm diameter) can be treated.

Segmental Resection[17]

When the nodules are large (>4 cm), multifocal or there is presence of stenosis, segmental resection followed by colorectal anastomosis (side to side or end to end) has to be performed.

Protective ileostomy or colostomy would depend on the distance of the nodule from the anal sphincter and if during the procedure, vagina, and rectum were opened. Mesenteric vascular and nerve-sparing surgery should be preferred.

Surgery for Ureteral and Bladder Endometriosis[18]

DIE can affect the ureter extrinsically (endometrial tissue invading adjacent connective tissue or the adventitia) or intrinsically (intrusion into the muscle layer, basement membrane, or invading the lumen).

The surgical procedure can be conservative (ureterolysis) or more aggressive (uretero-ureteric anastomosis, ureteroneocystostomy, after excision of the involved segment) or nephrectomy. The best approach is usually decided on the table, depending on the severity of the lesion, the distance from insertion into the bladder, after ureterolysis - ureter is still dilated or persistence of fibrosis.[19] The surgeon decides based on his experience. To do a prophylactic, preoperative stenting also would be his choice.

BLADDER ENDOMETRIOSIS[20]

Transurethral resection (TUR) or partial cystectomy (segmental bladder resection) are the treatments available. Adding a 1 cm deep myometrial resection of the anterior uterine wall under the vesical lesion helps. Decision to perform ureteral cannulation depends on the distance of the excised segment from the inter-ureteric ridge **(Fig. 4)**.

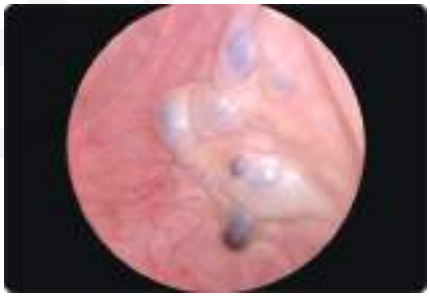

Fig. 4: Bladder endometriosis

Conclusion

DIE is most aggressive phenotype of endometriosis which affect the pelvic organs leading to severe pain and infertility. DIE lesions extend >5 mm depth below the peritoneum. Diagnosis of DIE is often delayed for 5–11 years. DIE involves posterior uterine wall involving uterosacral ligament, POD, bowel and rectovaginal septum. Anteriorly it can involve the bladder and ureters. DIE can be diagnosed by TV USG using contrast gel in the vagina. DIE is associated with adenomyoma which leads to infertility. Pregnancy can lead to both maternal and fetal complications. Management of DIE can be either medical or surgical. Commonly used drugs are GnRH analogs, progestins, aromatase inhibitors and SPRMs and SERMs. Surgical management is multidisciplinary; preoperative mapping and counseling is needed. Preoperative cystoscopy and colonoscopy are needed. Surgical procedure depends upon the involvement of the lesions. Excision,

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discoid excision, segmental resection and anastomosis are the common techniques followed in the management intestinal endometriosis. Ureteral endometriosis needs only surgery. Early bladder lesions can be managed medically for a short-term period. Bladder endometriosis also needs transurethral resection of endometriosis or partial excision of bladder with or without ureteral reimplantation.

References

1. Walter AJ, Hentz JG, Magtibay PM, et al. Endometriosis: correlation between histologic and visual findings at laparoscopy. Am J Obstet Gynecol.2001;184(7):1407-13.
2. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698-704.
3. Fraga MV, Brito LGO,Yela DA,et al. Pelvic floor muscle dysfunctions in women with deep infiltrative endometriosis: an underestimated association. Int J Clin Pract. 2021;75(8):e14350.
4. Defrère S,Lousse JC, González-Ramos R,et al. Potential involvement of iron in the pathogenesis of peritoneal endometriosis. Mol Hum Reprod. 2008;14(7):377-85.
5. Laganà AS, Garzon S, Götte M, et al. The pathogenesis of endometriosis: molecular and cell biology insights. Int JMol Sci. 2019;20(22):5615.
6. Cousins FL, McKinnon BD, Mortlock S, et al. New concepts on the etiology of endometriosis. J Obstet Gynaecol Res. 2023;49(4):1090-1105.
7. Gordts S, Koninckx P, Brosens I. Pathogenesis of deep endometriosis. Fertil Steril. 2017;108(6):872-85.e1.
8. Nisenblat V, Bossuyt PMM, Farquhar C, et al. Imaging modalities for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;2(2):CD009591.
9. Leyendecker G, Wildt L, Laschke MW, et al. Archimetrosis: the evolution of a disease and its extant presentation.pathogenesis and pathophysiology of archimetrosis (uterine adenomyosis and endometriosis). Arch Gynecol Obstet. 2023;307(1):93-112.
10. Mooney SS, Ross V, Stern C, et al. Obstetric outcome after surgical treatment of endometriosis: a review of the literature. Front Reprod Health. 2021;3:750750.
11. Barbara G, Buggio L, Facchin F, et al. Medical treatment for endometriosis: tolerability, quality of life and adherence. Front Glob Women's Health. 2021;2:729601.
12. Rafique S, Decherney AH. Medical management of endometriosis. Clin ObstetGynecol. 2017;60(3):485-96.
13. Thalluri AL, Knox S, Nguyen T. MRI findings in deep infiltrating endometriosis: a pictorial essay. J Med Imaging Radiat Oncol. 2017;61(6):767-73.
14. Rimbach S, Ulrich U, Schweppe KW. Surgical therapy of endometriosis: challenges and controversies. Geburtshilfe Frauenheilkd. 2013;73(9):918-23.
15. Payá V, Hidalgo-Mora JJ, Diaz-Garcia C, et al. Surgical treatment of rectovaginal endometriosis with rectal involvement. Gynecol Surg. 2011;8:269-77.
16. Roman H, Carilho J, Da Costa C, et al. Computed tomography-based virtual colonoscopy in the assessment of bowel endometriosis: the surgeon's point of view. GynecolObstetFertil. 2016;44(1):3-10.
17. Mabrouk M, Spagnolo E, Raimondo D, et al. Segmental bowel resection for colorectal endometriosis: is there a correlation between histological pattern and clinical outcomes? Hum Reprod. 2012;27(5):1314-9.
18. Mettler L, Gaikwad V, Riebe B, et al. Bladder endometriosis: possibility of treatment by laparoscopy. JSLS. 2008;12(2):162-5.
19. Wang Z, Liu B, Gao X, et al. Laparoscopic ureterolysis with simultaneous ureteroscopy and percutaneous nephroscopy for treating complex ureteral obstruction after failed endoscopic intervention: atechnical report. Asian J Urol. 2015;2(4):238-43.
20. Abid AF. Case report and video presentation: trans-urethral resection of bladder endometriosis. Urol Case Rep. 2019;24:100877.

Chapter 13

Endometriosis: Medical Management in Menopause

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INTRODUCTION

Endometriosis is not cancer, but it can be more devastating, and it is estrogen dependent. In this context, it is expected that, in the estrogen-deficit state in perimenopause and postmenopause, these lesions will subside completely and the women will be disease free thereafter. However, endometriosis is known to recur even in the postmenopausal state with activation of dormant lesions, which may lead to intractable pain.

Inflammation associated with endometriosis can lead to thick adhesions, causing pelvic pain. Incidence of pelvic pain due to endometriosis is 2–5% in menopause,[1] although much less than 48% prevalent in all women with pelvic pain.[2] Postmenopausal recurrence is more relevant as, endometriosis associated ovarian malignancy occurs 10 years earlier than non-endometriosis-associated ovarian malignancy.

SPECIAL CONSIDERATIONS IN MENOPAUSE AND PERIMENOPAUSE

- Pelvic pain due to endometriotic implants occurring due to endometriosis in postmenopausal women also requires drugs reducing estrogen. The usual estrogen-reducing drugs, such as GnRH analogues, danazole, and progestins,may be ineffective in the postmenopausal woman. The use of aromatase inhibitors is the recent development in tackling this problem.
- Use of aromatase inhibitors and GnRH analogues may worsen bone health in the perimenopausal woman and consequent osteoporosis has to be looked for and treated with Bisphosphonates.
- Endometriosis in the postmenopausal woman is more likely to go into malignancy; and, therefore, medical treatment without surgical intervention should be given only with caution and proper follow-up.
- Complete surgery for endometriosis quite often requires the removal of both ovaries and uterus and this may lead to severe vasomotor symptoms requiring

menopause hormone therapy (MHT). In conditions other than endometriosis, progesterone supplementation is not necessary after hysterectomy, since endometrial stimulation is not possible after hysterectomy; and, therefore, progesterone need not be given to prevent endometrial hyperplasia.
Endometriomas after menopause may become malignant, with estrogen therapy in a minority. In 2009, a Cochrane review cited 2 randomized controlled trials (RCTs) and had concluded that hormone replacement therapy (HRT) may increase the risk of symptomatic recurrence after surgically-induced menopause. All these reports require us to understand that, if MHT is needed in endometriosis patients, estrogen should always be supplemented with progesterone therapy, to avoid activation of these dormant implants.

- Symptomatic women, who need HRT should not be denied, just because they had endometriosis; but, while selecting MHT, care should be taken to supplement estrogen with progesterone or use tibolone.

PREMENOPAUSAL MANAGEMENT OF ENDOMETRIOSIS

Oral contraceptives, even the low dose ones can decrease pain of endometriosis effectively. Oral contraceptive pills (OCP) incorporating dienogest as a progestin, instead of the traditional ones, are now being tried for the treatment of endometriosis. Continuous progestin administration by various modalities are also effective. Even after surgical therapy, recurrence of dysmenorrhea may need OCP. Suppressing the pituitary with GnRH analogue, GnRH antagonist and aromatase inhibitors can stop estrogen production, reducing the severity of endometriosis. Although effective, these agents may lead to bone loss, as estrogen is needed for bone formation. Aromatase inhibitorsarethe second-line treatment. They do decrease estrogen production through aromatase, but may also increase gonadotrophin to the ovary. Thus, they are best used after oophorectomy or along with GnRH analogue therapy.

POSTMENOPAUSAL PATIENTS WITH ENDOMETRIOSIS

Women even after menopause may harbor endometriotic implants. Due to high risk of malignancy, surgical extirpation is the best mode of treatment and should be offered as the first-line treatment for postmenopausal masses with endometriosis. Even in the post-surgical patient, medical treatment may be required to tide over the symptoms caused by residual implants. These may need medical treatment. However, since the use of GnRH agonists, progestins or danazol, appears be ineffective in postmenopausal patients, the need for alternative drugs to reduce estrogen production is mandatory. Aromatase inhibitors, compared to other hormonal therapies, such as GnRH agonists, have

the ability to further block extraovarian estrogen production which is the main estrogen source for these women.

Aromatase inhibitors block estrogen activity outside the ovary and are effective in the management of severe endometriosis. Letrozole and anastrozole are triazole derivatives that are reversible, competitive aromatase inhibitors and, at doses of 1–5 mg/day, inhibit estrogen levels by 97% to more than 99%.[3] Not much data is available about the use of aromatase inhibitors in postmenopausal women. Letrozole and ananastrozole inhibit aromatase competitively, and may relieve pain when given for 4–15 months. Bladder and bowel symptoms are also apparently improved with letrozole, beside reduction in size of lesions of endometriosis.

Hot flushes, vaginal dryness, arthralgias, decreased bone mineral density (BMD) are some of the short-term and long-term side effects attributed to use of letrozole. Co-treatment with estradiol can be tried in these patients. Co-treatment with bisphopnatescan decrease the risk of osteoporosis in high-risk patients, during long-term treatment.

USE OF MENOPAUSE HORMONE THERAPY IN WOMEN WITH HISTORY OF ENDOMETRIOSIS

Women in the premenopausal and the immediate postmenopausal period with vasomotor symptoms and vaginal atrophy will benefit from HRT. In a woman with endometriosis, treatment has to be carefully tailored to selected patients for:

- Treatment of moderate-to-severe vasomotor symptoms due to menopause.
- Treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy due to menopause.
- Prophylactically in women who have undergone oophorectomy in a very young age, for cardio protection and bone protection, till natural age of menopause.

TIMING OF THERAPY

It is best to start HRT in the early menopause group around the age of 50 or within 10 years of going into menopause, whichever is earlier. This period is called the "Window of Opportunity." At older ages, women may harboratherogenic plaques. Use of MHT in older women will increase these plaques and cause strokes or coronary events.

INVESTIGATIONS

Menopause is a clinical diagnosis and no laboratory testing is required before initiating MHT. Checking levels of estradiol, progesterone, and follicle-stimulating hormone is not mandatory.[3]

TYPES OF HORMONE THERAPY

Hormone therapy may be given in the form of estrogens, progesterones, androgens, and tibolone.

Types of Estrogens

Oral estrogens may be natural, as in the estrogens normally used for HRT, viz., native estrogen– 17β-estradiol, estradiolvalerate, estrone, estriol, or conjugated equine estrogen.[4] Synthetic estrogens, such asethinylestradiol, are used in oral contraceptives and this is 4 times as potent as natural estrogens. Ethinylestradiol stays for longer time in the body and, therefore, has to be used with caution in women with hypertension or history of smoking, as it may cause deep vein thrombosis.

Transdermal estrogen has neutral effects on triglycerides, C-reactive protein (CRP), and sex hormone binding globulin, as against the oral estrogens, which may cause increase in the level of inflammatory markers like CRP. These are available as metered sprays in India. Combined estrogen/progestogen contraceptive pills (COCs) may be used continuously until the expected time of the menopause, but data are lacking regarding impact on bone and cardiovascular disease. Data from small randomized trials of surrogate markers suggest that bone mineralization and metabolic effects are more favorable with MHT compared to COCs. Transdermal estrogen is available in India in the form of sprays. Two metered sprays are to be applied on the arms and it has to be rubbed for 5 minutes for maximum effect **(Table 1)**.

Types of Progesterones

The role of progesterones by large in HRT is to reduce the chance of endometrial hyperplasia that may be caused by the long-term use of estrogens. Continuous therapy is preferred in women with endometriosis. In continuous therapy, lower doses of progesterones are used every day.

Progesterones, usually used for MHT, are medroxyprogesterone acetate MPA, norethisterone, dydrogesterone, and micronized progesterone. Levonogestrel intrauterine devices with lower doses of progesterone (releasing 14μg per day) are

Table 1 Dosage of estrogen

Estrogens	*Ultra-low*	*Low*	*Standard*	*High*
Conjugated equine estrogens (mg) oral	0.15	0.3, 0.45	0.625	1.25
17β-estradiol(mg)-oral	0.5	1	2	4
Estradiol valerate (mg) -oral		1	2	
Transdermal 17β-estradiol(μg)	14	25	50	100

Table 2 Dosage of progesterone

Progesterone	*Cyclic*	*Continuous*
Oral	(>12 days a month)	(Daily)
Medroxyprogesterone acetate	5 mg	2.5 mg
Norethisterone	1 mg	0.3 mg
Dydrogesterone	10 mg	10 mg
Micronized Progesterone	300 mg	200 mg

being used in Europe. This is different from the device used in India for abnormal uterine bleeding (releasing 20 μg) **(Table 2)**.

Traditionally, progestins, such as MPA and micronized progesterone, have been used to induce secretory changes in the endometrium to prevent endometrial hyperplasia in women with an intact uterus.

Estrogen Progesterone Therapy in Endometriosis

In women, who have undergone hysterectomy for endometriosis, residual implants may be present in the pelvis even after hysterectomy, which may get activated with estrogen-alone therapy. Therefore, estrogen with progesterone in a continuous fashion should be given.

The lowest effective dose of estrogen or progestogen should be used for treatment. However, lower daily doses have not been tested in long-term trials. Although progesterone supplementation is preferred in endometriosis patients even after hysterectomy, there are some studies which have not shown any increase in symptoms even when estrogen-only therapy was given and the American College of Obstetricians and Gynecologists (ACOG) published a bulletin stating that estrogen-only therapy is not contraindicated after definitive surgery for endometriosis. Nonoral routes may be advantageous in reducing risk for venous thromboembolism, for systemic symptoms.

Estrogen in a Woman with Vaginal Atrophy

Women experiencing vaginal atrophy can be offered any of the following effective vaginal estrogen replacement therapies: conjugated equine estrogen(CEE) cream, estriol or estradiolcream, a low-dose estradiol tablet, or a sustained-release intravaginal estradiol ring.

Vaginal estrogen creams are usually prescribed daily at bedtime for a week followed by twice weekly for a maximum of 3 months. The lowest dosage possible for the shortest length of time to control symptoms is advised. Creams provide lubrication, which may provide additional benefit for women with dyspareunia.

The 25-µg 17ß-estradiol vaginal tablet has been approved by the Food and Drug Administration (FDA) for atrophic vaginitis at a dosage of one tablet every day for 2 weeks. This is followed by one tablet twice every week.

The 17ß-estradiol tablets were equal in efficacy but preferred over creams by women in trials as they are less messy. Vaginal tablets are not freely available in India.

Vaginal rings are a new FDA-approved estrogen-delivery system, not available in India at present. These flexible 2-mg silicone rings deliver estradiol at a continuous rate of 6.5–15 µg/24 hours at a sustained rate for up to 12 weeks.

Although systemic absorption of estrogen can occur with local preparations, progesterone supplementation is not needed in asymptomatic women using local estrogens as the estrogen content is too low to cause endometrial hyperplasia.[5] Safety data is available for 52 weeks. Though oral estrogen has been shown to be effective to treat urogenital atrophy, up to 40% of women receiving systemic therapyfor treatment of vasomotor symptoms do not get an adequate effect of estrogen on the vaginal mucosa. These women may need additional vaginal creams.

Tibolone

Tibolone is a selective tissue estrogenic activity regulator (STEAR). It has estrogenic, progestogenic, and androgenic properties and so only one drug need to be given, with additional androgenic effect. Thus, it would be a good choice in women with endometriosis as only one drug need to be given. Tibolone is prescribed in a single daily dose of 2.5 mg orally. Recent data has shown a lower dose of 1.25 mg to be equally effective in many cases. Tibolone is effective in reducing episodes of flushing and sweating. It also helps relieve insomnia and also increases beta endorphin and beta lipoprotein levels, thus improving mood. The androgenic effect of tibolone helps to improve libido. The estrogenic effects on the vagina, decrease the vaginal dryness and decrease dyspareunia. The combined effects cause an overall improvement in mood, libido, and sexual enjoyment. Tibolone decreases the proliferation of cells in the breast, and also causes endometrial atrophy. It also inhibits bone resorption. Tibolone causes a decrease in triglycerides, total cholesterol, low-density lipoprotein (LDL), and lipoprotein (a) levels. However, it also lowers levels of high-density lipoprotein (HDL) cholesterol, which has been a cause for concern.

INDICATIONS FOR USE OF TRANSDERMAL ROUTE OF ESTROGENSAS FIRST LINE OF THERAPY

Transdermal estrogen has a neutral effect on triglycerides, CRP, and sex hormone-binding globulin, and should be used in patients with:

- Triglyceridemia, hyperlipidemia

- Increased CRP
- Migraine
- Diabetes.

STOPPAGE OF HORMONE THERAPY

Ideally, hormone therapy is used for only 2–3 years and rarely for more than 5 years.[5] Hot flashes and night sweats typically diminish in frequency and intensity after several years, whereas breast cancer risk increases with duration of hormone use, in particular, combined estrogen-progestin regimens if used for more than 5 years. Observational studies report that 40–50% of women who start hormone therapy stop within 1 year, and 65–75% stop within 2 years, often with no assistance from their health care provider. Women with persistent symptoms after stopping estrogen should first undergo trials with nonhormonal options such as gabapentin or selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs), returning to estrogen only if these alternatives are ineffective or cause significant side effects. In premature menopause, especially surgically induced in endometriosis, hormonetherapy is recommended until the typical age of menopause. These latter conditions are associated with lower breast cancer risk and earlier onset of cardiovascular disease and osteoporosis. Hormone therapy may also need to be stopped due to the onset of side effects.

Conclusion

In the postmenopausal woman with residual endometriosis, letrozole is more effective in controlling persistent pain. Women with severe vasomotor symptoms post hysterectomy after endometriosis should be given combined estrogen progesterone therapy, preferably in a continuous fashion, or tibolone should be used. In young women, who have undergone hysterectomy at a very young age, MHT should be given till the natural age of menopause.

References

1. Secosan C,Balulescu L, BrasoveanuS, et al.Endometriosis in menopause—renewed attention on a controversial disease. Diagnostics (Basel). 2020;10(3):134.
2. Mishra VV, Gaddagi RA, Aggarwal R, et al. Prevalence, characteristics and management of endometriosis amongst infertile women: a one year retrospective study. J Clin Diagn Res. 2015;9(6):QC01-3.
3. Polyzos NP, Fatemi HM, Zavos A, et al. Aromatase inhibitors in post-menopausal endometriosis. Reprod Biol EndocrinoL. 2011;9:90.
4. Campagnoli C, Clavel-Chapelon E, Kaaks R, et al. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol. 2005;96(2):95-108.
5. Sood R, Faubion SS, KuhleCL, et al. Prescribing menopausal hormone therapy: an evidence-based approach. Int J Womens Health. 2014;6:47-57.

Chapter 14

Epigenetics in Endometriosis

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INTRODUCTION

Endometriosis is a gynecological disorder that affects approximately 10% of women of reproductive age. It is characterized by the growth of endometrial-like tissue outside of the uterus. Many authors have described endometriosis as a "social disease" given the reality that it affects the quality of life and work potential to a great extent.[1] Women with endometriosis reported an average of 38% reduction in work productivity and absenteeism, which is because of reduced work effectiveness in the presence of incapacitating pelvic pain.

Endometriosis is an estrogen-dependent, benign, inflammatory disease that affects females during their premenarcheal, reproductive, and postmenopausal stages of life. The prevalence in general population can vary considerably. Endometriosis is characterized by the presence of endometrial glands and stroma outside of the uterine cavity. The lesions typical of endometriosis such as blebs, implants, and nodules additionally also, contain fibrous tissue, blood, and cysts. The lesions are described as pelvic where they commonly involve the ovaries, intestines as well as peritoneum and also, other extrapelvic sites including the diaphragm, pleural cavity, urinary system, and scar sites. These lesions are progressive and have the tendency to cause anatomical distortions. Endometriosis is a benign pathology and rarely do endometriomas become malignant. It is well known that ectopic endometrial tissue and resultant inflammation present as dysmenorrhea, dyspareunia, chronic pain, and infertility. The current treatment modalities for endometriosis include medical, surgical, or a combination of both, with surgery often being the treatment of choice. However, the recurrence risk after surgery is high. It is a well-known fact that repeated surgeries for endometriosis patients are associated with increased morbidity and damage to ovarian reserve. Damage to ovarian reserve is of particular concern in patients seeking fertility solutions.

The current medical treatment for endometriosis lays a lot of emphasis on creating a state of hypoestrogenism similar to pregnancy or menopause. Relief of symptoms appears to be short lived and at a high cost, especially in young women. Hence, the search for novel therapeutics in endometriosis is ongoing.

THE ENIGMA OF ENDOMETRIOSIS

The exact cause of endometriosis is not fully understood, but it is believed to result from a combination of genetic and environmental factors. Many hypotheses have been proposed to explain the pathogenesis of endometriosis which include retrograde menstruation also known as Sampsons theory, endometrial stem cell implantation, metaplastic transformation also known as Meyers theory, hormonal changes, müllerian remnant abnormalities, oxidative stress, inflammation, immune dysfunction, apoptosis suppression, alteration of endometrial cell fate, and genetic changes.[2] However, none of the hypothesis have been able to convincingly decode all aspects of endometriosis; and, hence, the search for a comprehensive explanation continues.

Symptoms may not necessarily correlate with the degree of anatomical distortion or stage of disease. In clinical practice,one often comes across minimal lesions that are most symptomatic and troublesome and often severe lesions are very much devoid of symptoms.

ABOUT EPIGENETICS

The concept of epigenetics though new to the field of genetics has changed the way that we think about inheritance, development, and disease. Epigenetics is explained as modifications to the deoxyribonucleic acid (DNA) molecule.[5] These modifications, however, do not change the underlying sequence of the genetic code. The behavior of a person's genes does not depend on the DNA sequence alone. It was a traditional thought that genes are "set in stone". With research in epigenetics, this has been disproven. Gene behavior, scientifically termed as gene expression, is now proven to be affected by epigenetic factors and modifications in these factors by environmental exposures, psychosocial stressors, and nutrition can play an important role in disease.

The term epigenetics was first coined by Conrad Waddington in 1940. He described the important role of environment and explained the way in which an organism's development is influenced by interactions between genes and the environment. At that time, since little was known about the molecular mechanisms which led to these interactions, the concept of epigenetics was by and large ignored and remained confined to theory books. In the following decades, however, advances in biotechnology, molecular biology, and genetics have resulted in a significantly better understanding of the mechanisms responsible for gene expression, including the role of delicate processes such as DNA methylation, histone modification, and non-coding ribonucleic acids (RNAs).[3] These discoveries have now provided a window to explain molecular basis for the concept of epigenetics, and allowed a better understanding of the ways in which epigenetic modifications can be transmitted across generations, influence development, and contribute to disease.

The most well-known and well-researched epigenetic modification is DNA methylation which represses gene expression. Histone modifications have the ability to either promote or repress gene expression.[4] This impact of epigenetics on gene expression can be seen in a wide variety of biological processes from development to disease. Environmental factors, such as pollution, chemicals, diet, and stress, can cause the above-mentioned changes and more significantly these changes can be passed down from one generation to the next.[3]

ROLE OF EPIGENETICS IN DISEASE

Epigenetic modifications have been shown to play a role in a variety of diseases, including cancer, autoimmune disorders, such as lupus and multiple sclerosis,neurological diseases, such as Alzheimer's and Parkinsonism, cardiovascular diseases, such as atherosclerosis and hypertension, metabolic disorders, such as diabetes and nonalcoholic fatty liver, and various developmental disorders.[5]

EPIGENETIC CHANGES IN ENDOMETRIOTIC TISSUE AND IN BLOOD OF PATIENTS WITH ENDOMETRIOSIS

Epigenetic changes have been observed in both endometrial tissue as well as blood of individuals suffering from endometriosis. Epigenetic changes in endometriosis tissue are attributed to the development and progression of the disease. Differential methylation is seen in endometriosis. Endometriotic tissue showed increased DNA methylation levels in the promoter region of the estrogen receptor 1 (ESR1) gene, which could lead to altered estrogen signaling and contribute to disease development. Hypermethylation of HOXA10 in eutopic endometrium, hypermethylation of PR-B in ectopic endometrium, hypomethylation of ERβ in ectopic endometrium, and hypomethylation of SF-1 in ectopic endometrium have also been extensively researched. Besides altered estrogen signaling, differences in methylation also result in pro-inflammatory and tissue-remodeling cytokine profiles which affect the T-cell response. The balance between T-helper-cell (Th)1/Th2/Th17 is not maintained in endometriosis.

Histone modifications in endometriotic tissue have been shown to increase expression of genes involved in angiogenesis.

These findings suggest that epigenetic changes thereby causing abnormal growth and survival of endometrial-like cells outside of the uterus.

Epigenetic changes are also seen in the blood of women with endometriosis such as dysregulation of genes involved in inflammation and immune function. Women with endometriosis had altered expression of certain microRNAs (miRNAs) in their blood, compared to healthy controls.[6]

STUDY OF EPIGENETICS AND IMPLICATIONS FOR PATIENTS WITH ENDOMETRIOSIS

Epigenetics provides hitherto unexplored insights into the underlying causes of many diseases and suggests new approaches to prevention and treatment. Such an exciting development holds potential in unravelling the enigma of endometriosis. Accurate diagnosis, unanswered questions regarding the etiology and development of therapeutics with minimal side effects are the greatest modern-day challenges in the treatment of endometriosis.

Some of the promising areas include detection of specific DNA methylation changes in the blood of affected individuals which may serve as a biomarker for the disease, and could potentially be used for noninvasive diagnosis.[7]

Environmental exposures, such as exposure to phthalates, was associated with changes in DNA methylation in genes involved in immune function and inflammation which may in turn contribute to the development of endometriosis by inducing epigenetic changes in key genes. Prevention of exposure and development of drugs which can reverse these changes hold great promise.

Another promising area of research in epigenetics is the use of epigenetic therapies to prevent or treat endometriosis. Epigenetic drugs, which target specific enzymes involved in epigenetic regulation, can modify the expression of specific genes and potentially treat a wide range of diseases. Normalization of T-cell function via epigenetic reprogramming is now a clear target for new therapies in endometriosis.

A PEEP INTO THE FUTURE

It is important to note that epigenetic changes associated with endometriosis are complex and likely involve multiple genetic and environmental factors. Further research is needed to fully understand the mechanisms underlying these changes and to develop effective treatments for endometriosis. Nonetheless, epigenetic changes in blood and endometrial tissue show great potential as diagnostic and therapeutic targets in endometriosis, and further studies in this area are ongoing.[8]

Conclusion

There is now undeniable evidence to show that epigenetics plays a pivotal role in pathophysiology of endometriosis. An understanding of epigenetics is a must for all clinicians treating endometriosis. Most of the novel diagnostic tests and therapeutic options in endometriosis are likely to be based on advances in epigenetics. We also need to understand that this knowledge is helpful not only in endometriosis but a plethora of other illnesses.

References

1. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012;98(3):511-9.
2. Malvezzi H, MarengoEB, Podgaec S, et al. Endometriosis: current challenges in modeling a multifactorial disease of unknown etiology. J Transl Med . 2020;18:311.
3. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet. 2012;13(7):484-92.
4. Qu X, Fang Y, Zhuang S, et al. Micro-RNA miR-542-3p suppresses decidualization by targeting ILK pathways in human endometrial stromal cells. Sci Rep. 2021;11(1):7186.
5. Paluch BE, Naqash AR, Brumberger Z, et al. Epigenetics: A primer for clinicians. Blood reviews. 2016;30(4):285-95.
6. Zubrzycka A, Zubrzycki M, Perdas E, et al. Genetic, Epigenetic, and Steroidogenic Modulation Mechanisms in Endometriosis. J Clin Med. 2020; 9(5):1309. Available from: https://www.mdpi.com/2077-0383/9/5/1309.
7. Nisenblat V, Bossuyt PMM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev. 2016;2016(5):CD012179.
8. Guo SW. Epigenetics of endometriosis. Mol Hum Rep. 2009;15(10):587–607.

Chapter 15

Endometriosis Fertility Index

KU Kunjimoideen

INTRODUCTION

Endometriosis is a common condition affecting women of reproductive age, where the tissue that lines the inside of the uterus grows outside of it, causing inflammation, scarring, and pain. One of the most significant concerns for women with endometriosis is their fertility, as the condition can cause infertility or difficulties in conceiving.[1] In this article, we will discuss the endometriosis fertility index (EFI), a tool for predicting the spontaneous pregnancy rate after surgery in women with endometriosis-related infertility and it also helps in making the therapeutic decision-making process as well.

WHAT IS THE ENDOMETRIOSIS FERTILITY INDEX?

The EFI is a scoring system that was developed in 2010 by Adamson and Pasta to predict the fecundity rate in women who underwent laparoscopic surgery for endometriosis.[2] It includes patient characteristics such as age, duration of infertility, prior pregnancy, intraoperative lesions description [American Society for Reproductive Medicine (ASRM)], and functional postoperative score (least functional score).

WHAT FACTORS ARE CONSIDERED IN THE EFI?

The EFI takes into account several factors that are known to affect fertility in women with endometriosis. These factors include:

- *Age:* As woman ages, her fertility declines, and this decline is more rapid for women with endometriosis.
- *Duration of infertility:* The more the duration of infertility, the chances of spontaneous conception is less.
- *Previous fertility:* Women who have had previous pregnancies are more likely to conceive than those who have not.
- *Endometriosis severity:* The severity of endometriosis is classified based on the location, extent, and depth of endometrial implants and adhesions. Severe endometriosis is associated with higher risks of infertility (ASRM staging).

- *Least function score:* It suggests the impact of endometriosis on the function of adnexal structures, such as fallopian tube, fimbria and ovary, and observed intraoperatively and lower score showed poor outcome for spontaneous pregnancy in patients.

HOW IS THE EFI CALCULATED?

The EFI is calculated by assigning points to each of the five factors mentioned above, with a higher score indicating a better chance of conceiving. The maximum score is 10 points, and the minimum score is 0 point. The points assigned to each factor are as follows.[2,3]

Historical Factors

- *Age:*
  - <35 years - 2 points
  - 35–39 years - 1 point
  - >40 years - 0 point
- *Duration of infertility:*
  - <3 years - 2 points
  - >3 years - 0 point
- *Previous fertility:*
  - Yes - 1 point
  - No - 0 point

Surgical Factors

- *Least function (LF) score:*
  - If LF score = 7 to 8 (high score) - 3 points
  - If LF score = 4 to 6 (moderate score) - 2 points
  - If LF score = 1 to 3 (low score) - 0 point
- *American Fertility Society (AFS) Endometriosis score:*
  - <16 - 1 point
  - >16 - 0 point
- *AFS total score:*
  - <71 - 1 point
  - >71 - 0 point

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS

Once the points have been assigned to each factor, they are added together to obtain a total score. The total score ranges from 0 to 10, with higher scores indicating a better chance of conceiving.

These scores are plotted in a graph, where it shows the chance of spontaneous conception over a period of 36 months.

WHY IS THE EFI IMPORTANT?

The EFI is important because it provides healthcare professionals with a standardized way of assessing a woman's fertility potential in the context of endometriosis. This information can be used to guide treatment decisions and to provide women with realistic expectations about their chances of conceiving.

The cumulative non-assisted reproductive technology (non-ART) pregnancy rate at 36 months was 10% for women with EFI of 0–2, which significantly increased to 69% for women with EFI of 9–10. Compared with women with an EFI of 3–4 (18%), the combined cumulative non-ART pregnancy rates were 44% for women with an EFI of 5–6, 55% for women with EFI of 7–8.[4]

The EFI can also be used to track changes in a woman's fertility potential over time. For example, if a woman has a low EFI score and undergoes treatment for endometriosis, her score may improve if the treatment is successful in improving the severity of her endometriosis or her ovarian reserve.[5,6]

LIMITATIONS OF EFI

While the EFI is a useful tool for assessing fertility in women with endometriosis, it is not without its limitations. One limitation is that the EFI only takes into account factors that are known to affect fertility in women with endometriosis. Other factors, such as male factor infertility or unexplained infertility, may also play a role in a woman's ability to conceive.[7]

Another limitation is that the EFI does not take into account the impact of lifestyle factors such as smoking, alcohol consumption, or body mass index (BMI) on fertility. These factors have been shown to affect fertility in both men and women and should be taken into account when making treatment decisions.

Finally, the EFI does not take into account the emotional impact of infertility on a woman's quality of life. Infertility can be a source of significant distress for many women and may impact their mental health, relationships, and overall well-being. Healthcare professionals should be sensitive to these issues and provide appropriate support and resources to women who are struggling with infertility.

DISCUSSION

In addition to the factors considered by the EFI, there are other factors that may impact a woman's fertility potential. For example, certain genetic mutations, such as mutations in the BRCA1 or BRCA2 genes, have been associated with a decreased ovarian reserve and increased risk of premature ovarian failure. Similarly, certain medical conditions, such as thyroid disorders, polycystic ovary syndrome (PCOS), and autoimmune disorders, can also impact a woman's fertility potential.

It is important for healthcare professionals to consider all of these factors when assessing a woman's fertility potential and making treatment decisions. For example, a woman with endometriosis who also has a genetic mutation associated with decreased ovarian reserve may have a lower EFI score and may require more aggressive treatment options such as in vitro fertilization (IVF) with donor eggs.

The EFI can also be used to predict the likelihood of success with different treatment options. For example, a woman with a high EFI score who undergoes ovulation induction or intrauterine insemination (IUI) may have a higher likelihood of success compared to a woman with a low EFI score. Similarly, a woman with a low EFI score, who undergoes IVF, may have a lower likelihood of success compared to a woman with a high EFI score.[8]

It is important to note, however, that the EFI is just one tool used to predict success with different treatment options. Other factors, such as the woman's age, the quality of her partner's sperm, and the success rates of the specific treatment center, should also be taken into account when making treatment decisions.[9]

While the EFI is primarily used to assess fertility potential in women with endometriosis, it can also be used in other contexts. For example, the EFI has been used to predict the likelihood of success with IVF in women with other conditions such as uterine fibroids and pelvic adhesions. The EFI has also been used to predict the likelihood of spontaneous pregnancy in women with unexplained infertility.[10]

In addition to the EFI, there are other tools and tests that can be used to assess fertility in women with endometriosis. For example, a pelvic ultrasound can be used to assess the size and location of endometrial implants and to check for other conditions such as uterine fibroids and ovarian cysts. A hysterosalpingogram (HSG) can be used to check for tubal patency, which is an important factor in natural conception. Blood tests, such as anti-Müllerian hormone (AMH) and follicle-stimulating hormone (FSH), can be used to assess ovarian reserve.

In some cases, surgery may be necessary to assess fertility potential in women with endometriosis. For example, laparoscopy can be used to visualize the severity of endometriosis and to check for other conditions such as pelvic adhesions and tubal damage.

It is important to work closely with women with endometriosis to develop an individualized treatment plan that takes into account their unique medical history, fertility potential, and personal preferences. Treatment options may include medical management of endometriosis, surgery to remove endometrial implants, and fertility treatments such as ovulation induction, IUI, and IVF.[11,12]

In addition to medical treatment, there are also lifestyle factors that can impact fertility potential in women with endometriosis. Maintaining a healthy weight, quitting smoking, reducing alcohol consumption, and managing stress can all improve fertility potential.

Women with endometriosis who are struggling with infertility may also benefit from psychological support and counseling. Infertility can be a source of significant distress and anxiety, and it is important for women to have access to support and resources to help them cope with these feelings.[13,14]

Conclusion

Endometriosis is a common condition that can have a significant impact on a woman's fertility. The EFI is a useful tool for healthcare professionals to assess a woman's fertility potential and likelihood of conceiving. The EFI takes into account several factors that are known to affect fertility in women with endometriosis including historical factors such as age, duration of infertility, history of prior pregnancy, and surgical factors such as endometriosis severity according to ASRM surgical staging, least function score on adnexal structures to provide a score that can be used to predict the likelihood of natural conception and success with fertility treatments.. The EFI provides a standardized way of assessing fertility in women with endometriosis and can be used to guide treatment decisions and provide women with realistic expectations about their chances of conceiving. While the EFI is a useful tool, it is not without its limitations, and healthcare professionals should consider other factors, such as lifestyle factors and the emotional impact of infertility on a woman's quality of life, when making treatment decisions.

It is important to work closely in women with endometriosis to develop an individualized treatment plan that takes into account their unique medical history, fertility potential, and personal preferences. Treatment options may include medical management of endometriosis, surgery to remove endometrial implants, and fertility treatments such as ovulation induction, IUI, and IVF.

Overall, the EFI is a valuable tool for healthcare professionals in assessing fertility potential in women with endometriosis. It can provide important information to guide treatment decisions and improve the chances of achieving a successful pregnancy. However, it is important to remember that each woman's situation is unique, and treatment decisions should be made on a case-by-case basis, taking into account all of the relevant factors.

References

1. Johnson NP, Hummelshoj L, World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. Hum Reprod. 2013;28(6): 1552-68.
2. Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010;94(5):1609-15.
3. Duffy JMN, Arambage K, Correa FJS, et al. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev. 2014;(4):CD011031.
4. Vesali S, Razavi M, Rezaeinejad M, et al. Endometriosis fertility index for predicting non-assisted reproductive technology pregnancy after endometriosis surgery: a systematic review and meta-analysis. BJOG. 2020;127(7):800-9.
5. Alborzi S, Momtahan M, Parsanezhad ME, et al. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. Fertil Steril. 2004;82(6):1633-7.
6. Vercellini P, Somigliana E, Viganò P, et al. Surgery for endometriosis-associated infertility: a pragmatic approach. Hum Reprod. 2009;24(2):254-69.

7. Benaglia L, Somigliana E, Santi G, et al. IVF and endometriosis-related symptom progression: insights from a prospective study. Hum Reprod. 2011;26(9):2368-72.
8. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis. Fertil Steril. 2012;98(6):1370-9.
9. Wei JJ, William J, Bulun S. Endometriosis and Ovarian Cancer: A Review of Clinical, Pathologic, and Molecular Aspects. Int J Gynecol Pathol. 2011;30(6):553-68.
10. Dunselman GAJ, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29(3):400-12.
11. Harb HM, Gallos ID, Chu J, et al. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. BJOG. 2013;120(11):1308-20.
12. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril. 2012;98(3):591-8.
13. Kitajima M, Defrère S, Dolmans M-M, et al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil Steril. 2011;96(3):685-91.
14. Vercellini P, Crosignani PG, Abbiati A, et al. The effect of surgery for symptomatic endometriosis: the other side of the story. Hum Reprod Update. 2009;15(2):177-88.

Chapter 16

Genitourinary Endometriosis

Pandit Palaskar,
Abhijeet Patil

INTRODUCTION

Endometriosis is chronic and benign condition in which there is presence of ectopic endometrium outside the endometrial cavity. Patients usually present with pelvic pain and infertility. Ectopic endometrial tissue is predominantly located in pelvis but can be present anywhere in the body where it is called as extragenital endometriosis. The two most common sites affected in extragenital endometriosis are bowel and urinary tract. The term urinary tract endometriosis (UTE) defined as the presence of endometriotic implants in the bladder, ureter, kidney, and urethra. The most commonly affected organs in UTE are bladder and ureter. This chapter will cover the incidence, epidemiology, pathogenesis, clinical presentation, diagnosis, and management of UTE.[1,2]

INCIDENCE

The UTE is the second most common site of extrapelvic endometriosis after gastrointestinal tract (GIT). About 50% women with UTE will be asymptomatic. The prevalence of UTE is 0.3–12% of all women affected by endometriosis and 20–52.6 of women with deep endometriosis.[1,2] The prevalence of disease at specific sites, bladder 85%, ureter 10%, kidney 4%, and urethra 2%.

PATHOGENESIS

There are two types of endometriosis that is superficial endometriosis (SE) and deep endometriosis (DE). Depending on the degree of fibrosis, hemorrhage superficial endometriosis can be identified as red and black spots. Deep endometriosis involves penetration of endometriotic tissue >5 mm beneath the peritoneal surface. With each menstrual cycle, this deep endometriotic implant will bleed and cause fibrosis and proliferation of smooth muscle. This will cause pelvic adhesions consequently pelvic pain and ultimately infertility. The various mechanisms by which this endometriosis develops are explained by the following theories:

- Retrograde menstruation
- Coelomic metaplasia
- Altered genetic factor
- Immunological theory
- Spread of endometrium-derived progenitor cells.[3,4]

CLINICAL PRESENTATION

While ureteral and bladder endometriosis are both diseases of urinary tract, they are not always found together in the same patient. In case of UTE, urinary bladder is affected most commonly followed by ureter and at last kidney. Bladder endometriosis is present with lower urinary tract symptoms. Ureteral endometriosis usually does not present clinically, but may cause silent loss of kidney function.[5,6]

Ureteral Endometriosis

It is very difficult to do early diagnosis of ureteral endometriosis as ureteral endometriosis does not present clinically often. Cyclical hematuria is present in less than 15% cases. Most patients present with cyclical lower abdominal pain and infertility. Severe endometriosis may cause obstruction of ureter and ultimately silent loss of kidney function.[7]

Bladder Endometriosis

Patients with bladder endometriosis are symptomatic and may present with dysuria, cyclical hematuria, recurrent micturition, and pelvic pain.

DIAGNOSIS

Diagnosis has to be considered as step-by-step procedure.

Physical Examination

The physical examination (bimanual per vaginal examination) is considered positive and, therefore, suggestive of endometriotic infiltration of the pelvis if there is palpable nodule, or thickened area, or palpable cystic expansion with topographic anatomical correlation to uterosacral ligament, vagina, rectovaginal space, pouch of Douglas (POD), rectosigmoid, and posterior wall of urinary bladder. Moreover, the presence of lesion in these area might suggest the involvement of ureter with or without consequent different grades of hydronephrosis up to silent renal function loss.

Blood Investigations

In case of extensive endometriosis, anemia is a common finding; that is why, patients should be investigated for the same. Renal function test which includes

serum urea and serum creatinine should be done as the extensive endometriosis of ureter and bladder also leads to silent loss of kidney function.

Urine Examination

Urine routine microscopy and urine culture sensitivity are the two important investigations which should be routinely done in suspected UTE. Microscopic as well as macroscopic hematuria should be evaluated. Urine culture sensitivity should be done to rule out infections.

Ultrasound

Transvaginal ultrasonography (TVS) is an important first-line radiological investigation in case of bladder endometriosis, bladder nodule can be easily diagnosed with partially full bladder. If hydroureter and hydronephrosis are seen on transabdominal ultrasonography (TAS), then the possibility of ureteric endometriosis should be considered.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) modality is used for confirmation and more accurate diagnosis or to support TVS findings of UTE. MRI is having greater sensitivity than TVS for bladder DE. MRI is particularly relevant for diagnosing bladder endometriosis with an accuracy of 96% and with sensitivity and specificity ranging from 88% to 100%.

Ureteral endometriosis typically appears as a nodule at low-intensity signal in T2-weighted sequences associated with retractile adhesion on surrounding fatty tissue. MRI demonstrates sensitivity of 91% and specificity of 59% in comparison to performance of laparoscopy as a diagnostic tool which has sensitivity of 82% and specificity of 67%. MRI is more sensitive than surgery considering severe anatomic distortion which limits visibility of disease location and extent via direct visualization or via surgery.[8]

Cystourethroscopy

When there is proven hematuria or bladder nodule visible on TVS or MRI, we find that performing cystourethroscopy may be helpful to confirm diagnosis. Cystourethroscopy can also aid in excluding malignancies and in measuring the distance of lesion from the ureteral opening to help the operating surgeon to anticipate the type of urological procedure necessary to perform.

TREATMENT

Medical Management

Medical management of endometriosis aims to reduce or stop menstruation so that this will suppress the activity of established ectopic endometrium. Medical treatment includes the use of gonadotropin-releasing hormone (GnRH) agonist,

GnRH antagonist, danazol, combined oral contraceptive (COC), progestins, and aromatase inhibitors.

Indications

The following are the indications for the medical management of UTE:

- Patients who are unfit for surgery
- Patients who decline surgery
- If endometriotic lesion is present in close proximity of trigone of bladder and if surgical excision is done, then it may lead to neurogenic bladder and retrograde reflux bladder.
- Mild disease or disease in early stage.

Contraindications

The following are contraindications of the medical management:

- Ureteral obstruction due to endometriosis
- Recurrent endometriosis
- Deranged renal function secondary to endometriosis of urinary tract.

Medical treatment for patients with endometriosis of bladder is generally considered a temporary solution as hormonal suppression, with its associated adverse effect, must be maintained throughout menopause.[9]

Surgical Management

The objectives of surgical treatment for genitourinary tract endometriosis are:

- To excise all visible disease.
- To prevent or delay recurrence of disease to the extent possible and to avoid any further morbidity.
- To preserve renal function in case of ureteric endometriosis.[10]

Ureteral Endometriosis

Surgical management of ureteral endometriosis includes conservative ureterolysis with the removal of adjacent deep endometriosis or radical approach such as ureterectomy with end-to-end anastomosis, ureteroneocystotomy (UNC), or nephron-ureteroneocystotomy, or nephron-ureterectomy. The surgical choice depends on the renal function and the extension of ureteral segment involved.

Ureterolysis: Ureterolysis is a surgical procedure which involves exposing the ureter in order to free it from the external pressure or adhesions.

Indications:

- Minimal extrinsic disease
- Nonobstructive ureteral endometriosis.

Contraindications: Obstructive ureteral endometriosis.

All the endometriotic tissues present in the surrounding are excised and ablation is usually avoided as ablating the surrounding tissues involves the risk

of thermal damage to ureter, ureteral injury. All the infiltrating endometriotic tissues are excised completely under vision with the preservation of vascularity of ureter.[2]

Ureterolysis, Ureterectomy, Ureteroneocystostomy: This is procedure of choice in distal third of ureter. In case of intrinsic endometriosis, endometriotic implant involves muscularis and lamina propria, and finally ureteral lumen leading to fibrosis and stricture of ureter which causes proximal ureter dilatation, i.e. hydroureter and hydronephrosis and ultimately loss of kidney function. In such a situation, to save kidney function resection of distal third of ureter and reimplanting proximal ureter in bladder is necessary **(Figs. 1 to 4)**. Intrinsic disease is suspected when there is presence of rectovaginal nodule on clinical examination or it could be identified on MRI. The procedure chosen to re-establish functional ureter following resection depends on the location and extent of involved ureter. Resection in close proximity of bladder can be repaired with ureteroneocystostomy with or without psoas hitch.[2,7]

Uretero-ureteral anastomosis: Lesions in the upper and middle third are repaired with uretero-ureteral anastomosis, Boari flap, ileal interposition, or autotransplantation.

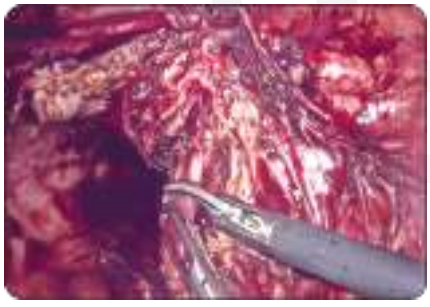

Fig. 1: Distal third of ureter dissected

Fig. 2: Opening created in bladder

Fig. 3: DJ stent inserted in ureter

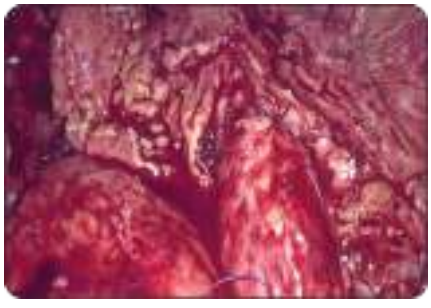

Fig. 4: Distal end of ureter sutured with bladder

Bladder Endometriosis

The surgical treatment for bladder endometriosis includes different surgical approaches. An accurate preoperative work-up, such as clinical history, physical examination, and imaging information, is necessary for planning the correct surgical procedure. Moreover, it is essential to rule out:

- Vesical epithelial malignancy,
- To confirm precise location of bladder nodule,
- Ureteral status. This leads to specify definite surgical procedure to achieve complete excision of symptomatic deep infiltrative endometriosis (DIE).

This is the only way to prevent the recurrence of disease. The recurrence of disease corresponds to the actual persistence of bladder endometriosis lesion that were left in place as the result of incomplete initial surgical removal. One study has shown that the most important risk factor which is responsible for the recurrence of the disease is the patient's age. Surgeons are more likely to be conservative in case of young population; and, hence, they avoid radical surgery in partial cystectomy. That is why, the risk of recurrence is greater in the younger population as compared to the older one.

Transurethral Surgery: Transurethral resection (TUR) might include both bladder lesion and 0.5–1 cm deep portion of adjacent muscle layer in order to reduce recurrence.[10]

Indications:

- Postmenopausal women
- Patient desirous for pregnancy
- Women who approach menopause (because lesion usually disappears spontaneously when menopause takes place)
- First diagnosis of bladder lesion and necessity of histopathological examination.

However, it should be kept in mind that extensive TUR may induce bladder perforation making the method nonradical and even hazardous with short-term recurrence. Nevertheless, the therapeutic approach most commonly used is TUR combined with GnRH agonist hormonal therapy, which has good results and clinical symptoms are improved.[11]

Partial Cystectomy: In this procedure, bladder endometriosis along with surrounding bladder wall is surgically excised. Generally, segmental bladder resection for detrusor endometriosis is relatively simple and safe procedure. Concomitant cystoscopy can be useful for better defining margins of endometriotic lesions to be resected. Moreover, according to the surgeon's preference, preventive cystoscopic catheterization of ureters may be advisable, especially when the distance between caudal border of the endometriotic lesion and interureteric ridge is <2 cm.

Laparoscopic partial cystectomy procedure begins with careful recognition of the limits of nodule and lysis of any adhesion between anterior uterine wall and vesicouterine fold of peritoneum. As it is usually not possible to remove the detrusor nodule without opening bladder lumen, an intentional perinodular incision through vesical dome is suggested. It is very easy to excise endometriotic nodule when it is situated over bladder dome, while complicated anatomical situation is when the endometriotic lesion is located on the posterior wall of bladder. In these cases, segmental bladder resection might be performed by lysis of any adhesion between anterior uterine wall and vesicouterine fold of peritoneum. The lesion is excised with mechanical scissor or unipolar electricity, and bladder is finally sutured with two transverse water-tight fine synthetic absorbable suture **(Figs. 5 to 8)**. A cystoscopy at the end of procedure is advisable in order to ensure water-tight closure and to check ureteral orifices integrity. Bladder is catheterized for 14 days. Outcome is excellent and pain relief is reported in 95–100% cases.[12]

Laparoscopic partial cystectomy offers the same result as open surgery with several advantages, including less bleeding, shortened operative time, shortened hospital stay, quicker return to work, a major reduction in postoperative pain, and decreased risk of postoperative morbidity.[12]

Fig. 5: Bladder endometriosis (Endometriotic nodule over bladder dome)

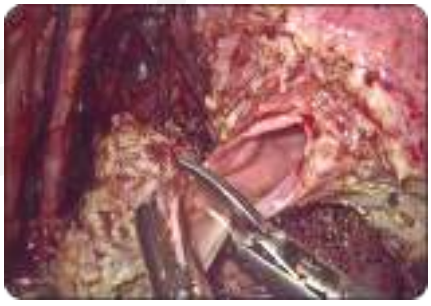

Fig. 6: Excision of bladder endometriosis with partial cystectomy

Fig. 7: Suturing mucosa of bladder

Fig. 8: Bladder sutured in two layers

Robotic Approach: Robot-assisted laparoscopy is a recent advancement in the technique of laparoscopy, but it has its own advantages as well as disadvantages. Robotic approach allows enhanced level of freedom of instrumentation and improved quality of suturing technique. Disadvantages of robotic technique include its highly expensive instruments, increased cost of treatment, set-up time is also increased, and large space is required for set-up, which ultimately increase the cost of treatment and limit its use.[13,14]

Conclusion

Genitourinary endometriosis is chronic benign disease that affects women's day-to-day life activity. It usually present with pelvic pain and infertility and may lead to serious sequelae such as ureteral obstruction and silent loss of kidney function. Clinical examination and radiological investigations like USG and MRI helps to reach at final diagnosis of GUE. Medical management is available but does not eliminate disease completely and chances of recurrence of the disease are higher after stopping the treatment. Surgical management is better option in treating GUE but require expertise.

References

1. Nezhat C, Nezhat F, Nezhat CH, et al. Urinary tract endometriosis treated by laparoscopy. Fertil Steril. 1996;66(6):920–4.
2. Leonardi M, Espada M, Kho RM , et al. Endometriosis of urinary tract: from diagnosis to surgical treatment. Diagnostics (Basel). 2020;10(10):771.
3. Koninckx PR, Ussia A, Adamyan L, et al. Deep endometriosis: definition, diagnosis, and treatment. Fertil Steril. 2012;98(3):564-71.
4. Espada M, Alvarez-Moreno E, Jimenez de la Pena M, et al. Imaging techniques in endometriosis. J Endometr Pelvic Pain Disorders. 2018;10(3):136-50.
5. Maggiore ULR, Ferrero S, Salvatore S. Urinary incontinence and bladder endometriosis: conservative management. Int Urogynecol J. 2014;26(1):159-62.
6. Maccagnano C, Pellucchi F, Rocchini L, et al. Ureteral endometriosis: proposal for a diagnostic and therapeutic algorithm with a review of the literature. Urol Int. 2013;91(1):1-9.
7. Berlanda N, Vercellini P, Carmignani L, et al. Ureteral and vesical endometriosis. Two different clinical entities sharing the same pathogenesis. Obstet Gynecol Surv. 2009;64(12):830-42.
8. Gutiérrez AH, Spagnolo E, Hidalgo P, et al. Magnetic resonance imaging versus transvaginal ultrasound for complete survey of the pelvic compartments among patients with deep infiltrating endometriosis. Int J Gynaecol Obstet. 2019;146(3):380-5.
9. Comiter CV. Endometriosis of the urinary tract. Urol Clin North Am. 2002;29(3):625-35.
10. Seracchioli R, Mabrouk M, Montanari G, et al. Conservative laparoscopic management of urinary tract endometriosis (UTE): surgical outcome and long-term follow-up. Fertil Steril. 2010;94(3):856-61.
11. Maccagnano C, Pellucchi F, Rocchii L, et al. Diagnosis and treatment of bladder endometriosis: state of the art. Urol Int. 2012;89(3):249-58.
12. Merino JMS, Maquieira CG, Alonso JG. The treatment of bladder endometriosis. Spanish literature review. Arch Esp Urol. 2005;58(3):189-94.
13. Nezhat C, Hajhosseini B, King LP. Robotic-assisted laparoscopic treatment of bowel, bladder, and ureteral endometriosis. JSLS. 2011;15(3):387-92.
14. Chammas MF Jr, Kim FJ, Barbarino A, et al. Asymptomatic rectal and bladder endometriosis: a case for robotic-assisted surgery. Can J Urol. 2008;15(3):4097-100.

Chapter 17

Fertility Preservation in Endometriosis and Adenomyosis

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Manisha Nandi

INTRODUCTION

Pelvic endometriosis and uterine adenomyosis are variants of the same disease process, which involves the dislocation of basal endometrium and results from a dysfunction and disease primarily at the level of the archimetra. Moreover, uterine adenomyosis is an important factor in causing sub- and infertility in women with pelvic endometriosis by impairing directed sperm transport and possibly by directly affecting ovarian function via the utero-ovarian counter-current system.[1]

PATHOPHYSIOLOGYOF THE DISEASE

Tissue Injury and Repair

In clinical practice, there are 3 typesof pelvic endometriosis commonly encountered: superficial peritoneal, ovarian endometriomas, and deep infiltrative endometriosis. One more distinct phenotype recognized is adenomyosis which is distinguished by the typical infiltration of endometrial tissue into the myometrium causing chronic inflammation and hypertrophy. Adenomyosis usually presents in various configurations, which include: focal, diffuse, and, cystic adenomyomas (rare).

Endometriosis in association with adenomyosis and premenopausal adenomyosis is a common phenomenon that occurs in a continuum and is termed as the syndrome of dislocated basal endometrium (SDBE), which at present defines the pathophysiology of the disease **(Figs. 1 and 2)**.[2]

The definitive diagnosis of adenomyosis uteri is contrived when certain histological criteria are met. In the recent times, based on several correlation studies, Ultrasound imaging [transvaginal ultrasound (TVUS)] criteria have been accepted. However, magnetic resonance imaging (MRI) stands out to be the gold standard modality for the diagnosis of the disease in vivo. With the concerns of infertility, adenomyosis has been found to be commonly associated with peritoneal endometriosis in a significant number of infertile patients (Barrier et al., 2004).

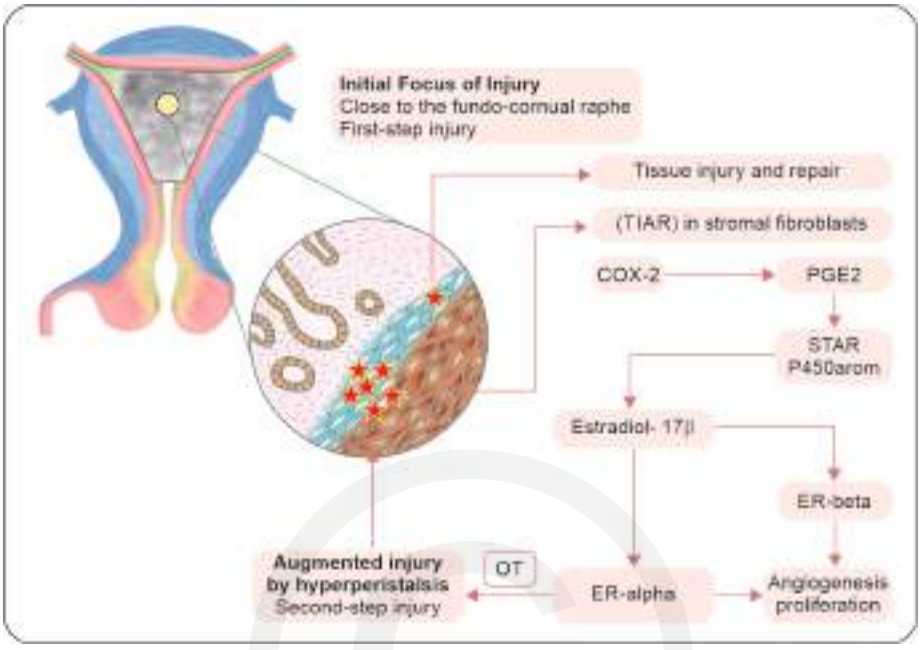


Fig. 1: Model of 'tissue injury and repair' (TIAR) on the level of the endometrial–myometrial interface at the fundo-cornual raphe. Persistent uterine peristalsis activity and hyperperistalsis are responsible for perpetuation of injury with permanently increased paracrine estrogen action[2]

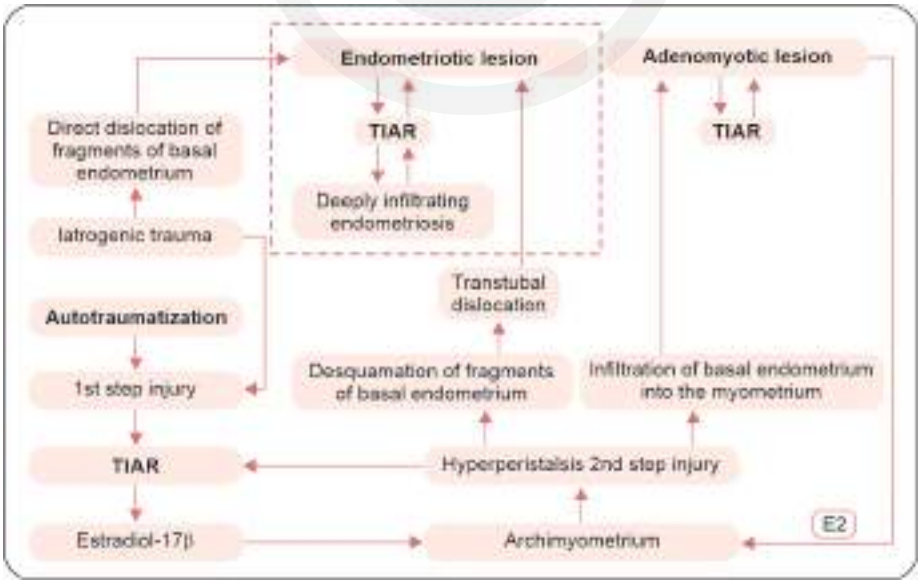
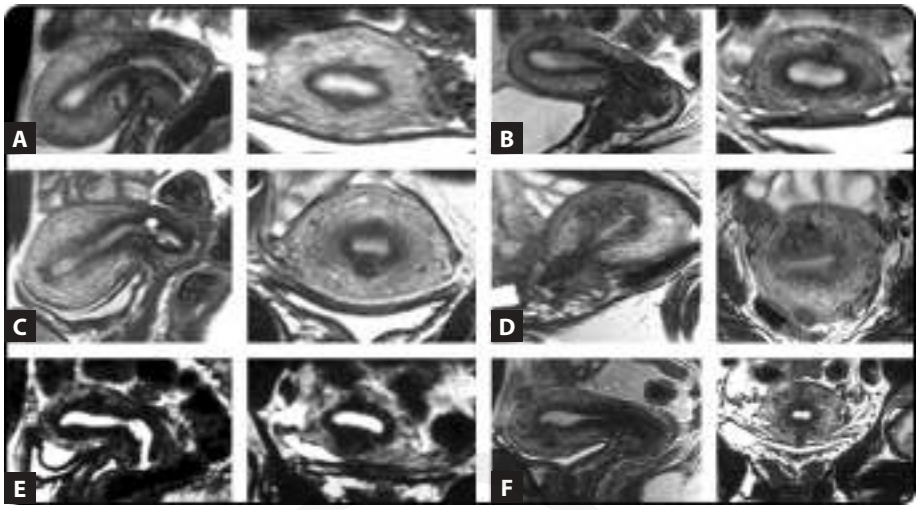


Fig. 2: Model of the pathophysiology of endometriosis and adenomyosis. Tissue injury in the depth of the endometrium and the activation of the TIAR system constitute the primum movens (prime mover) in the disease development



Figs. 3A to F: Coronary and sagittal scans of adenomyosis uteri in 6 women. (A to E) Pelvic endometriosis of grade I–IV diagnosed by laparoscopy; (F) Laparoscopy not performed

MRI images of adenomyosis uteri in 6 women. The coronary and sagittal scans are depicted in **Figures 3A to F**. For the patients with primary infertility: aged between 30 and 32 years: **(Figs. 3A to E)** pelvic endometriosis of grade I–IV was diagnosed by laparoscopy. In the parous patients aged 40 years and above **(Fig. 3F)**, laparoscopy was not performed. For all the patients, the scans performed had a preponderance of expanded junctional zone: pathognomonic of adenomyotic lesions.[2]

EVALUATING THE OVARIAN RESERVE

Age of the woman signifies as the foremost predictor of the ovarian reserve and also marks the success of assisted reproductive techniques (ART), with the pregnancy and live birth rate found to be on a declining trend with advancing age of the patients. With the concerns of success in ART, assessment of the ovarian reserve must be included with proper counseling of patients with regards to the expected success rates before proceeding with surgery for endometriosis and focusing on fertility preservation.

The various tests for determining the ovarian reserve includes:

- FSH level in the early follicular phase
- AMH (Anti-Müllerian Hormone)
- AFC (Antral Follicle Count)
- Ovarian volume.

Hence, TVUS and hormonal assays play a vital role in determining the dosage of the drugs for ovarian stimulation and the number of oocytes retrieved which

predicts the success of ART. The markers show a change from adolescence to late reproductive period and challenges clinicians in selecting protocols and treating infertility in the older age group.

Moreover, ovarian endometriosis is often associated with diminished serum AMH, low AFC, and a poor response to ovarian stimulation, and requires the administration of higher doses of gonadotropins in ART cycles. A lower ovarian reserve has been observed not only in patients with endometriomas, but also in women with minimal-to-mild disease.

While discussing the management of endometriosis, clinicians should be concerned and focused towards the early recognition of the risk factors leading to infertility and provide proper and immediate referral to a specialist when required. A low AFC or serum AMH level can aid in predicting the necessity of repeated ovarian stimulation cycles to retrieve an adequate oocyte yield that would enhance the chances of a successfulin vitro fertilization (IVF). These tests also indicate the surgeons in planning for a less aggressive technique so as to minimize the harm posed towards the fertility potential of the patients post-surgery. AFC associates well with the response of the ovaries to the gonadotropin stimulation protocols.

TREATMENT MODALITIES

- Choosing the best endometrioma/endometriosis surgical techniques
- Avoiding unnecessary ovarian surgery
- Measuring ovarian reserve or before surgery
- Utilizing emergency IVF before surgery
- Using gonadotropin-releasing hormone (GnRH) analogues
- Using cryopreservation techniques
- Maintaining a healthy lifestyle.

MANAGEMENT OF INFERTILITY

Medical Management

The management of endometriosis-related subfertility should be individualized. Hence, clinicians should be considering the medical, surgical, and ART treatments alone or in combinations. When medical management is the treatment modality, various hormonal treatments can be used which causes suppression of ovulation and, therefore, do not have a significant role to play for infertile women. This modality of treatment only serves the purpose of pain relief in most patients. A recent Cochrane review published by Hughes and coworkers observed that suppression of ovulation in patients with endometriosis and adenomyosis had no role when pregnancy was planned. Neither did the preoperative or postoperative usage of various hormonal form of therapy had a role in enhancing the chances of spontaneous conception.

Another Cochrane review that included 3 randomized controlled trials (RCTs), with 165 patients, reported the benefit of the GnRH agonists in the pre-IVF phase. This is attributed to the fact that GnRH agonists cause a 'pseudomenopausal' change in the HPO pathway. They reached a conclusion that the odds of achieving clinical pregnancy in patients with endometriosis increase by four times when GnRH agonists were administered for a period of 3–6 months prior to IVF/intracytoplasmic sperm injection (ICSI). Hence, GnRH agonists should be administered for at least 3–6 months before planning for IVF as per the recent European Society of Human Reproduction and Embryology (ESHRE) recommendations so as to increase the clinical pregnancy rates.

Surgical Treatment

Minimal-mild Endometriosis

The use of ablative techniques involves laser methods (CO_2 or argon laser) and bipolar coagulation. The ESHRE currently recommends CO_2 laser as a better option when compared to the use of monopolar electrocoagulation. A Cochrane review by Dufy and coworkers has observed a higher live birth rates and reduced pain scale in patients after undergoing laparoscopy for mild-to-moderate endometriosis. The overall clinical pregnancy rates increase in infertile patients with the American Fertility Society (AFS)/American Society of Reproductive Medicine (ASRM) stage I/II post laparoscopy.

Moderate and Severe Endometriosis

Moderate/severe endometriosis (r-ASRM III-IV) usually causes distortion of the normal anatomy of the pelvis; hence, surgery as the mode of treatment leads to restoration of the pelvic anatomy and the tubo-ovarian relationship might be hampered due to extensive pelvic adhesions. This form of the disease might involve the colorectal and the rectovaginal spaces and may be deep infiltrative. The use of oxidized regenerated cellulose during laparoscopy has been shown to improve the success of the surgery as it prevents adhesion formation.[5] After laparoscopy, suspension of the ovaries temporarily may help in reducing the postoperative chances of adhesion formation in women with severe form of the disease.

Options of the Best Surgical Techniques

The gold standard treatment for ovarian endometriomas is laparoscopy. The other techniques include bipolar coagulation, laser vaporization, drainage, bipolar coagulation, and stripping of the endometriomas; however, studies at present still have not reported the ideal and the most effective method to avoid ovarian damage. Surgical treatment may cause a decline in the ovarian reserve by 3 mechanisms: over stripping of ovarian cortex, the usage of bipolar so as

tominimize bleeding, and the surgery-induced inflammation of the ovaries. It has been stated that laparoscopic cyst stripping results in loss of normal ovarian cortex, which can decline the ovarianreserve as the follicles are within the ovarian cortex. Moreover, there is a concern that with cystectomy there is more harmful to adjacent normal ovarian tissues than with the use of laser ablation as the technique.[3]

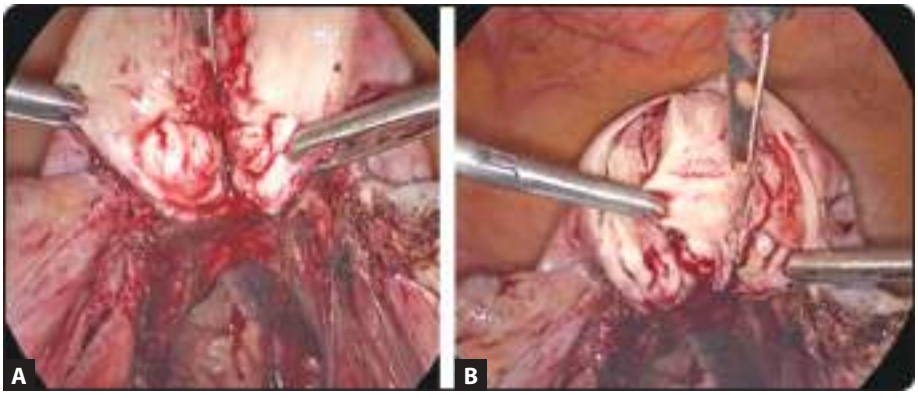
ENDOMETRIOSIS AND ASSISTED REPRODUCTIVE TECHNIQUES

The recent ESHRE guidelines recommend, IVF pre-treatment with the administration of GnRH agonists for 3–6 months. For controlled ovarian stimulation in patients with endometriosis, both antagonist andagonist protocolscan be equally beneficial. Recent studies also suggest GnRHa agonist triggering, which is possible considering the antagonist protocols, and additionally limits pain progression in the time period immediately after IVF.

ROLE OF CYTOREDUCTIVE SURGERY IN ADENOMYOSIS

The operative techniques include an open approach with either partial or complete excision or laparoscopy. The adenomyotic lesions can be approached with a classic myomectomy technique which includes the steps of myomectomy. The tissues are dissected and excised by scalpel or diathermia, and the walls of the uterus are sutured in layers, with various standard closure techniques, for the restoration of the normal thickness of myometrium **(Figs. 4A and B)**.

The incidence of uterine rupture in pregnancy is the leading concern after uterine surgery for adenomyosis and was observed after extensive surgical treatment. In a study, 2 out of 23 pregnant women after cytoreductive surgery had



Figs. 4A and B: Laparoscopic adenomyomectomy procedure. (A) The uterus is longitudinally incised with the scalpel to access the adenomyotic tissue; (B) The nucleation is resected in a wide wedge shape with the scalpel in the posterior uterine wall

uterine rupture in the second trimester. In 5 patients with myometrial thickness less than 7 mm, only 2 were reported to have a normal pregnancy. The authors reported from their study that the optimum myometrial thickness for pregnancy and uterine rupture prevention after surgery should be between 9 mm and 15 mm.

OTHER TREATMENT MODALITIES FOR ADENOMYOSIS

High-intensity focused ultrasound (HIFU) and uterine artery embolization (UAE) are the other two treatment options available and have been found to be effective for treating symptomatic adenomyosis. The benefits of both the techniques with regards to symptom relief is dependent on achieving necrosis of the adenomyotic lesions, and the aim is to control the location and size of necrosis. Subsequently, the myometrial tissue gets affected, which might cause reduction of the strength of the walls of the uterus and increase the risk of uterine rupture in pregnancy. No large studies on pregnancy outcomes have been reported till date after these procedures. Currently, these techniques are not recommended for patients with adenomyosis who wish to plan pregnancy.[4]

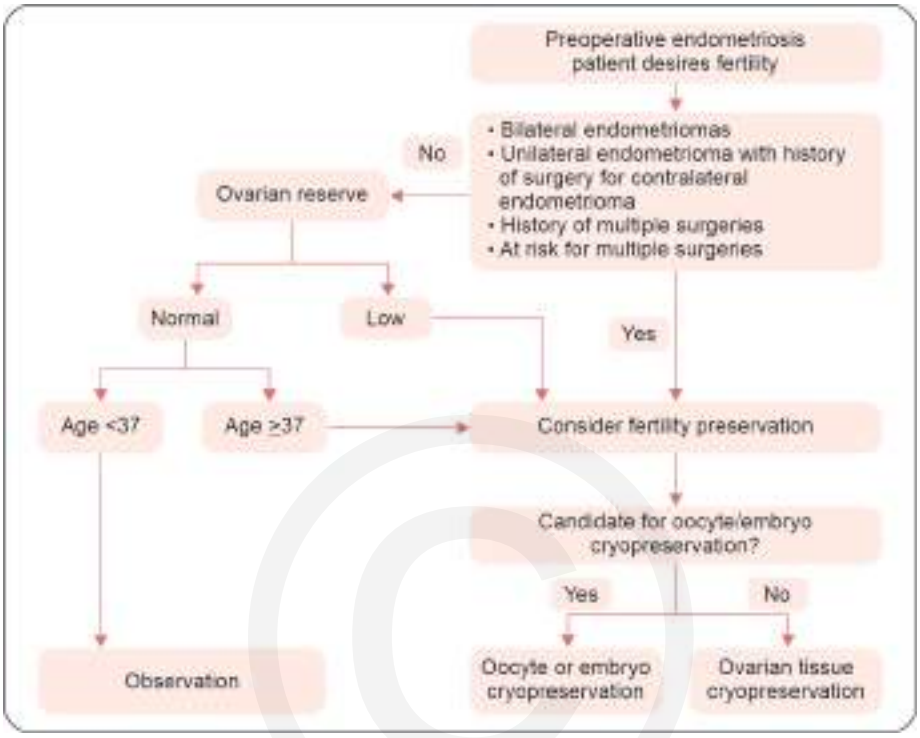
OPTIONS FOR FERTILITY PRESERVATION[5]

The techniques of oocyte, ovarian tissue, and embryo cryopreservation have been used in oncology patients for fertility preservation. Sherman and colleagues were the first to develop the technique of cryopreservation with the use of mouse oocytes, and the technique has evolved to slow freezing, then rapid thawing, a method started by Whittingham that promises a clinical pregnancy rate of 25%. Hence, oocyte and embryo cryopreservation are a good option for preservation of fertility in young patients who are at a high risk of premature ovarian failure **(Flowchart 1)**. The ovarian tissue is cryopreserved by twotypes of surgery: excision of the ovarian tissue and autografting.

Another common method, called vitrification, is done by the ultra-rapid cooling technique that leads to solidification of an aqueous solution. This process is proved to be better than the slow-freezing/rapid-thawing method with regards to the survival of the oocytes, implantation, and pregnancy rates. Vitrification is one of the cryopreservation techniques that applies high concentration of cryoprotectant to solidify the cells in a glass state without the formation of ice. It also uses carbohydrate-penetrating cryoprotectants to help with the process of dehydration. A recent study, at the McGill Reproductive Centre, Canada, reported that thevitrified oocytes had a better survival rate of 85%, with a fertilization rate of 75%, and a clinical pregnancy rate of 40%.

Another method, cryopreservation of the ovarian tissue, involves reimplantation of the tissues of the ovarian cortex into the pelvic cavity or at

Flowchart 1: Preoperative endometriosis patient desires fertility



another heterotopic site. After completion of all treatments and once the patient is disease-free, the implanted tissue is used in an IVF–embryo transfer (ET) procedure. This method has found to have a 25% follicle survival rate, but is most successful when women are less than 40 years **(Table 1)**.

The patients with endometriosis might benefit considering the advancement of fertility preservation techniques; however, due to the lack of data, fertility preservation and counseling of women with endometriosis should be done on an individual basis. Cobo and colleagues in an observational retrospective study observed the outcome of fertility preservation (FP) with the use of cryopreserved oocytes in women with endometriosis with or without surgery. They noted that women without surgery in the past had a high number of cryopreserved oocytes in each cycle compared to the bilateral/unilateral surgery groups, but was comparable amongst the surgical patients. FP gives women with endometriosis a better chance to achieve a successful pregnancy. Therefore, opting for surgery after oocyte pickup for fertility preservation in young patients is an excellent option.

Table 1 Benefits and risks of cryopreservation

	Oocyte embryo cryopreservation	***Ovarian tissue cryopreservation***
Benefits	High success rates, particularly with embryos	Option for women who are unable or unwilling to undergo ovarian stimuation
	Avoides a laparscopic procedure	Option for women who require oophorectomy
	Avoids risk of damage to ovarian tissue	Could be performed at the time of excision surgery for at-risk patients
Risks	Reproduction potential of follicles from endometriosis patients requires further study	Experimental technology
	Need to cyropreserve large numbers of oocytes (15–20 in women aged <38 years and 25–30 in women aged ≥38 years	Potential for damage to viable ovarian tissue
	Possibility of impaired oocyte and embryo quality	Risks of laparoscopy

ROLE OF LIFESTYLE MODIFICATION IN PATIENTS WITH ENDOMETRIOSIS

As alcohol intake, obesity, and smoking rates increase in the general population, it is crucial to study their effects on patients with endometriosis and to step towards lifestyle modifications, which should be the plan of action not only for the overall health but also for improving and preserving fertility. The term 'Modifiable Risk Factors' suggest,that these habits once developed can be changed and the risks could be significantly lowered. Various studies have reported the effects of lifestyle modifications on endometriosis and subfertility. Endometriosis is estrogen dependent, so any form of lifestyle that reduces the production of estrogenmight cause reduction of the risk of the disease process. Parazzini and colleagues observed a positive correlation between red meat consumption and endometriosis, and a negative correlation between vegetable and fruit consumption with endometriosis. Diet of the patient, is a modifiable risk factor, and is vital in the etiology and pathogenesis of endometriosis.

Conclusion

With surgery as the mode of treatment, there is a correlation with regards to the pathogenesis of endometriosis that contributes towards a decline in the ovarian reserve. The optimization and preservation of fertility in patients with endometriosis commences with the prevention of iatrogenic injury. Henceforth, surgery should be accomplished with attention towards the higher chances of serious damage to the ovarian reserve. Repeated surgical treatment for recurrent endometriosis usually has no role in improving

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the fertility outcomes, and women who do not conceive after the first procedure should be counseled for IVF treatment. However, the recent data are mixed, and suppression of the ovaries may provide with a low-risk and cost-effective method for the prevention of developing recurrent endometriomas, which is a major threat to fertility. The preservation of fertility with ovarian tissue or oocyte cryopreservation should be on individual basis for patients with severe endometriosis. More studies are required for the establishment of the outcomes for fertility preservation in patients with endometriosis and development of guidelines with regards to those most likely to benefit.

References

1. Sudoma I. The evaluation of pinopode formation in patients with adenomyosis. Fertil Steril. 2002;77(Suppl 1):S27.
2. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. Arch Gynecol Obstet. 2009;280(4):529-38.
3. Carvalho L, Nataraj N, Rao J, et al.Seven ways to preserve female fertility in patients with endometriosis. Expert Rev Obstet Gynecol. 2012;7(3)227-40.
4. Dueholm M. Uterine adenomyosis and infertility, review of reproductive outcome after in vitro fertilization and surgery. Acta Obstet Gynecol Scand. 2017;96(6):715-26.
5. Llarena NC, Falcone T, Flyckt RL. Fertility preservation in women with endometriosis. Clin Med Insights Reprod Health. 2019;13:1179558119873386.

Chapter 18

Role of Progesterone in Endometriosis and Adenomyosis

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INTRODUCTION

Endometriosis is a chronic inflammatory estrogen-dependent condition characterized by the presence of ectopic implantation of functional endometrial-like tissue (endometrial glands and stroma) outside of the uterine cavity. Adenomyosis is characterized by ectopic endometrial tissue within the uterine myometrium associated with the enlargement of the uterus. Due to the unclear pathophysiology and nature of both the diseases, there are no standard management and there are no fixed criteria that prioritize one treatment modality over the other; management depends upon the patient's age, desire for fertility, and symptoms.

WHY PROGESTERONE IN ENDOMETRIOSIS?

Endometriosis and adenomyosis are estrogen-dependent chronic diseases.[1] Endometriosis frequently coexists with adenomyosis or endometriosis interna. The exact etiology of both the diseases remains unclear. Endometriosis is a chronic inflammatory disease and progesterone has anti-inflammatory effects on uterine cells.

Progesterone is one of the oldest hormones known and it is the essential hormone for pregnancy maintenance. Today, we see tremendous potential of its use in gynecology. Progesterone is an endogenous steroid hormone produced by ovaries, adrenal glands, and placenta, and is involved in the regulation of menstrual cycle.

Whenever considering the treatment, often long-term or repeated medications are necessary. Therefore, not only the efficacy, but also the tolerability and costs of the drugs are relevant, when choosing the treatment. The first-line medical treatment should focus on the drugs that can be used for long term with minimal adverse effects.

MECHANISM OF PROGESTIN ACTION

Progestins acts by suppressing the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and ultimately inhibiting the ovarian steroid formation

and allaying adenomyosis and endometriosis related hyperestrogenism.[2] As in endometriosis, progesterone receptors in adenomyotic uteri are either reduced or resistant, thus, inhibiting the action of both local and synthetic progesterone forms in one-third patients. There is an imbalance of estrogen and progesterone levels, which disrupts their complex regulatory mechanisms, leading to estrogen dominance and progesterone resistance.[3]

Progestins causes the decidualization of uterine endometrium, but the doses required to achieve this effect differ among the different derivatives. As the continuous progestin therapy results in low serum estradiol levels, because of this breakthrough bleeding is a common side effect.

PAIN RELIEF MECHANISMS

The suggested mechanisms of progestins in resolving endometriosis-related pain are effects on endometrial morphology (decidualization, atrophy and alteration in steroid receptor ligand binding), local modulation of immune response [interleukin (IL)-8 suppression, increasing nitric oxide production, reducing tumor necrosis factor (TNF)-α-induced nuclear factor-χ-β], effects on angiogenesis [suppression of transcription of basic fibroblast growth factor (bFGF), suppression of vascular endothelial growth factor (VEGF), and cysteine-rich angiogenic inducer (CYR61)], and direct effect on nerve fiber intensity.

TYPES OF PROGESTERONE

Progestogens (all natural metabolites) and p*rogestins* (synthetic progestogens with same effects as that of natural hormone) have demonstrated benefits in reducing pain and suppressing the extent of endometriotic lesions. Natural progesterone is orally less effective as it is degraded in liver. Semisynthetic progesterone in micronized form is orally active for 8 hours but in sustained release form (SR), it maintains serum levels for 24 hours. Synthetic progesterones have the side effects of central nervous system (CNS), virilization, possible teratogenic effect and decrease in high density lipoproteins (HDLs).[4]

Generations of Progesterone

- *First generation*: norethindrone, norethisterone, and medroxy progesterone acetate
- *Second generation*: levonorgestrel and norgestrel
- *Third generation*: desogestrel, gestodene, norgestimate, and etonogestrel
- *Fourth generation*: dienogest, drospirenone, and nomogestrol.

Progestogens/progestins have very little impact on the coagulation system and epidemiological studies have shown that there is no significant risk for thromboembolic venous or arterial disease.[5]

TYPES AVAILABLE FOR USE

Progestins are available in many forms, including oral preparations, injections, subdermal implants, and intrauterine systems. Progestins used in the treatment of endometriosis include dienogest (2 mg or 4 mg per day), medroxyprogesterone acetate (150 mg intramuscularly every 3 months or oral 10–100 mg per day for 3–6 months), norethisterone acetate (2.5 mg per day for 12 months), as well as dydrogesterone, gestrinone, and megesterol acetate. In addition, levonorgestrel-releasing intrauterine devices which contain 52 mg levonorgestrel and release 20 micrograms of hormone per day valid over a 5-year period. Another route of progestins delivery is the subdermal implant (etonogestrel),[6] which offers contraceptive benefits for at least 3 years. The main advantages of the vaginal route include the avoidance of the hepatic-first pass metabolic effect, the possibility of using lower therapeutic doses, and the reduced systemic side effects compared to oral administration.[7]

DIFFERENT ROUTES OF USE

ORAL

Norethisterone (Norethindrone) Acetate

Norethisterone (norethindrone) acetate is a C-19-nortestesterone derivative. It has been approved for the treatment of endometriosis (2.5–5 mg daily continuous administration) by the Food and Drug Administration (FDA). Advantages are reduced bleeding, pain relief, and no effect on lipid profile with better compliance and minimal side effects.

Medroxyprogesterone Acetate

Medroxyprogesterone acetate (MPA) is a C-21-progestogen derivative, 15–50 mg doses daily in continuous administration for effective pain relief; however, breakthrough bleeding is a problem on long-term use.

Dienogest

Dienogest (DNG) is a fourth-generation progesterone that first received the approval for the treatment of endometriosis in the European Union in 2009.[8] It is a C-19-nortestosterone progestogen derivative which has gained popularity in recent times in the treatment of endometriosis. DNG has a short plasma half-life of approximately 10 hours and high oral bioavailability of more than 90%. DNG causes endometrial tissue decidualization followed by the atrophy of endometriotic lesions. Additionally, DNG lacks any effect on the metabolic and cardiovascular systems and exhibits considerable antiandrogenic activity, weak antigonadotropic activity, and most importantly, no antiestrogenic effect; thus,

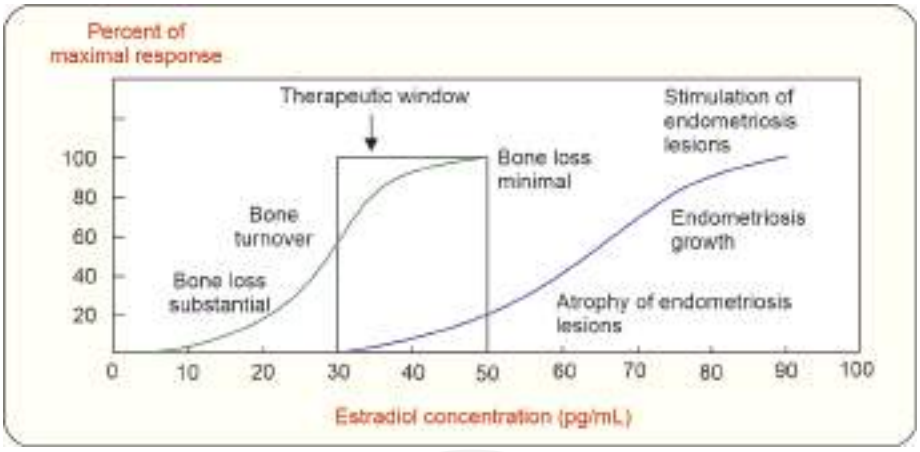

Fig. 1: Estradiol therapeutic window

making it an ideal candidate for the treatment of endometriosis. So, it is effective with good tolerability with doses 2–4 mg daily in continuous administration for 3–24 months in patients with endometriosis.[9]

It can be safely administered to adolescents. In the VISADO study (VISsane study to assess safety in ADOlescents), administration of 2 mg DNG in adolescents with symptoms suspicious of endometriosis for one year has been reported to be associated with significant pain reduction and minimal decrease in bone mineral density (BMD), which recovers to some extent after the treatment discontinuation of dienogest.[10]

In a randomized controlled trial (RCT) involving 252 participants, the efficacy of DNG in relieving endometriosis-related pelvic pain was compared to that of leuprolide acetate (LA). There was a significant reduction in visual analog scale (VAS) score and it maintains estrogen levels within the therapeutic window which is 30–50 pg/mL **(Fig. 1)**. Therefore, DNG has a lower incidence of hypoestrogenic effects compared to LA. A recent study in 2023 compared the efficacy of dienogest with gonadotropin-releasing hormone (GnRH) agonist after endometriosis surgery showed that dienogest is better than GnRH agonist in postoperative recurrence with improved VAS score.[11]

Two notable studies, the Visanne Post-approval Observational Study (VIPOS) and the effectiveness of dienogest in improving quality of life in Asian women with endometriosis (ENVISIOeN), aimed to evaluate the safety and effectiveness of dienogest. The VIPOS enroled approximately 27,840 women across six European countries for up to 7 years. The results of this study are expected to provide valuable insights into the long-term use of dienogest. In ENVISIOeN study, Asian women receiving dienogest (2 mg/daily) were followed for 24 months. The effectiveness of dienogest to improve the health-related quality

of life (HRQoL) and endometriosis-associated pelvic pain (EAPP) was assessed by patient-reported outcomes. Dienogest therapy decreased the Endometriosis Health Profile-30 (EHP-30) scores, thus better HRQoL and reduced EAPP score.[12]

Although there have been a few interventional studies to investigate treatment durations beyond 15 months, supportive evidence for long-term dienogest treatment is available from a number of studies.[13-15] These studies show that the administration of dienogest for up to 5 years is effective in preventing the recurrence of disease and/or symptoms following surgery, and reducing endometriosis-associated pain.

A retrospective cohort study assessed the tolerability of dienogest use for more than 2 years and found that the long-term use of dienogest may be associated with a decrease in uterine size (38.7–26.9 cm^2, $p < 0.01$), suggesting that it may be a tolerable alternative treatment option for patients with adenomyosis.[16]

A study by Michele et al,[17] to evaluate dienogest in endometrioma size reduction and symptoms over a period of 6 and 12 months, showed that the reduction of mean volume of endometrioma size by 66.71% and 76.19% over 6 and 12 months respectively; reduction in dysmenorrhea seen in 74.05% and 96.55% after 6 months and 12 months. Patients reported a reduction in dyspareunia and chronic pelvic pain of 42.71% and 48.91% after 6 months and 51.93% and 59.96% after 12 months, respectively. So, it has been found that dienogest leads to a statistically significant reduction of endometrioma's volume and pain symptoms.[17]

Side Effects: Dienogest is as effective as GnRH agonists, with low adverse effects. Main side effect was breakthrough bleeding that was observed in 80% of patients within the first 3 months of treatment, which later on were reduced. Other side effects include breast tenderness, acne, hot flushes, headache, loss of libido and fatigue between 10% and 38% of the patients.

Micronized Natural Progesterone

Micronized natural progesterone 12–14 days/month at 200–300 mg/day for up to 5 years can act on the eutopic endometrium and effect quiescent changes. Useful to women with worrisome lipid profile or hypertension. There is no clear evidence indicating the superiority of one progestin over the other. High adherence and low dropout rates have been reported with the use of progestins for the management of endometriosis-associated pain.[18]

Dydrogesterone

Dydrogesterone is a synthetic progesterone. It can be administered as 10 mg twice daily from day 5 to day 25 and effectively relieves dysmenorrhea, dysperunia, and chronic pelvic pain without affecting the fertility potential of women.[19] For those desiring fertility – dydrogesterone is preferable since it does not inhibit ovulation.

The studies utilized dydrogesterone in the doses of 10–60 mg/day and for the periods of 3–9 months. The cyclic administration of dydrogesterone has the advantage of regular menstruation with reduced blood loss.

Injectable

Injectable depot medroxyprogesterone acetate (DMPA) subcutaneous (SC) 104 mg/DMPA intramuscular (IM) 150 mg given once in 3 months has shown to be as efficacious as other progestin in the treatment of endometriosis-associated pelvic pain. The main side effect is marked reduction in BMD, breakthrough bleeding, and the long time taken to regain ovulation. The main advantage is the cost – injectable MPA has an advantage of 3 monthly injection without daily monitoring and action is not affected by erratic gastrointestinal (GI) absorption.[20]

Subdermal Implant

Implanon

A single rod has 68 mg Etonogestrel with a life span of 3 years. Takes a year for pain relief. It is a safe, well-tolerated, and long-term contraception option.

Intrauterine Device

Levonorgestrel intrauterine system (LNG IUS) contains 52 mg of levonorgestrel, releasing 0.02 mg levonorgestrel/day into the uterus over a period of up to 5–7 years. It is effective in symptomatic rectovaginal endometriosis and in treating adenomyosis. The main advantages of LNG-IUS are the long duration of action, highly effective contraception, and minimal hypoestrogenic side effects. The disadvantages are cost, possible weight gain, and the probability of unexpected bleeding. Initial irregular bleeding is a frequent side effect, but 70% of the women will be amenorrheic in 6 months. LNG-IUS reduces the recurrence of dysmenorrhea after the surgical treatment of endometriosis.

A systematic review of RCTs comparing the LNG-IUS with GnRH agonist included five trials with a total of 255 women (Lan, et al., 2013). In three of the trials, LNG-IUS was found to reduce pain scores. In a fourth trial, LNG-IUS treatment decreased American Society for Reproductive Medicine (ASRM) staging scores and improved HRQoL similar to GnRH agonist. One study reported reduced cardiovascular risk factors [low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC)] compared to GnRH agonist.

A recent RCT with randomized 103 women with endometriosis-associated chronic pelvic pain and/or dysmenorrhea to an etonogestrel-releasing subdermal implant (ENG) or a 52-mg (LNG-IUS) (Margatho, et al., 2020). The study reported that both the ENG implant and the LNG-IUS significantly reduced endometriosis-related pain, dysmenorrhea, and chronic pelvic pain.

Special Category

Rectovaginal endometriosis – more than monotherapy add-on drug gives better relief as an alternative to morbid surgical excision. Dyschezia, pelvic pain, deep dyspareunia, and dysmenorrhea were reduced significantly with add-on drugs.

Recurrence

Most patients are not amenable to long-term treatment. It requires a lot of counseling to make them understand that endometriosis and adenomyosis are chronic gynecologic diseases with remission and exacerbations; hence, recurrence preparedness is essential. Long-term medication is required to eliminate the symptoms. The data regarding the requirement of surgery for endometriosis subsequent to progestin therapy are limited.

Vercellini et al. study shows the recurrence rate after treatment with dienogest was 2.6% in comparison to GnRH which was 53.4% at the end of 5 years.[21]

In a recent review, the effect of progestins on endometriotic lesions as generating different levels of downregulation of ERs, a drop in local E2 production, a reduction in inflammation, and the creation of a pseudopregnancy condition was clear.[22]

RECOMMENDATIONS BY GUIDELINES

Six national [College National des Gynecologues et Obstetriciens Francais, National German Guideline (S2k), Society of Obstetricians and Gynaecologists of Canada, American College of Obstetricians and Gynecologists(ACOG), American Society for Reproductive Medicine (ASRM), and National Institute for Health and Care (NICE)] and two international (World Endometriosis Society, European Society of Human Reproduction and Embryology) guidelines are included in this review.

Combined oral contraceptive pill, progestogens are therapies recommended for endometriosis-associated pain. No clear consensus about surgical treatment. No other difference in perioperative outcomes between robotic and conventional laparoscopic surgery, except the longer time that is needed in robotic surgery. Skilled surgeon is ideal to do advanced surgery and multiple surgical procedures should be avoided because of the adhesions and reduction of ovarian reserves. It is clear that the judicious use of surgery and mainly long-term medical therapy for endometriosis and adenomyosis is the correct approach of management. All eight guidelines recommend progestins as the first-line medical treatment for pain in endometriosis.[23]

Currently, progestins alone or in combination with pain-relieving strategies are very important for the medical treatment of endometriosis and adenomyosis. Levonorgestrel IUD is effective, non-invasive, and fertility-preserving, and seems to be the superior choice to reduce pain and reduce uterine volume.[24] Long-

term (60-month) treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced endometriosis associated pelvic pain and avoided recurrence post-surgery.[15]

Conclusion

Considering endometriosis a chronic disease, the ideal drug should not be contraceptive, should not interfere with spontaneous ovulation, should suppress the growth of already existing lesions and prevent the development of new ones, and it should be efficacious for all endometriosis phenotypes. The new drugs under development for the medical treatment of endometriosis are targeting different steps in the pathogenesis – inhibitors of vascular epithelial growth factors, matrix metalloproteinase inhibitors or immunomodulatory substances such as TNF-α inhibitors. Progestins are exceptionally useful especially when long-term treatment is indicated and repeated courses of treatment are necessary in both adenomyosis and endometriosis. There is a lack of sufficient prospective randomized trials comparing different progestins and different dosages, which is a need for the future.

References

1. Stephens VR, Rumph JT, Ameli S, et al.. The potential relationship between environmental endocrine disruptor exposure and the development of endometriosis and adenomyosis. Front Physiol. 2022;12:807685.
2. Stratopoulou CA, Donnez J, Dolmans M-M. Conservative management of uterine adenomyosis: medical vs. surgical approach. J Clin Med. 2021;10(21):4878.
3. MacLean JA 2nd, Hayashi K. Progesterone actions and resistance in gynecological disorders. Cells. 2022;11(4):647.
4. Gezer A, Oral E. Progestin therapy in endometriosis. Womens Health (Lond). 2015;11(5):643-52.
5. Gheorghisan-Galateanu AA, Gheorghiu ML. Hormonal therapy in women of reproductive age with endometriosis: an update. Acta Endocrinol (Buchar). 2019;15(2):276–81.
6. Ribeiro BC, Nogueira-Silva C, Afonso H, et al. Use of etonogestrel implant beyond approved duration: prolonged contraceptive effectiveness. Eur J Contracept Reprod Health Care. 2018;23(4):309–10.
7. Karim AKA, Shafiee MN, Aziz NHA, et al. Reviewing the role of progesterone therapy in endometriosis. Gynecol Endocrinol. 2019;35(1):10–6.
8. Visanne. Summary of product characteristics. Pymble (NSW): Bayer Australia. 2016.
9. Shilpa V, Pravin S, Raisa NK. Dienogest - The Millennium Molecule!! J Gynecol Women's Health [Internet]. 2018;13(2):555860. Available from: http://dx.doi.org/10.19080/jgwh.2018.13.555860.php
10. Ebert AD, Dong L, Merz M, et al. Dienogest 2 mg daily in the treatment of adolescents with clinically suspected endometriosis: the VISanne Study to Assess Safety in ADOlescents. J Pediatr Adolesc Gynecol. 2017;30(5):560-7.
11. Tang M, Yang W, Zhang H. Comparison of the efficacy of dienogest and GnRH-a after endometriosis surgery. BMC Women's Health. 2023;23:85. Available from: https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-022-02118-w
12. Techatraisak K, Hestiantoro A, Ruey S, et al. Effectiveness of dienogest in improving quality of life in Asian women with endometriosis (ENVISIOeN): interim results from a prospective cohort study under real-life clinical practice. BMC Women's Health. 2019;19:68.

13. Petraglia F, Hornung D, Seitz C, et al. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment. Arch Gynecol Obstet. 2012;285(1):167–73.
14. Chandra A, Rho AM, Jeong K, et al. Clinical experience of long-term use of dienogest after surgery for ovarian endometrioma. Obstet Gynecol Sci. 2018;61(1):111–7.
15. Römer T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. Arch Gynecol Obstet. 2018;298(4):747–53.
16. Neriishi K, Hirata T, Fukuda S, et al. Long-term dienogest administration in patients with symptomatic adenomyosis. J Obstet Gynaecol Res. 2018;44(8):1439–44.
17. Vignali M, Belloni GM, Pietropaolo G, et al. Effect of dienogest therapy on the size of the endometrioma, Gynecol Endocrinol. 2020;36(8):723-7.
18. Barbara G, Buggio L, Facchin F, et al. Medical treatment for endometriosis: tolerability, quality of life and adherence. Front Glob Womens Health. 2021;2:729601.
19. Schweppe K-W. The place of dydrogesterone in the treatment of endometriosis and adenomyosis. Maturitas. 2009;65(Suppl 1):S23-7.
20. Jain J, Jakimiuk AJ, Bode FR, et al. Contraceptive efficacy and safety of DMPA-SC. Contraception. 2004;70(4):269-75.
21. Vercellini P, Somigliana E, Daguati R, et al. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. Am J Obstet Gynecol. 2008;198(5):504.e1-5.
22. Donnez J, Dolmans M-M. Endometriosis and medical therapy: from progestogens to progesterone resistance to GnRH antagonists: a review. J Clin Med. 2021;10(5):1085.
23. Kalaitzopoulos DR, Samartzis N, Kolovos GN, et al. Treatment of endometriosis: a review with comparison of 8 guidelines. BMC Women's Health. 2021;21(1):397.
24. Sharara FI, Kheil MH, Feki A, et al. Current and prospective treatment of adenomyosis. J Clin Med. 2021;10(15):3410.