A FOGSI Presidential Initiative

ENDOMETRIOSIS VISION

PROTOCOLS FOR PRACTICE

By Dr. Nandita Palshetkar

DIAGNOSIS OF ENDOMETRIOSIS

MEDICAL MANAGEMENT OF ENDOMETRIOSIS

Bayer Zydus Pharma

science integra®

Dear FOGSIans,

Greetings !!

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

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

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

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

Best wishes!

Dr. Nandita Palshetkar
MD, FCPS, FICOG
President 2019 - Federation of Obstetrics and Gynecological Societies of India (FOGSI)

Conveners:-

Dr. Pratik Tambe
Chairperson,
FOGSI Endocrinology
Committee (2017-19)

Dr. Kuldeep Jain
Chairperson,
FOGSI Endometriosis
Committee (2017-19)

CONTENTS

DIAGNOSIS OF ENDOMETRIOSIS

MEDICAL MANAGEMENT OF ENDOMETRIOSIS

ENDOMETRIOSIS VISION

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

Gynec Stalwarts from across India meet at Mumbai on 19th February 2019

236 THINK TANKS across India voicing their opinion on **ENDOMETRIOSIS** contributing hugely to the **VISION**

TOPICS	Diagnosis	Medical management	Surgical management	Fertility issues
	Dr. Hrishikesh Pai	Dr. Bhaskar Pal	Dr. Prakash Trivedi	Dr. Nandita Palshetkar
Conveners	Dr. Jayam Kannan	Dr. Kuldeep Jain	Dr. Shantha Kumari	Dr. Ameet Patki
	Dr. Basab Mukherjee	Dr. Jaydeep Tank	Dr. Ashwath Kumar	Dr. Parikshit Tank
	Dr. Suvarna Khadilkar	Dr. Madhuri Patel	Dr. Indrani Lodh	Dr. Fessy Louis
	Dr. Ameya Purandare	Dr. P. K. Shah	Dr. Parul Kotdawala	Dr. Tushar Kar
	Dr. Haresh Doshi	Dr. Sudha Prasad	Dr. Divyesh Shukla	Dr. Monica Singh
Panelists	Dr. Mandakini Megh	Dr. Pratik Tambe	Dr. Vidya Bhat	Dr. Kanthi Bansal
	Dr. Dibyendu Banerjee	Dr. Atul Ganatra	Dr. Mala Raj	Dr. Rakhi Singh
	Dr. Geeta Chadha	Dr. Maninder Ahuja	Dr. Savitha Devi	Dr. Venugopal M
	Dr. Pradip Chakravarty	Dr. Arun Madhab Boruah	Dr. Shobhana Mahadevan	Dr. Sachin Dalal
	Dr. Vibha Mishra	Dr. Sini Venugopal		
	Dr. Brajbala Tiwari	Dr. Sandhya Chasatia		
	Dr. Meenakshi Ahuja	Dr. Sonia Naik		
Reporters	Dr. Garima Sharma	Dr. Parzan Mistry	Dr. Riddhi Desai	Dr. Rohan Palshetkar

ENDOMETRIOSIS VISION

Ahmedabad – 3rd April, 2019

Mumbai 19th February, 2019

Delhi – 11th March, 2019

Kolkata – 9th April, 2019

Chennai – 20th March, 2019

DIAGNOSIS OF ENDOMETRIOSIS

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. Hrishikesh Pai, Dr. Jayam Kannan

Panelists : Dr. Basab Mukherjee, Dr. Suvarna Khadilkar, Dr. Ameya Purandare, Dr. Haresh Doshi, Dr. Mandakini Megh, Dr. Dibyendu Banerjee, Dr. Pradip Chakravarty, Dr. Brajbala Tiwari, Dr. Vibha Mishra, Dr. Geeta Chadha, Dr. Meenakshi Ahuja

Clinical Reporter : Dr. Garima Sharma

From left to right: Dr. Suvarna Khadilkar, Dr. Brajbala Tiwari, Dr. Garima Sharma, Dr. Dibyendu Banerjee, Dr. Jayam Kannan, Dr. Haresh Doshi, Dr. Nandita Palshetkar, Dr.Meenakshi Ahuja, Dr. Ameya Purandare, Dr. Mandakini Megh, Dr. Basab Mukherjee, Dr. Vibha Mishra, Dr. Geeta Chadha, Dr. Pradip Chakravarty

ENDOMETRIOSIS VISION

DIAGNOSIS OF ENDOMETRIOSIS

Introduction

- Endometriosis is defined as the presence of endometrial tissue outside the endometrium and myometrium.
- Endometriosis is described as a benign disease of the female genital system that is principally characterized by endometrial-like tissue, consisting of glands and/or stroma, found outside the uterine cavity.
- Endometriosis is a common gynecological disorder, affecting about 10% of women in the reproductive age group.[1]
- The incidence increases to 35%–50% in symptomatic patients.
- Although implanted ectopically, this tissue presents histopathological and physiological responses that are similar to the responses of the endometrium.[2]
- The most commonly affected sites include ovaries, uterine ligaments, recto- and vesicovaginal septae, pelvic peritoneum, cervix, labia, and vagina.
- The three main entities of pelvis endometriosis are peritoneal, ovarian or deep endometriosis.[3]
- Deep endometriosis affects 20% of women with pelvic endometriosis and is a source of pain and infertility.
- Depending on the relation between the depth of infiltration and intensity of pain, deep endometriosis has been arbitrarily defined as endometriosis infiltrating the peritoneum by > 5 mm.
- Pathologically, deep endometriosis has been defined as adenomyosis externa.[4]

The symptomatic endometriosis patients with or without suggestive clinical examination, require additional routine investigations mainly comprising transvaginal sonography (TVS) and MR imaging (MRI), to determine therapeutic strategy.[5]

Endometriosis is defined as the presence of endometrial tissue outside the endometrium and myometrium.

The incidence increases to 35%–50% in symptomatic patients.

The three main entities of pelvis endometriosis are peritoneal, ovarian or deep endometriosis.

Pathologically, deep endometriosis has been defined as adenomyosis externa.

Epidemiology

The prevalence of endometriosis depends on patient profile and diagnostic tools utilized.

- The prevalence of endometriosis in reproductive age women is 2%–10% and can be as high as 35–50% in women with pain and/or unexplained infertility.[6]

- Among young women about half of those who are less than 20 years of age and chronic pelvic pain or dyspareunia have endometriosis. About 5% of endometriosis cases are observed in postmenopausal women.[2]
- About 25% to 50% of infertile women have endometriosis and 30%–50% of women with endometriosis may be infertile.[7]
- Endometriosis is reported in 45%–82% of women with chronic pelvic pain and in 2.1%–78% of infertile women. Its prevalence is 6–21 times higher in infertile as opposed to fertile women.[8]
- Endometriosis has been reported in 4.1% of asymptomatic women undergoing laparoscopy for tubal ligation, 20% of women undergoing laparoscopic investigation for infertility, and 24% of women with pelvic pain may have endometriosis.[2]

Types and locations of endometriosis lesions

The prevalence of endometriosis in reproductive age women is 2%–10% and it can be as high as 35%–50% in women with pain and/or unexplained infertility.

American Society for Reproductive Medicine revised classification of endometriosis.[2]

Table 1. American Society for Reproductive Medicine revised classification of endometriosis[2]

	Endometriosis	<1 cm	1–3 cm	>3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Ovary	Right superficial	1	2	4
	Deep	4	16	20
	Left superficial	1	2	4
	Deep	4	16	20
	Posterior cul-de-sac obliteration	Partial complete	4	40
	Adhesions	<1/3 enclosure	1/3–2/3 enclosure	>2/3 enclosure
Ovary	Right filmy	1	2	4
	Dense	4	8	16
	Left filmy	1	2	4
	Dense	4	8	16
Tube	Right filmy	1	2	4
	Dense	41	81	16
	Left filmy	1	2	4
	Dense	41	81	16

1If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16. Staging: Stage I (minimal): 1–5; stage II (mild): 6–15; stage III (moderate): 16–40; stage IV (severe): > 40

Stages of endometriosis

- Staging the endometriosis may have a role in designing the treatment plan and evaluating the response to therapy.
- According to the American Society for Reproductive Medicine, endometriosis may be classified as stage I (minimal), II (mild), III (moderate), or IV (severe), based on number, location, and depth of implants and presence of filmy or dense adhesions (Tables 1 and 2).[2]

Table 2. Stages of endometriosis

Stage	Disease	Description
I	Minimal	A few superficial implants
II	Mild	More and slightly deeper implants
III	Moderate	Many deep implants, small endometriomas on one or both ovaries, and some filmy adhesions
IV	Severe	Many deep implants, large endometriomas on one or both ovaries, and many dense adhesions, sometimes with the rectum adhering to the back of the uterus

Staging systems

- Offer endometriosis treatment according to the woman's symptoms, preferences and priorities, rather than the stage of the endometriosis.[9]
- When endometriosis is diagnosed, the gynecologist should document a detailed description of the appearance and site of endometriosis.

Signs and symptoms

Suspect endometriosis in women (including young women aged ≤17 years) presenting with one or more of:

- Chronic pelvic pain
- Period related pain (dysmenorrhea) affecting daily activities and quality of life
- Deep pain during or after sexual intercourse
- Period related or cyclical gastrointestinal symptoms, in particular painful bowel movements
- Period related or cyclical urinary symptoms, in particular blood in the urine or pain passing urine
- Infertility in association with one or more of the above

Staging the endometriosis may have a role in designing the treatment plan and evaluating the response to therapy.

Do not exclude the possibility of endometriosis if the abdominal or pelvic examination, ultrasound scan, or magnetic resonance imaging is normal. If clinical suspicion remains or symptoms persist further investigation is warranted.

- Do not exclude the possibility of endometriosis if the abdominal or pelvic examination, ultrasound scan, or magnetic resonance imaging is normal. If clinical suspicion remains or symptoms persist further investigation is warranted.

Clinical diagnosis

The first step in diagnosing deep endometriosis is to establish the patient's clinical history with particular emphasis on symptoms (dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain) as well as, age, height, weight, ethnic origin, gravidity, parity, previous surgery for endometriosis, family history of endometriosis, previous non-surgical treatment for endometriosis, and infertility.

Physical examination should include systematic analysis of the posterior vaginal fornix with a speculum to look for retraction and dark nodules.

- Presumptive clinical diagnosis of endometriosis is based on the clinical manifestations.
- The most common symptoms are dysmenorrhea, dyspareunia, and lower back pain that worsens during menses.[10]
- Depending on the anatomic location the diagnostic accuracy of physical examination can be as high as 86%–99%.[12]
- The gold standard for diagnosing endometriosis is laparoscopy with biopsy to demonstrate the histological presence of the endometrial tissues.[11]

First step: Clinical history

- The first step in diagnosing deep endometriosis is to establish the patient's clinical history with particular emphasis on symptoms (dysmenorrhea, dyspareunia, dysuria, dyschezia, and chronic pelvic pain) as well as, age, height, weight, ethnic origin, gravidity, parity, previous surgery for endometriosis, family history of endometriosis, previous non-surgical treatment for endometriosis, and infertility.
- About 2% to 50% of women could have asymptomatic endometriosis.[5]

Second step: Physical examination

Physical examination can identify endometriosis with high accuracy, using defined criteria for a positive bimanual pelvic examination (ie, palpable nodularity, stiffened and/ or thickened pelvic anatomy, especially the uterosacral ligaments, vagina, rectovaginal space, pouch of Douglas, adnexa, rectosigmoid, or posterior wall of the urinary bladder).[12]

Physical examination should include systematic analysis of the posterior vaginal fornix with a speculum to look for retraction and dark nodules.

Digital examinations should be performed of the vagina to assess the characteristics of the uterus and adnexa, of the vesico-uterine pouch to detect bladder invasion, and of the retrocervical area to detect infiltration of the torus

uterinum, uterosacral ligaments (USLs), pouch of Douglas (POD), vagina, and rectovaginal septum (RVS).

Rectal digital examination can help in assessing the involvement of the rectum, parametrium and visceral pelvic fascia. In a retrospective study, researchers have reported that routine clinical examination enables detection of deep endometriosis only 36% and suggest that the accuracy of physical examination improves during menstruation.[13]

Digital vaginal examination had a sensitivity of 72% and 68%, a specificity of 54% and 46%, a positive predictive value of 63% and 45%, and negative predictive value of 64% and 69%, respectively.[14]

- The sensitivity, positive and negative likelihood ratios were 73.5%, 3.3%, and 0.34% for uterosacral ligament endometriosis, 50%, 3.88%, and 0.57% for vaginal endometriosis, and 46%, 1.67%, and 0.75% for intestinal endometriosis.[15]
- Clinical examination may be complicated by the high prevalence of myofascial trigger points in the pelvic floor in women with deep endometriosis, a source of severe pain limiting the evaluation of deep endometriosis locations.[5]
- Anterior vaginal wall tenderness has low sensitivity for detecting endometriosis in women with chronic pelvic pain.

A bimanual examination may not be feasible for non-sexually active adolescents/young adults and may not identify early-stage, superficial disease.[2]

- Inform women with suspected or confirmed endometriosis that keeping a pain and symptom diary can aid discussion and diagnosis.
- Offer an abdominal and pelvic examination to women with suspected endometriosis to identify abdominal masses and pelvic signs, such as reduced organ mobility and enlargement, tender nodularity in the posterior vaginal fornix, and visible vaginal endometriotic lesions.[1]

Digital vaginal examination had a sensitivity of 72% and 68%, a specificity of 54% and 46%, a positive predictive value of 63% and 45%, and negative predictive value of 64% and 69%, respectively.

A bimanual examination may not be feasible for non-sexually active adolescents/young adults and may not identify early-stage, superficial disease.

Diagnostic laparoscopy

For a definitive diagnosis of endometriosis, visual inspection of the pelvis at laparoscopy is the gold standard investigation unless disease is visible in the posterior vaginal fornix or elsewhere.[16]

- Laparoscopy may help identify typical black or dark bluish or deep red spots on the peritoneal surface, but less marked discoloration showing endometriosis may be missed.

- These ‘faint’ lesions include white opacification of the peritoneum, red flame-like lesions, yellowish patches, peritoneal defects, and adhesions.
- White lesions may be more common and possibly more active than the dark lesions.[17]
- Laparoscopically, deeply infiltrating endometriosis may have the appearance of minimal disease, resulting in an underestimation of disease severity.[16]
- A positive laparoscopic examination increases the likelihood of detecting the disease to 32% (95% CI; range, 21%–46%) and a negative laparoscopy decreases the likelihood to 0.7% (95% CI; range, 0.1%–5%).[18]
- Laparoscopy is gold standard in diagnosis. Tissue of biopsy may be used to confirm diagnosis and negative biopsy does not rule out endometriosis.[19]
- Types of lesions on laparoscopy are powder burn or black lesions, white opacified peritoneum, glandular excrescences, flame like red lesions, peritoneal pockets or windows, clear vesicles, yellow brown patches, unexplained adherence of ovary to peritoneum of ovarian fossa, encysted collection of thick chocolate colored or tarry fluids, adhesions to posterior lip of broad ligaments or other pelvic structures.[19]
- Consider laparoscopy to diagnose endometriosis in women with suspected endometriosis, even if the ultrasound scan was normal.[1]
- During a diagnostic laparoscopy, a gynecologist with training and skills in laparoscopic surgery should perform a systematic inspection of the pelvis.[1]

Imaging studies

Ultrasound

Transvaginal ultrasound (TVS) is a noninvasive reliable test that has been used to diagnosis endometriosis for a long time. Due to cost, tolerability, and availability TVS is a useful tool for gynecologists. However, the experience of the examiner can exert profound influences on the results and its reproducibility.

In a study, researchers critically analyzed the diagnostic value TVS for non-invasive, presurgical detection of bowel endometriosis. A total of 10 studies involving 1,106 patients with suspected endometriosis included for analysis. The meta-analysis concluded that the TVS with or without the use of prior bowel preparation is an accurate test for non-invasive, presurgical detection of deep infiltrating endometriosis of the rectosigmoid.[20]

TVS has been shown to be an accurate diagnostic method for the assessment of women with suspected pelvic endometriosis. In a study by Holland et al, there was a high level of agreement between TVS and laparoscopy in assessing the severity of disease. The accuracy of TVS in diagnosing cases of moderate and severe pelvic endometriosis was 94%. However, the sensitivity of diagnosis in minimal and mild pelvic endometriosis was relatively low, probably because of the small size of lesions in these cases.[21]

As compared with laparoscopy, TVS has limited value in diagnosing peritoneal endometriosis, but it is a useful tool to make or exclude the diagnosis of an ovarian endometrioma.[22] According to Exacoustos et al. the ultrasonographic diagnosis of deep infiltrating endometriosis has inconsistent results with a wide range of accuracies described between studies. This may reflect variations in the examination technique, quality of ultrasound equipment, and experience of the operators.[23]

With scientific developments, 3D ultrasonography has a significantly higher diagnostic accuracy in the diagnosis of posterior locations of deep endometriosis without intestinal involvement, such as the uterosacral ligaments, vaginal, and rectovaginal endometriosis.[24]

- Clinicians should recommend TVS to diagnose or exclude ovarian endometrioma.[19]
- TVS or endorectal ultrasonography may reveal ultrasonographic features varying from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of internal vascularity but shows pericystic flow with high resistance.
- In women with symptoms and signs of endometriosis, TVS is useful for identifying rectal endometriosis. Probe tenderness may be elicited.
- Clinicians should be aware that usefulness of 3D USG to detect recto-vaginal endometriosis is not well established.
- Bladder endometriosis may be seen by transabdominal USG in clinically suspected cases.

CT Scan

According to Biscaldi et al., multislice computerized tomography (CT) enteroclysis for the evaluation of bowel endometriosis gave a sensitivity and specificity of 98.7% and 100%, respectively.[25] However, Belghiti et al. reported a lower accuracy of CT scan enema for the diagnosis of multifocal and multicentric endometriotic lesions in a recent study comparing CT enema to 1.5T MRI.[26]

- CT may reveal endometriomas appearing as cystic masses; however, appearances are nonspecific and imaging modalities should not be relied upon for diagnosis.[19]

MRI

MRI can help guide surgical approaches for patients with suspected endometriosis, especially for deep infiltrating endometriosis and other unusual sites of presentation. Both ultrasound and MRI may suggest endometriosis, but given the significant cost differential between MRI and ultrasound, MRI is most useful for ultrasonographically-indeterminate pelvic masses. MRI is also superior to ultrasound in diagnosing rectosigmoid lesions and endometriosis of the bladder.[27]

In a prospective clinical trial, Stratton et al. determined the utility of fat-suppressed MRI for the diagnosis of endometriosis. The study included 48 women with pelvic pain and a preoperative MRI was carried out which showed sensitivity of 69% in detecting biopsy-proven endometriosis for any woman and the specificity was 75%. Although MRI identifies fewer areas of endometriosis than seen at surgery, it suggested endometriosis in 75% of those with at least mild disease. Only 67% of lesions identified at surgery contained histologic evidence of endometriosis.[28]

At present, there is insufficient evidence to indicate that MRI is a useful test to diagnose or exclude endometriosis compared to laparoscopy.[29]

- Clinicians should be aware that peritoneal lesions can not be detected by MRI.[19]
- MRI may detect small lesions more than 1 cm and distinguish endometrioma vs dermoids.[19]
  - » Clinician should be aware that MRI can accurately detect recto-vaginal disease and obliteration of POD in more than 90% of the cases.[19]
  - » Do not use pelvic MRI as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.[1]
  - » Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder, or ureter.[1]
  - » Ensure that MRI scans are interpreted by a healthcare professional with specialist expertise in gynecological imaging.[1]

Clinicians should be aware that peritoneal lesions will not be detected by MRI.

MRI may detect small lesions more than 1 cm and distinguish endometrioma Vs dermoids.

Clinician should be aware that MRI can accurately detect recto vaginal disease and obliteration of POD in more than 90% of the cases.

Do not use pelvic MRI as the primary investigation to diagnose endometriosis in women with symptoms or signs suggestive of endometriosis.

Consider pelvic MRI to assess the extent of deep endometriosis involving the bowel, bladder, or ureter.

Serum markers

Blood is a potential source of biomarkers as it allows repeated measurements, is easily obtained, and is highly suitable for high-throughput measurements. Some of the recognized endometriosis biomarkers are glycoproteins, growth or adhesion factors, hormones, or proteins related to immunology or angiogenesis. However, despite research, no single biomarker nor a panel of biomarkers in peripheral blood has been validated as a diagnostic test for endometriosis.[6]

Serum CA-125

- Cancer Antigen- (CA-) 125 is a blood biomarker for endometriosis and the utility of CA-125 for the diagnosis of endometriosis and it's correlation to disease severity, especially endometriotic ovarian cysts have been extensively evaluated.
- CA-125 is not specific for endometriosis, being a tumor marker elevated in ovarian cancer.
- There is lack of specificity, the sensitivity to detect all endometriosis stages is low.
- The sensitivity for stage I–IV endometriosis was 50% and specificity was 72%.
- For stage III-IV endometriosis, a sensitivity of 60% could be obtained with a specificity of 80%.[30]
- A panel of CA-125, chemokine receptor (CCR) type- 1 mRNA, and monocyte chemoattractant protein- (MCP) 1 showed a sensitivity of 92.2% and specificity of 81.6% to detect endometriosis. CA-125 combined with interleukin-8 (IL- 8) and tumor necrosis factors-α (TNF-α) in the secretory phase had a sensitivity of 89.7% and specificity of 71.1%.[6]

- Apart from research settings, biomarkers are not recommended for routine clinical use.[19]
- CA-125 may be of value to rule out ovarian malignancies and presence of extensive peritoneal lesions. In some cases it may be of some value for treatment follow-up.[19]
- Do not use serum CA-125 to diagnose endometriosis.[9]
- If a coincidentally reported serum CA-125 level is available, be aware that:
  - » A raised serum CA-125 titre (≥35 IU/mL) may be consistent with having endometriosis.
  - » Endometriosis may be present despite a normal serum CA-125 level (<35 IU/mL).

A panel of CA-125, chemokine receptor (CCR) type- 1 mRNA, and monocyte chemoattractant protein- (MCP) 1 showed a sensitivity of 92.2% and specificity of 81.6% to detect endometriosis. CA-125 combined with interleukin-8 (IL- 8) and tumor necrosis factors-α (TNF-α) in the secretory phase had a sensitivity of 89.7% and specificity of 71.1%.

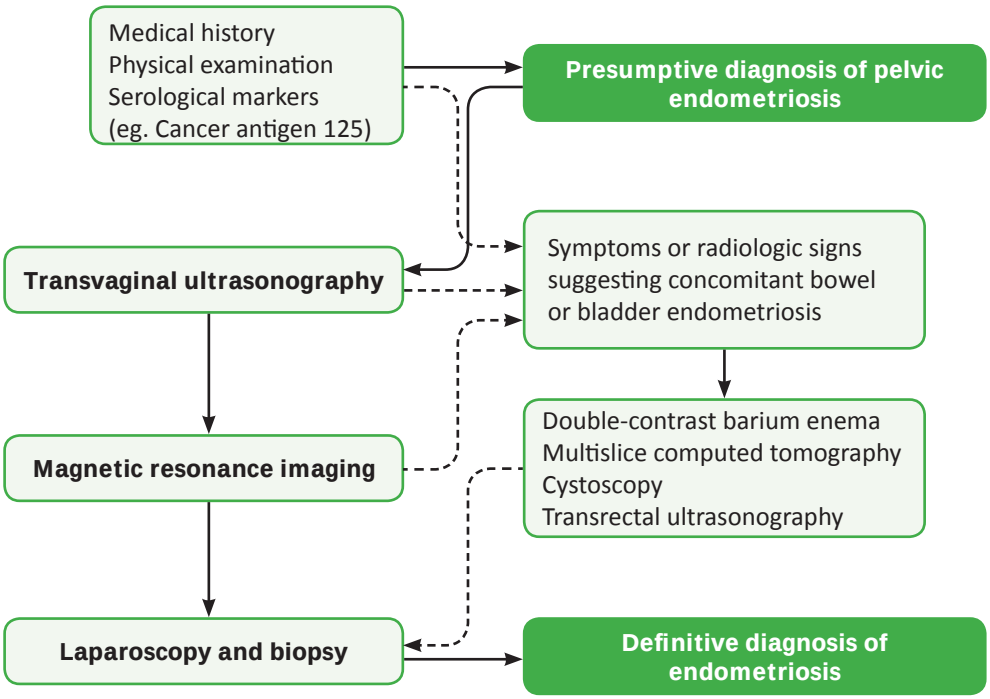
Endometrial biomarkers

- The endometrium has several unique characteristics with respect to biomarker discovery.
- About 200 potential endometrial biomarkers, including hormones and their receptors, cytokines, factors identified through proteomics, and histology showed a sensitivity and specificity from 0 to 100%.[31]

Differential diagnosis

- The differential diagnosis of endometriosis includes pelvic inflammatory disease, tubo-ovarian abscess, ectopic pregnancy, irritable bowel syndrome, interstitial cystitis, adenomyosis, pelvic adhesions, uterine fibroids, chronic or acute endometritis, ovarian neoplasms, musculoskeletal disease, gastrointestinal neoplasms, appendicitis, and diverticular disease.[32]

Algorithm for imaging diagnosis of endometriosis[33]



Algorithm for the clinical diagnosis of endometriosis[12]

Consistent with endometriosis

Evaluate presence of symptoms	
• Persistent and/or worsening cyclic or constant pelvic pain • Dysmenorrhea • Deep dyspareunia • Cyclic dyschezia • Cyclic dysuria • Cyclic catamenial symptoms located in other systems (e.g, lung, skin)	• Severe pain, amenorrhea, or cramping without menstruation in an adolescent could indicate a reproductive tract anomaly • Concomitant symptoms » Severe noncyclic constipation and diarrhea suggests irritable bowel syndrome » Painful voiding or flank pain could suggest urinary tract stones » Urinary symptoms (e.g, hematuria, frequent urination) could indicate interstitial cystitis/painful bladder syndrome
Review patient history	
• Infertility • Dysmenorrhea in adolescence; current chronic pelvic pain • Previous laparoscopy with diagnosis • Dysmenorrhea unresponsive to NSAIDs • Positive family history	• Absence of menses or other obstructive conditions in adolescence • History of pain directly associated with surgery (e.g, post-operative nerve entrapment or injury, bowel adhesions)
Perform physical examination	
• Nodules in cul-de-sac • Retroverted uterus • Mass consistent with endometriosis • Obvious endometrioma that is external (seen on speculum or on skin)	• Pelvic floor spasms • Severe allodynia along pelvic floor/vulva or elsewhere • Masses not consistent with endometriosis (e.g, fibroids)
Perform/order imaging	
• Endometrioma on ultrasound • Presence of soft markers (e.g, sliding sign) • Nodules and masses	• Adenomyosis and fibroids (although these may be present with endometriosis)

*Alternative diagnoses indicated by symptoms on the right side of the chart may coexist with endometriosis and do not rule out the presence of endometriosis.

Consider other diagnosis in addition to endometriosis

Algorithm for the diagnosis of endometriosis (NICE)[9]

Suspect endometriosis (including in young women aged 17 and under) with 1 or more of:

- Chronic pelvic pain
- Period-related pain (dysmenorrhea) affecting daily activities and quality of life
- Deep pain during or after sexual intercourse
- Period-related or cyclical gastrointestinal symptoms, in particular, painful bowel movements
- Period-related or cyclical urinary symptoms, in particular, blood in the urine or pain passing urine
- Infertility in association with 1 or more of the above

↓

- Do not use pelvic MRI or CA-125 to diagnose endometriosis.
- Consider transvaginal ultrasound:
  - » To investigate suspected endometriosis even if pelvic and/or abdominal examinations are normal
  - » For endometriomas and deep endometriosis involving the bowel, bladder or ureter.
  - » Consider a transabdominal US of the pelvis, if a TVS is not appropriate.

↓

- Do not exclude the possibility of endometriosis if the abdominal and/or pelvic examinations or ultrasound or MRI are normal.
- Consider referral for assessment and investigation if clinical suspicion remains or symptoms persist.

↓

Consider laparoscopy to diagnose endometriosis, even if the ultrasound was normal.
Discuss surgical management options with women with suspected/confirmed endometriosis:

- What laparoscopy involves, and that it may include surgical treatment (with prior patient consent)
- How laparoscopic surgery could affect endometriosis symptoms
- The possible benefits and risks of laparoscopic surgery
- The possible need for further surgery, including the possible need for further planned surgery for deep endometriosis involving the bowel, bladder, or ureter.

During diagnostic laparoscopy, a gynecologist with training and skills in laparoscopic surgery for endometriosis should perform a systematic inspection of the pelvis.
If a full systematic laparoscopy is performed and is normal, explain to the woman that she does not have endometriosis and offer alternative management.

References

1. Kuznetsov L, Dworzynski K, Davies M. Diagnosis and management of endometriosis: Summary of NICE guidance. BMJ 2017;358:j3935.
2. Agarwal N, Subramanian A. Endometriosis – Morphology, clinical presentations and molecular pathology. J Lab Physicians. 2010; 2(1): 1–9.
3. Giudice LC, Kao LC. Endometriosis. Lancet 2004;364:1789–99.
4. Koninckx PR, Ussia A, Adamyan L, et al. Deep endometriosis: Definition, diagnosis, and treatment. Fertil Steril. 2012;98:564–71.
5. Bazot M, Daraï E. Diagnosis of deep endometriosis: Clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. Fertil Steril. 2017;108(6):886–94.
6. Fassbender A, Burney RO, O DF, et al. Update on biomarkers for the detection of endometriosis. Biomed Res Int. 2015;2015:130854.
7. Missmer SA, Hankinson SE, Spiegelman D, et al. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol. 2004;160:784–96.
8. 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–QC03.
9. NICE: Endometriosis: Diagnosis and management. 2017; Available from https://www.nice.org.uk/Guidance/NG73 Accessed on. 15-02-2019
10. American College of Obstetricians and Gynecologists. Washington DC: ACOG; 1993. Endometriosis. ACOG technical bulletin no. 184
11. Alimi Y, Iwanaga J, Loukas M, Tubbs RS. The clinical anatomy of endometriosis: A review. Cureus. 2018;10(9):e3361.
12. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: A call to action. Am J Obstet Gynecol. 2019 Jan 6. doi: 10.1016/j.ajog.2018.12.039. [Epub ahead of print]
13. Koninckx PR, Meuleman C, Oosterlynck D, Cornillie FJ. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. Fertil Steril 1996;65:280–7.
14. Abrao MS, Goncalves MO, Dias JA Jr, et al. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. Hum Reprod. 2007;22:3092–97.
15. Bazot M, Lafont C, Rouzier R, et al. Diagnostic accuracy of physical examination, transvaginal sonography, rectal endoscopic sonography, and magnetic resonance imaging to diagnose deep infiltrating endometriosis. Fertil Steril. 2009;92:1825–33.
16. Daniilidis A, Giannoulis H, Tantanasis T, et al. Diagnostic laparoscopy, infertility, and endometriosis—5 years experience. Gynecol Surg. 2008; 5:231–34.
17. Mettler L,Schollmeyer T, Lehmann-Willenbrock E, et al. Accuracy of laparoscopic diagnosis of endometriosis. JSLS. 2003; 7(1): 15–18.
18. Wykes CB, Clark TJ, Khan KS. Accuracy of laparoscopy in the diagnosis of endometriosis: A systematic quantitative review. BJOG. 2004; 111:1204–1212.
19. FOGSI. Good clinical practice recommendations on endometriosis. Under the agesis of FOGSI Endometriosis Committee 2014–2016
20. Hudelist G, English J, Thomas AE, et al. Diagnostic accuracy of transvaginal ultrasound for non-invasive diagnosis of bowel endometriosis: Systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2011;37(3):257–63.
21. Holland TK, Yazbek J, Cutner A, et al. Value of transvaginal ultrasound in assessing severity of pelvic endometriosis. Ultrasound Obstet Gynecol. 2010;36(2):241–8.
22. Moore J, Copley S, Morris J, et al. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. Ultrasound Obstet Gynecol. 2002;20: 630–34.
23. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol. 2014; 28: 655–81.
24. Guerriero S, Saba L, Ajossa S, et al. Three-dimensional ultrasonography in the diagnosis of deep endometriosis. Human Reproduction. 2014; 29(6):1189 –198.
25. Biscaldi E, Ferrero S, Fulcheri E, et al. Multislice CT enteroclysis in the diagnosis of bowel endometriosis. Eur Radiol. 2007;17:211–19.

26. Belghiti J, Thomassin-Naggara I, Zacharopoulou C, et al. Contribution of Computed Tomography enema and Magnetic Resonance Imaging to diagnose multifocal and multicentric bowel lesions in patients with colorectal endometriosis. J Minim Invasive Gynecol. 2015;22:776–84.

27. Hsu AL, Khachikyan I, Stratton P, et al. Invasive and non-invasive methods for the diagnosis of endometriosis. Clin Obstet Gynecol. 2010; 53(2): 413–19.

28. Stratton P, Winkel C, Premkumar A, et al. Diagnostic accuracy of laparoscopy, magnetic resonance imaging, and histopathologic examination for the detection of endometriosis. Fertil Steril. 2003;79(5):1078–85.

29. Royal College of Obstetricians and Gynecologists (2006) Greentop guideline no 24. The investigation and management of endometriosis. RCOG, London

30. Mol BWJ, Bayram N, Lijmer JG et al. The performance of CA-125 measurement in the detection of endometriosis: A metaanalysis. Fertility and Sterility. 1998; 70(6):1101–108.

31. May KE, Villar J, Kirtley S, et al. Endometrial alterations in endometriosis: A systematic review of putative biomarkers. Hum Reprod Update. 2011;17(5):637–53.

32. Olivia J Carpinello, MD, Lauren W Sundheimer, MD, Connie E Alford, MD, et al. Endometriosis. Endotext. Last Update: October 22, 2017. www.endotext.org

33. Monte GL, Wenger JM, Petignat P, et al. maging in practice: Role of imaging in endometriosis. Cleveland Clinic Journal of Medicine. 2014; 81(6):361–66.

MEDICAL MANAGEMENT OF ENDOMETRIOSIS

FOGSI President	: Dr. Nandita Palshetkar
Moderators	: Dr.Bhaskar Pal, Dr. Kuldeep Jain
Panelists	: Dr. Jaydeep Tank, Dr. Madhuri Patel, Dr. P. K. Shah, Dr. Sudha Prasad, Dr. Pratik Tambe, Dr. Atul Ganatra, Dr. Maninder Ahuja, Dr. Arun Madhab Boruah, Dr. Sini Venugopal, Dr. Sandhya Chasatia, Dr. Sonia Naik
Clinical Reporter	: Dr. Parzan Mistry

From left to right: Dr. Sonia Naik, Dr. Sandhya Chasatia, Dr. Madhuri Patel, Dr. Sudha Prasad, Dr. Kuldeep Jain, Dr. Atul Ganatra, Dr. Nandita Palshetkar, Dr. Pratik Tambe, Dr. Maninder Ahuja, Dr. Arun Madhab Boruah, Dr. PK Shah, Dr. Ameya Purandare, Dr. Bhaskar Pal, Dr. Parzan Mistry, Dr. Sini Venugopal

MEDICAL MANAGEMENT OF ENDOMETRIOSIS

Pathophysiology of endometriosis

The key molecular hallmarks for the development of endometrium are: genetic predisposition, estrogen dependence, progesterone resistance, and inflammation.[1]

- **Genetic predisposition:** A striking difference in gene and protein expression of the eutopic endometrium from women with and without endometriosis may predispose to disease development. [1]
- **Hormonal alterations:** In the endometriotic tissue relative to eutopic endometrium an increased locally bioavailable estradiol concentration is reported. In addition to this, an overall reduction in progesterone receptor expression in the endometriotic lesions vs. eutopic endometrium suggests that progesterone resistance also plays a role in the pathophysiology of endometriosis. [1]
- **Inflammation:** Endometriosis is considered as a pelvic inflammatory disease. An increased number of activated macrophages and important differences in the cytokine/chemokine profile is observed in the peritoneal fluid of women with endometriosis.[1]

Medical management of endometriosis

Approximately one-third of women suffering from endometriosis are clinically asymptomatic. However, when symptomatic the most common presenting symptom is pelvic pain. Therefore, the two main goals for the medical management of endometriosis are:[2]

- **Pain control[2]**
- **Suppression of estrogen production[2]**

1. Empirical management of endometriosis associated pelvic pain

- Before starting empirical treatment, other causes of pelvic pain symptoms should be ruled out.[3,4]

NSAIDs[5]

- To reduce empirical management of endometriosis associated pelvic pain (EAPP),, NSAIDs or other analgesics should be considered.
- The commonly used NSAID is mefenamic acid.

Oral progestin: DIENOGEST[5]

- Dienogest for 65 weeks is effective for reducing EAPP.
- After excision of endometrioma, long-term treatment with dienogest 2 mg once-daily for 5 years significantly reduced the recurrence of lesions, and prevented the necessity of reoperation for a prolonged period.[6]
- Dienogest improves the quality of life of the patients.

Use of combined low dose hormonal contraceptives

- Oral pills, vaginal contraceptive ring, or a transdermal [estrogen/progestin] patch.
- Continuous use of combined oral contraceptive (COC) may be considered.

GnRH agonist[4]

- GnRH agonists are effective for EAPP.
- Commonly used GnRHs agonists are leuprolide and goserelin.

Dienogest for 65 weeks is effective for reducing EAPP.

After excision of endometrioma, long-term treatment with dienogest 2 mg once-daily for 5 years significantly reduced the recurrence of lesions, and prevented the necessity of reoperation for a prolonged period.

Dienogest improves the quality of life of the patients.

2. Management of endometriosis in adolescents[7]

Adolescent endometriosis is underdiagnosed or the diagnosis is usually delayed. Medical management is usually the first-line of therapy.

- For EAPP the first-choice of drugs are COCs or oral progestogens including dienogest.
- COCs: Continuous use is more effective than the cyclical regimens.
- NSAIDS can be given additionally for the symptomatic relief.
- Depot medroxyprogesterone acetate (MPA) and GnRH analogues may result in bone loss and should be avoided in women who have not achieved peak bone mass.
- 12 months use of dienogest results in loss of bone mineral density (BMD) which can be partially reversible after the stoppage.
- Levonorgestrel releasing intrauterine system (LNG-IUS) is not contraindicated in this population.

The main goal of treatment of endometriosis in adolescents includes:

- Symptom control
- Prevention of further disease progression, and
- Preservation of fertility.

The management algorithm of adolescent endometriosis is given in Figure 1. The medical management of endometriosis in adolescents include:

A. Oral Progestins

- Oral progestins can be used as the first-line option.
- Dienogest is the most effective oral option. Optimum dose is 2 mg a day. Its safety has been established till 5 years of use.
- Side effects: Initial breakthrough bleeding and other side effects associated with progestins.
- In suspected cases of endometriosis, empirical treatment should be started, based on the symptoms and after counselling the woman thoroughly.[3,4]
- Progestin therapy is associated with bone loss. Therefore, long-term therapy of progestins should be used with caution in adolescents.

B. Combined oral contraceptives (COCs)

- COCs provide symptomatic relief but do not suppress disease or prevent progression. They offer a cheaper option with good safety profile. Continuous COCs work better than cyclical regimen.
- COCs can be used continuously for prolonged periods but a break of 4-7 days can be given if breakthrough bleeding occurs.
- COCs have traditionally being considered as the first-line therapy in adolescents.
- COCs inhibit ovulation, decrease gonadotropin levels, reduce menstrual flow, and cause decidualisation of endometriotic implants.
- COC therapy is only suppressive and not curative.
- After stopping therapy for 6 months, the recurrence of the symptoms is common.

C. GnRH agonists

- GnRH agonists (Leuprolide acetate, Nafarelin, Buserelin, and Goserelin) are reported to be effective in alleviating symptoms associated with endometriosis.

Oral Progestins can be used as the first line option.

Dienogest is the most effective oral option. Optimum dose is 2 mg a day. Its safety has been established till 5 years of use.

In suspected cases of endometriosis, empirical treatment should be started, based on the Symptoms and after counselling the woman thoroughly.

- Like goserelin, triptorelin, and leuprolide are very effective, and are usually used monthly for 3–6 months. Side effects include hypo-estrogenic symptoms and bone loss.
- They should be used with add back therapy to prevent bone loss and can be used for longer periods in supervised conditions.
- The addition of add back therapy does not modify the success of treatment. Add back is recommended with estrogen only (estradiol 1 mg/day orally or estrogen gel)
- In the treatment of endometriosis, GnRH agonist are reported to be more effective vs. oral contraceptive pills taken in the conventional manner.
- Long-term use of GnRH agonists alone may lead to bone demineralization. Therefore, their use is limited to patients more than 16 years of age and for a maximum period of 6 months.

In the treatment of endometriosis, GnRH agonist are reported to be more effective vs. oral contraceptive pills taken in the conventional manner.

Long-term use of GnRH agonists alone may lead to bone demineralization. Therefore, their use is limited to patients more than 16 years of age and for a maximum period of 6 months.

D. Hormonal add back therapy

- To protect adolescents from GnRH associated side-effects (bone demineralization, vasomotor symptoms, vaginal dryness, and mood swings), add-back therapy (norethindrone acetate and combined conjugated estrogens/medroxyprogesterone acetate) options are recommended. This regimen is reported to have the therapeutic effects of GnRH with minimal side effects and bone loss.

E. Long-acting Progesterone

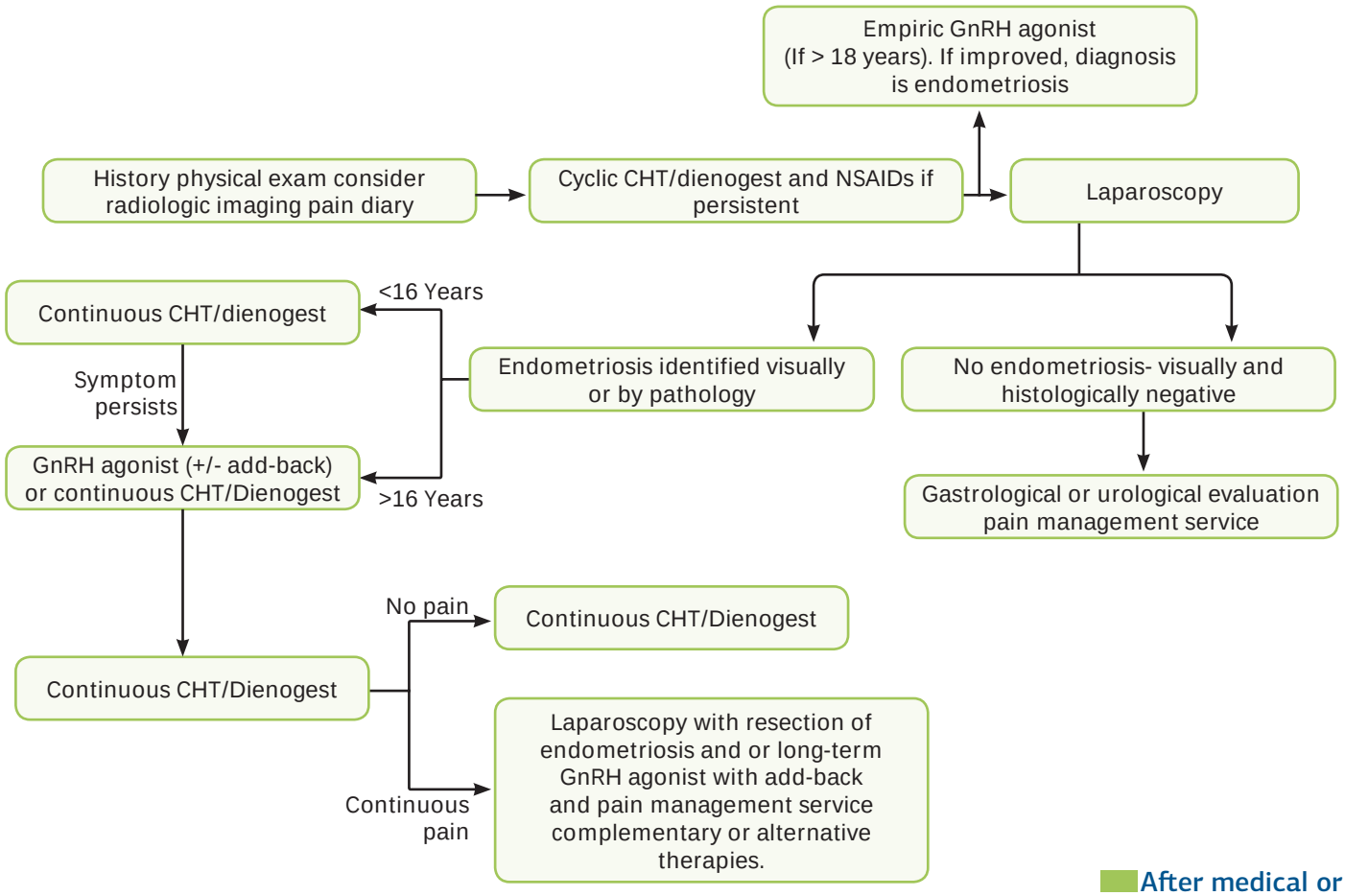
- Depot MPA (use with caution in women > 45 years of age)
- Etonorgestrol implants

LNG-IUS* Breakthrough bleeding (BTB) is common with progesterone is usually transient and requires good counselling. Estrogen can be added in prolonged BTB.

- Recurrence is common following discontinuation of medical therapy.

Management algorithm of adolescent endometriosis[7]

Figure 1. Management algorithm of adolescent endometriosis



NSAIDS-nonsteroidal anti-inflammatory drugs; CHT-combination hormone therapy; GnRH-gonadotropin-releasing hormone.

3. Management of long-term/recurrent endometriosis after surgery[4]

- After medical or surgical therapies, endometriosis is likely to recur. The cause of recurrence is that the basic pathophysiology cannot be corrected and endometriosis is a progressive disease.
- Recurrent endometrioma without suspicion of malignancy, medical management should be the first choice.

After medical or surgical therapies, endometriosis is likely to recur. The cause of recurrence is that the basic pathophysiology cannot be corrected and endometriosis is a progressive disease.

- Medical management should be offered as first-line:
  - » Dienogest,
  - » LNG-IUS,
  - » GnRH analogues,
  - » Depot MPA,
  - » Surgery should be offered to patients refractory to medical management, obstructive symptoms (urinary and GI tract), or suspicion of malignancy.

Role of medical management in infertility

- No role in infertility except for pre IVF long GnRH protocol.

Hormonal treatment or GnRH agonist

- In women not desirous of pregnancy, for the prevention of recurrence hormonal treatment or GnRH agonist are recommended.

Combined treatment is effective to prevent recurrence of endometriosis:[4]

- Long-term post-operative oral contraceptive pills or progestins are recommended to reduce the risk of recurrence.
- Post-operative use of GnRH agonist for 6 cycles prevent the recurrence of endometriosis.
- Oral progestins (MPA, Dienogest, Danazol) are reported to be effective in reducing pain and preventing the growth of lesions after surgery.
- After conservative surgery, prolonged therapy of endometriosis with LNG-IUS controls symptoms, prevents recurrence, and protects against bone loss.
- Recurrence of pain is managed with medical suppression (NSAIDs, oral progestins GnRH analogues, combined hormonal therapy, and aromatase inhibitors).[4]

Recurrent endometrioma without suspicion of malignancy, medical management should be the first choice..

Comparisons of Endometriosis recurrence with different treatment options post surgery 6 months of use of Visanne post-surgery offers least comparable recurrence rate of 4% at 2 years

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

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

4. Management of endometriotic cysts of <4 cms

- Endometriotic cysts under 4 cm can be treated with Dienogest or GnRH analogues. Also, recurrent endometriomas can be treated medically.

5. Recurrent endometrioma, after ruling out malignancy

Treatment options for endometriosis

A. NSAIDs[8]

- The first-line agents in the management of endometriosis related pain and dysmenorrhea are NSAIDs.
- Elevated levels of PGs, interleukins, and cytokines during endometriosis leads to pain.

Mechanism

- NSAIDs block the cyclooxygenase (COX) enzymes which are essential for the production of the inflammatory mediators.
- Selective COX2 inhibitors like rofecoxib also inhibit the growth of the endometrial tissue.

Pros

- Empirical treatment: NSAID, COC, and progestogen can be, given to patients with suspected endometriosis associated pelvic pain.
- NSAIDs are the first-line agents in the management of pain and dysmenorrhea due to endometriosis.
- Women who are desirous of fertility, mefenamic acid is given in EAPP.

Empirical treatment: NSAID, COC, and progestogen can be given to patients with suspected endometriosis associated pelvic pain.

B. Combined hormonal contraceptives[8]

Mechanism

- In endometriosis, hormonal contraceptives act by the suppression of ovaries and disease activity.
- Estrogen and progesterone combinations or progesterone alone decidualize the endometriotic tissue and also slow down the progression of disease.

Pros

- Continuous and cyclical estrogen and progesterone: For relieving endometriosis associated pelvic pain, both continuous and cyclical estrogen and progesterone are effective.

- **Continuous oral progestin therapy:** Continuous oral progestin therapy [MPA, Norethisterone acetate, Cyproterone acetate, Dienogest, and Danazol] are also effective for treatment for EAPP.
- Depot MPA: Depot MPA is effective and comparable to GnRH agonist for treating EAPP.

Cons

- Limitations of COC include long-term administration, risk of thromboembolism, high rates of recurrence after discontinuation, and impaired fertility due to contraceptive action.

GnRH agonists are associated with side effect secondary to hypoestrogenism like bone loss, vaginal atrophy and dryness, hot flashes, and abnormalities in lipid profile. These side effects limit their continuous use for only 6 months.

In the treatment of EAPP, the most effective treatment is GnRH agonist. But its prolonged use is limited due to associated side effects. To prevent the side effects, add back therapy is recommended.

C. GnRH agonists[8]

Mechanism

- GnRH act by blocking ovarian production in turn leading to hypoestrogenism, and hence regression of endometriotic implants.

Pros

- GnRH are treatment of choice in patients who have failed initial therapy with combined hormonal contraceptives or in those in whom combined hormonal contraceptives cannot be used due to their medical history.

Cons

- GnRH agonists are associated with side effect secondary to hypoestrogenism like bone loss, vaginal atrophy and dryness, hot flashes, and abnormalities in lipid profile. These side effects limit their continuous use for only 6 months.
- In the treatment of EAPP, the most effective treatment is GnRH agonist. But its prolonged use is limited due to associated side effects. To prevent the side effects, add back therapy is recommended.

D. Progesterone containing contraceptives

Mechanism[9]

- Progestins stimulate atrophy or regression of endometrial lesions. Progestins are effective in treating endometriosis by inhibiting its growth, induction of anovulation, inhibition of blood vessel growth, and anti-inflammatory actions. Progestins exert the following effects:
  - » Ovarian suppression
  - » Effects on endometrial morphology (desidualization, atrophy, and alteration in steroid receptor ligand binding)
  - » Local modulation of immune response (suppression of IL-8 production, increase of nitric oxide production, reduction of TNF-α induced nuclear factorκβ).

  - » Effects on angiogenesis (suppression of transcription of basic fibroblast growth factor [bFGF], suppression of vascular endothelial growth factor [VEGF] and cysteine rich angiogenic inducer [CYR61]).
  - » Progesterone receptor expression and progesterone resistance
  - » Direct effect on nerve fiber intensity.
- Several hypotheses have been formulated to explain the mechanism of action of LNG-IUS:[10]
  - » Local effect on the ectopic endometrium resulting from depletion of the estrogen and progesterone receptors through the inhibition of synthesis and expression of estrogen and progestin receptors.
  - » Direct effect on the eutopic endometrium by inhibition of endometrial production of estrogen-induced growth factors or growth factor-binding protein, as resulting in an anti-proliferative effect, glandular atrophy, and decidualization.
  - » LNG-IUS effect might be a function of a reduction of local vascular angiogenesis, a reduction in pelvic-vessel congestion and an increase in apoptosis, a reduction in peritoneal fluid macrophage activity, and a modification in the production of cytokines responsible for the maintenance of lesions and pain.
- Aromatase inhibitors cause a decrease in estrogen concentration, making them useful for treating estrogen-dependent conditions including endometriosis. The combination of aromatase inhibitors and progesterone or a progestin may decrease pain and reduce the amount of visible endometriotic lesions.[11]

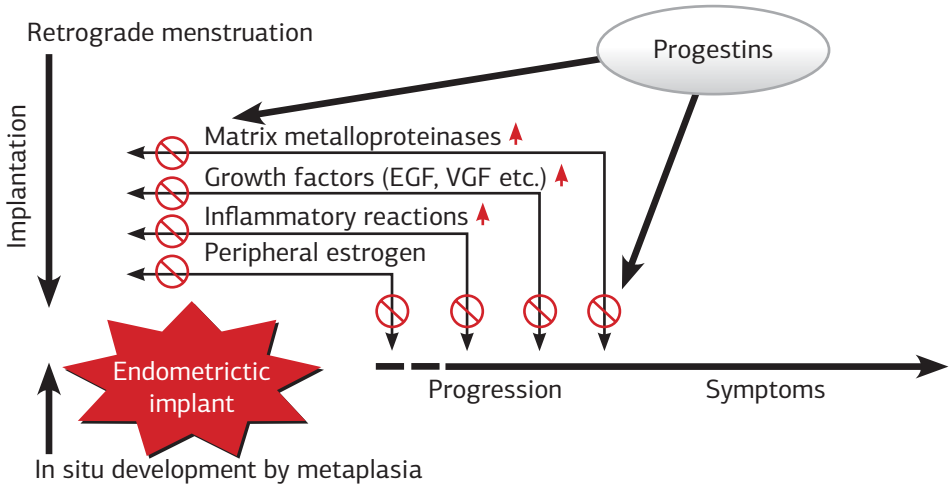
Pros

- For the initial management of pelvic pain, progestins are lower in cost and appear to demonstrate similar efficacy to GnRH agonists when administered as a stand-alone therapy.[12]
- L**evonorgestrel releasing intrauterine system**: For endometriosis associated pelvic pain, LNG-IUS is effective and comparable to GnRH with less side effects.
- **Aromatase inhibitors in combination with progestins:** In rectovaginal endometriosis, the use of aromatase inhibitors in combination with progestins is recommended to reduce EAPP.

Dienogest in the treatment of endometriosis[8]

- Dienogest, a 19-nortestosterone derivative is another progestin used for the treatment of endometriosis.
- Dienogest is associated with high specificity for progesterone receptors and has less anti-androgenic side effects. Decidualization and atrophy of the endometrial lesions have been reported with continuous administration of dienogest.
- Dienogest also has anti-inflammatory, anti-angiogenic, and anti-proliferative effects.

Figure 2. Mechanism of action of progestins in the treatment of endometriosis



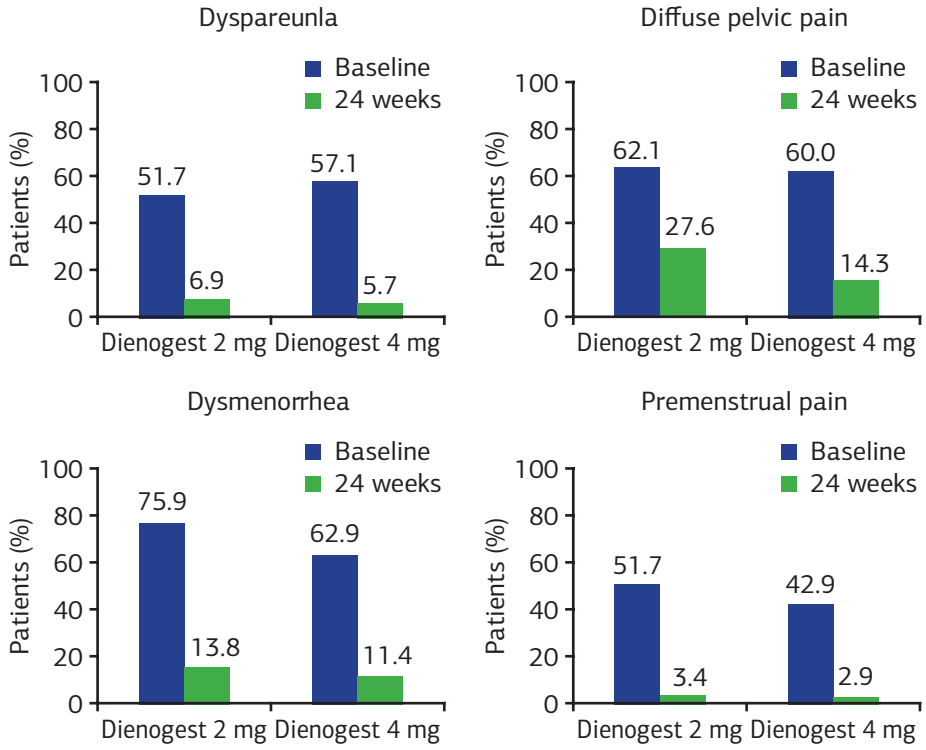
Karl-Werner Schweppe. Expert Rev of Obstet Gynecol. 2012;7(2):141-148.

Dienogest 2 mg once a day: An effective and optimal dose in the treatment of endometriosis

A 24-week study was conducted to evaluate the efficacy and safety of dienogest at doses of 1, 2, and 4 mg/day orally in the treatment of endometriosis. The mean revised American Fertility Society scores reduced from 11.4 to 3.6 ($n=29$; $p<0.001$) in the 2 mg dienogest group and from 9.7 to 3.9 ($n=35$; $p<0.001$) in the 4 mg group. Dienogest at 2 and 4 mg/day was associated with symptom improvements in substantial proportions of women (Figure 3). Both doses were generally well tolerated, with low rates of treatment discontinuation due to adverse events. The 1 mg dose arm was discontinued owing to insufficient bleeding control. Hence, Dienogest at 2 mg once a day is recommended as the optimal dose in the treatment of endometriosis.[13]

Figure 3. Proportions of women (%) with symptoms of endometriosis at baseline and after treatment with dienogest 2 mg or 4 mg for 24 weeks[13]

Endometriosis related symptoms: Dyspareunia, Diffuse pelvic pain, Dysmenorrhea, and Premenstrual pain.

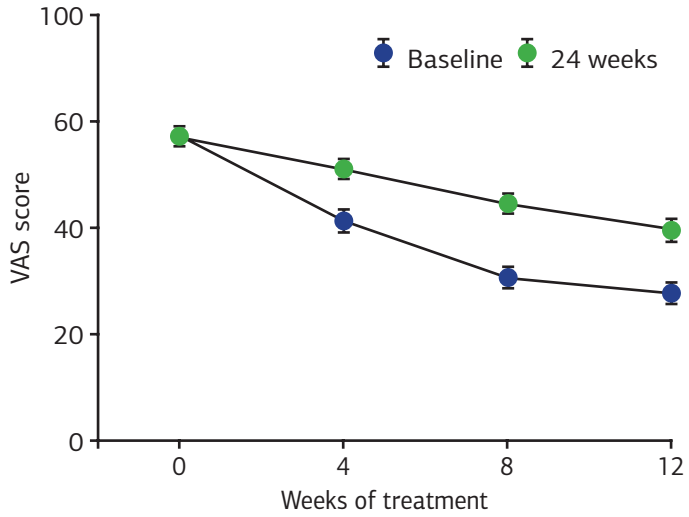


Dienogest at 2 mg once a day is recommended as the optimal dose in the treatment of endometriosis. The 2 mg dose of dienogest is effective for reducing EAPP, the severity of signs such as dysmenorrhea, and dyspareunia, and is well tolerated with few adverse events.

Another study by Strowitzki et al. demonstrated that dienogest at a dose of 2 mg daily for 12 weeks was effective for reducing EAPP. Women aged 18-45 years with laparoscopically confirmed endometriosis and EAPP score ≥ 30 mm on a visual analog scale (VAS) were administered dienogest 2 mg orally once daily. The primary efficacy variable was absolute change in EAPP from baseline to Week 12, as determined by change in VAS score and change in intake of supportive analgesic medication (ibuprofen) for pelvic pain.[5] The Biberoglu and Behrman (BandB) scale scores were recorded as a secondary efficacy variable between baseline and study end to assess changes in severity of symptoms (pelvic pain, dysmenorrhea, and dyspareunia) and signs (pelvic tenderness and induration).

- Mean reductions in VAS score between baseline and Week 12 were 27.4 mm and 15.1 mm in the dienogest and placebo groups, respectively; a significant score difference of 12.3 mm in favor of dienogest ($p<0.0001$; Figure 4).
- Changes in intake of supportive analgesic medication were modest in both groups. Intake during the study decreased by 4.4±6.4 tablets/28 days in the

Figure 4. Change in VAS score (mean±SEM) over 12 weeks in dienogest and placebo groups (FAS)[5]



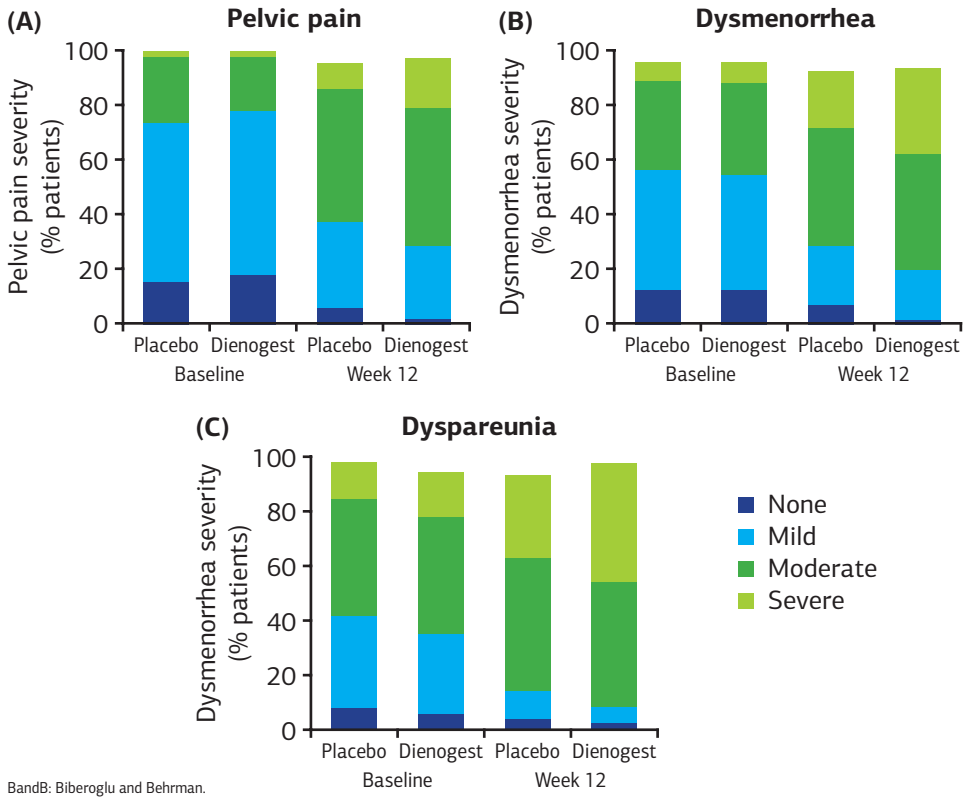
dienogest group and by 3.7±8.2 tablets/28 days in the placebo group (group difference: 0.74 tablets/28 days)

- The primary efficacy measure of absolute change in EAPP demonstrated the superiority of dienogest over placebo.
- A tendency to more frequent shifts toward lower severity categories were observed in the dienogest groups than placebo groups. The BandB signs also showed reductions in overall severity by week 12 in both groups, with a tendency toward greater reduction in severity of pelvic tenderness in the dienogest group Figure 5.
- Dienogest was generally well tolerated and few adverse events were associated with therapy.
- Dienogest at 2 mg once a day is recommended as the optimal dose in the treatment of endometriosis. The 2 mg dose of dienogest is effective for reducing endometriosis-associated pelvic pain, the severity of signs such as dysmenorrhea, and dyspareunia, and is well tolerated with few adverse events.

Dienogest in the long-term treatment of endometriosis

- Effective management of endometriosis over the longer term is an important objective. The painful symptoms and impairment in quality of life associated with endometriosis may persist or deteriorate in the absence of an effective treatment.

Figure 5. The BandB severity profile at baseline and week 12 in dienogest and placebo groups for single symptoms



BandB: Biberoglu and Behrman.

- Recurrence is frequent even after successful surgery. Dienogest has been investigated as a long-term treatment of endometriosis in two large trials performed in Europe and Japan, which included assessments of efficacy, change in quality of life, safety, and tolerability.[5]

Favourable efficacy and safety profile with Dienogest: A 65-week treatment period

Women who completed the 12-week placebo-controlled study were offered the opportunity to enter an open-label extension study of dienogest for up to 53 additional weeks, providing an overall treatment period of up to 65 weeks. Of the 188 women completing the placebo-controlled study, a large proportion (n=168, 89%) were enrolled in the long-term extension study.[14]

Efficacy variables

- The intensity of pain showed significant, sustained improvements during the long-term study, in addition to the improvements associated with dienogest during the placebo-controlled phase.

- Regarding pelvic pain, the mean VAS score was statistically significantly reduced by 43.2 (±21.7) mm over the total treatment period of 65 weeks (i.e., the placebo-controlled plus extension study; $p < 0.001$).
- Mean VAS decreased from 56.9 mm at baseline of the placebo-controlled study to 34.1 mm at baseline of the long-term study, to 11.5 mm at the end of the 53 additional weeks of treatment.
- During a 24-week treatment-free period following the long-term study, VAS increased only moderately, suggesting that dienogest induces a beneficial effect that may persist after treatment cessation.
- Short Form 36 Health Survey scores during the treatment-free period indicated minimal changes in physical or mental indices of quality of life over 6 months after cessation of dienogest.

Safety variables

- Laboratory parameters, vital signs, and body weight remained stable or underwent minimal changes during the extension study. Laboratory parameters continued to show no or minimal changes during treatment-free follow-up, while vital sign and body weight assessments provided stable results.
- The maximal intensity of treatment-related adverse events was rated mild or moderate in the majority (92.5%) of cases.
- In agreement with trends observed in the 12- and 24-week studies, the intensity and frequency of bleeding reduced progressively over the course of the long-term study.

During post-treatment follow-up, bleeding returned to normal intensity and cyclic patterns resumed within 4–6 weeks. Treatment compliance during the long-term study was high (98%) and discontinuation rates due to adverse events or lack of efficacy were both low (2.4% and 0.6%, respectively).

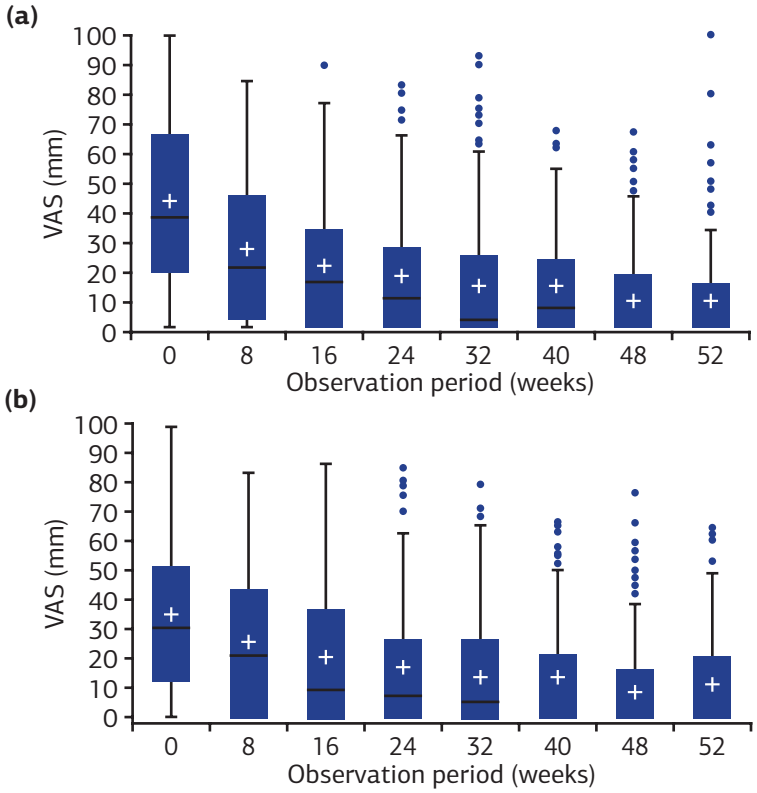
Dienogest treatment for up to 65 weeks is associated with reduced pelvic pain in women with endometriosis, and that this effect persists for at least 24 weeks after the end of treatment.

The prolonged pain relief even after the return of normal menses suggests a sustained effect on endometrial lesions.

Bleeding irregularities demonstrated a tendency toward reduced frequency and intensity during continued treatment.

- Dienogest treatment for up to 65 weeks is associated with reduced pelvic pain in women with endometriosis, and that this effect persists for at least 24 weeks after the end of treatment.
- The prolonged pain relief even after the return of normal menses suggests a sustained effect on endometrial lesions.
- Bleeding irregularities demonstrated a tendency toward reduced frequency and intensity during continued treatment.

Figure 6. Changes in the Visual Analog Scale (VAS) for lower abdominal pain (a) and lumbago (b) during the treatment period[15]



+, mean; – (horizontal lines in boxes), median; top ends of boxes (top hinges), 75% quartile point; bottom ends of boxes (bottom hinges), 25% quartile point; *Outliers (more than 1.5 times the hinge distribution from top hinge).

Safety and efficacy of 52 weeks of dienogest treatment

Another study was conducted to investigate the safety and efficacy of 52 weeks of dienogest treatment in patients with endometriosis. One hundred and thirty-five patients with endometriosis received 2 mg of dienogest orally each day for 52 weeks.[15]

Efficacy

- Moderate or marked global improvement (measured by change in the severity of five subjective symptoms [lower abdominal pain, lumbago, dyschezia, dyspareunia, and pain on vaginal examination] and two objective findings [induration involving POD and uterine mobility]) was recorded in 72.5% of patients after 24 weeks and in 90.6% after 52 weeks of dienogest treatment.
- Changes in VAS for lower abdominal pain and lumbago decreased progressively (Figure 6), while the proportion of patients demonstrating a reduction in cyst size >25% was 85% at 52 weeks.

Dienogest treatment led to marked global improvement, reduction in the lower abdominal pain and lumbago as well as reduction in cyst size.

The long-term effect of dienogest on BMD was slight, whereas the efficacy increased cumulatively. None of the treatment related adverse events was rated as serious.

- Quality of life assessments using the Short Form 36 Health Survey score indicated improvements in bodily pain by 23.57 and 27.37 points (on a 100-point scale) at 24 and 52 weeks, respectively, compared with baseline.
- Patient satisfaction with dienogest at the end of treatment was high, with 88.9% of women responding that they were 'certainly willing' or 'would prefer' to use dienogest again.

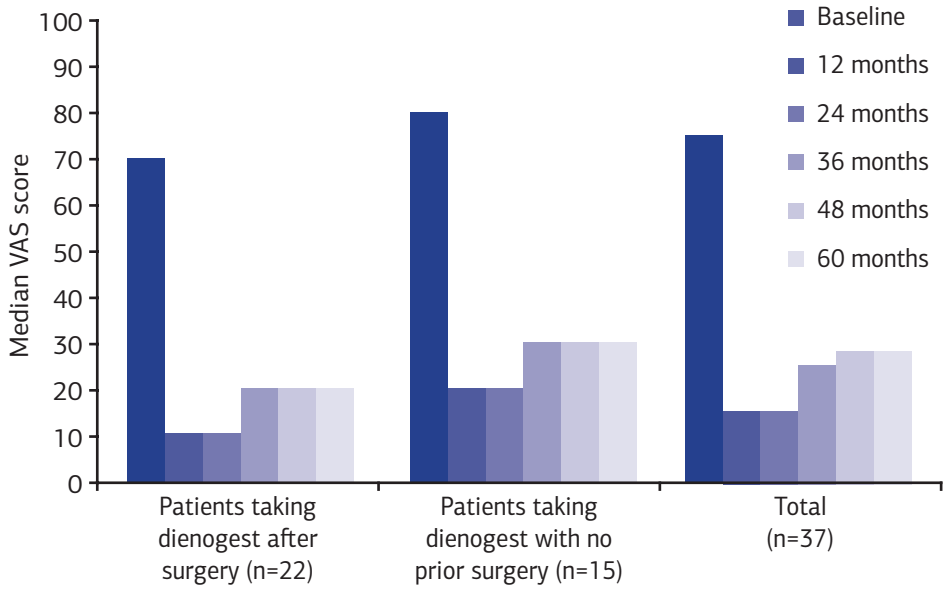
Safety

- The most commonly reported treatment-related adverse event was metrorrhagia (71.9%), followed by headaches (18.5%) and constipation (10.4%). None of the treatment related adverse events was rated as serious. Metrorrhagia resolved in 96 of the 97 affected patients either during the study or within two months of the study cessation.
- The frequency of bleeding lessened as treatment progressed, so that 40.5% of women were experiencing no bleeding by 49–52 weeks. Resumption of menses was confirmed in all women at the end of the study.
- The discontinuation rate due to treatment- related adverse events was 5.2%.
- Lumbar BMD decreased by 1.7 ± 2.2% between baseline and week 52, with the greatest change in the first 24 weeks. This BMD change may be considered mild and not significantly greater than that observed in untreated women of similar age.
- No biochemical markers of bone metabolism indicated changes outside the normal reference range.
- Dienogest treatment led to marked global improvement, reduction in the lower abdominal pain and lumbago as well as reduction in cyst size.
- The long-term effect of dienogest on BMD was slight, whereas the efficacy increased cumulatively. None of the treatment related adverse events was rated as serious.

A long-term treatment with dienogest effectively reduced EAPP and avoided pain recurrence post-surgery

A 60-month treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced EAPP and avoided pain recurrence post-surgery. Dienogest was administered in 37 women (age 39 ± 8 years) with laparoscopically diagnosed endometriosis based on the need for a long-term treatment to manage severe and/or recurrent endometriosis, either to prevent lesion recurrence post-laparotomy or to provide a hormone therapy for women unsuitable or unwilling to undergo surgery. Majority of these women (n = 30) were previously treated with different COCs. The EAPP was measured on a 0-100 mm VAS at baseline and every 12 months.[12]

Figure 7. Endometriosis-associated pain assessed by median VAS score (mm) in women at base-line and after 12, 24, 36, 48, and 60 months of dienogest 2 mg treatment. Baseline was before surgery or initiation of medical treatment[12]



VAS: visual analog scale.

Treatment with dienogest 2 mg once-daily for 24 weeks in patients with endometrioma excision prevented endometrioma recurrence 60 months after surgery.

- The VAS (median) was 10 mm at 12 and 24 months, and 20 mm at 36, 48, and 60 months of dienogest treatment, (Figure 7).
- In the 15 women treated with dienogest with no prior surgery (group 2), the median baseline VAS for EAPP was 80 mm.
- The VAS (median) was 20 mm at 12 and 24 months, and 30 mm at 36, 48, and 60 months (Figure 7) of dienogest treatment.
- The patient satisfaction with dienogest providing pain relief was very high.
- All laboratory parameters remained within the normal range; hemostasis, lipid and liver parameters did not defer from the reference range.
- Another 15 women began dienogest without prior surgery; median EAPP score was 80 mm pretreatment and 20, 20, 30, 30, and 30 mm, respectively, after 12, 24, 36, 48, and 60 months.
- Mean serum estradiol was 28 ± 12 pg/ml after 60 months.
- Seven women experienced spotting episodes and 4 women presented with phases of depressed mood, which could all be clinically managed.

Another study including 568 women with MRI-based diagnosis of ovarian endometrioma, who underwent laparoscopic stripping, was conducted to

evaluate the pain-relieving effects of dienogest vs. LA for 24 weeks. Researchers also assessed if the long-term dienogest administration reduced recurrence after endometrioma excision. It was found that:[6]

- Cumulative recurrence rates at the 5th postoperative year in the no-postoperative-medication and 2 mg dienogest groups were 69 and 4%, respectively, showing significant decreases (odd ratio [OR] = 0.09, 95% confidence interval, 0.03-0.26; Figure 8). Therefore, dienogest was observed to significantly prevent postoperative endometrioma recurrence.

Dienogest 2 mg/day is effective in reducing endometriotic lesions (11.4±1.71 to 3.6±0.95, $p<0.001$). The extended therapy with dienogest 2 mg/day also showed an improvement in pelvic pain after 24–52 weeks (-22.5±32.1 and -28.4±29.9 mm, respectively) with tolerable side effects.[16]

Efficacy and safety of Dienogest vs. leuprolide acetate in women with endometriosis

After excision of endometrioma, long-term treatment with dienogest 2 mg once-daily for 5 years significantly reduced the recurrence of lesions, and prevented the necessity of reoperation for a prolonged period.

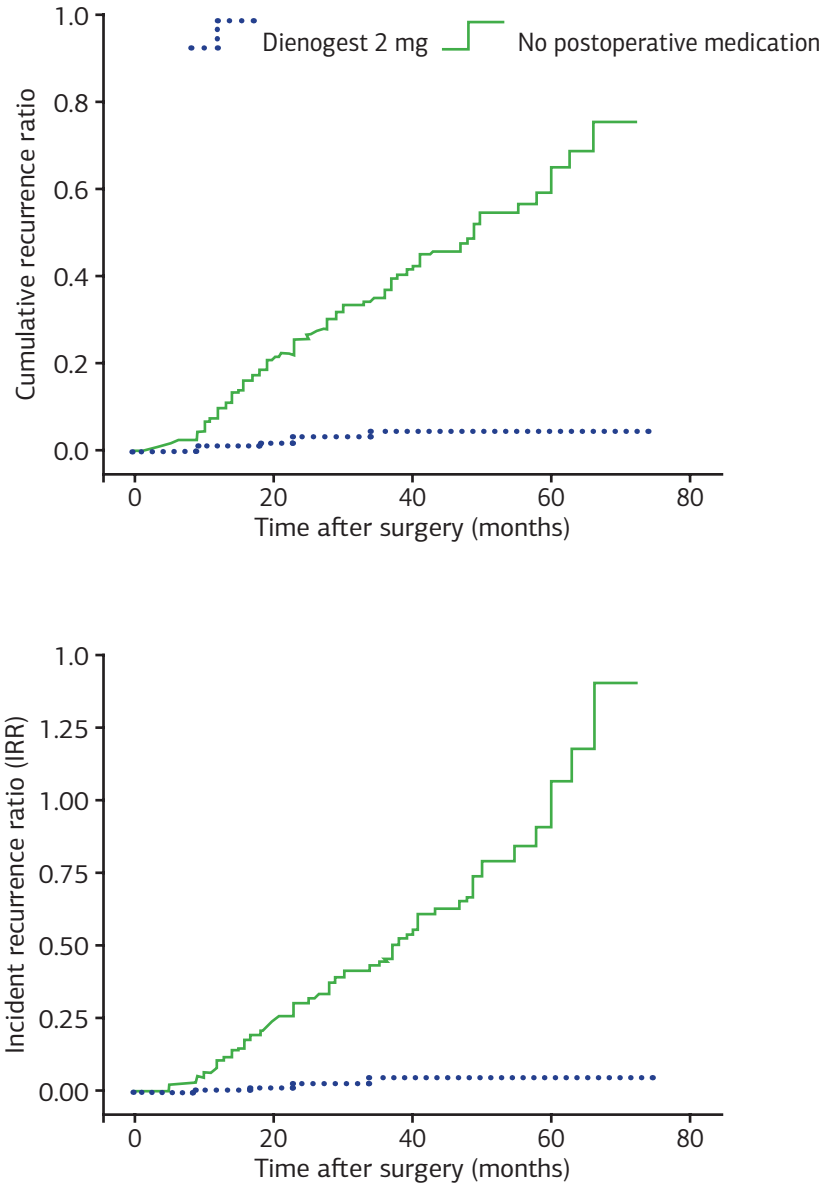
In a study, researchers evaluated the secondary efficacy and safety outcomes from a trial comparing dienogest with leuprolide acetate in women with endometriosis.[17]

Outcomes such as responder rates (using predefined thresholds of pain relief), changes in single symptoms/signs and sum scores from the BandB scale, clinical laboratory parameters, and measures of quality of life were assessed.

Findings revealed that: [17]

- The absolute reduction in mean VAS over 24 weeks, reported previously, was 47.5±28.8 mm with dienogest and 46.0±24.8 mm with leuprolide, representing a treatment difference of 1.5 mm in favor of dienogest. Therefore, dienogest was non-inferior to leuprolide for relief of endometriosis-related pelvic pain.
- The treatment responses of patients at study end, based on various predefined thresholds for absolute or proportional VAS score change, are shown in Figure 9.
- By week 24, more than half of the women in each treatment group were free from total pelvic symptoms (dienogest, 53%; leuprolide, 53%), compared with none at baseline.
- At the end of treatment, quality of life showed more pronounced absolute improvements in the dienogest group than in the leuprolide group, including both the physical health (dienogest, 10.2 points; leuprolide, 7.0 points) and

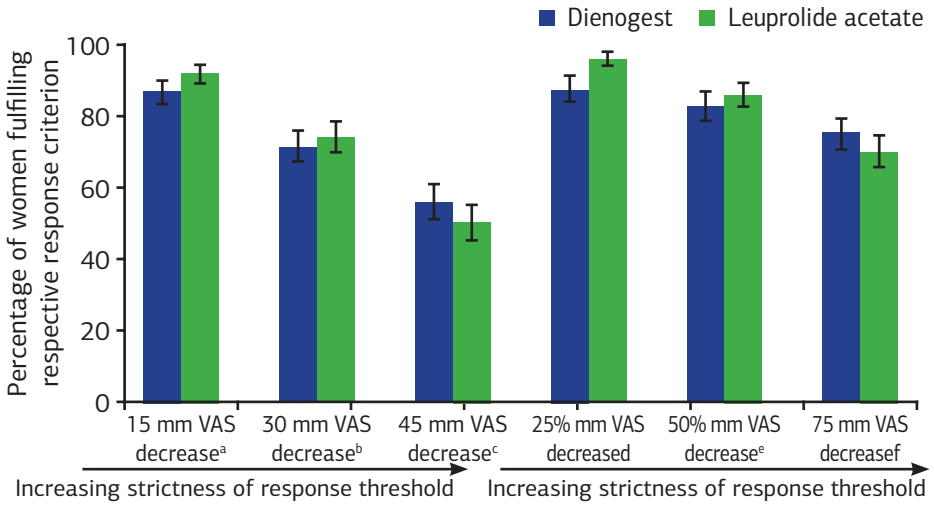
Figure 8. Recurrence ratios after surgery in the no-postoperative-medication and dienogest groups[16]



the mental health (dienogest, 3.3 points; leuprolide, 1.9 points) summary scale scores (Figure 10).

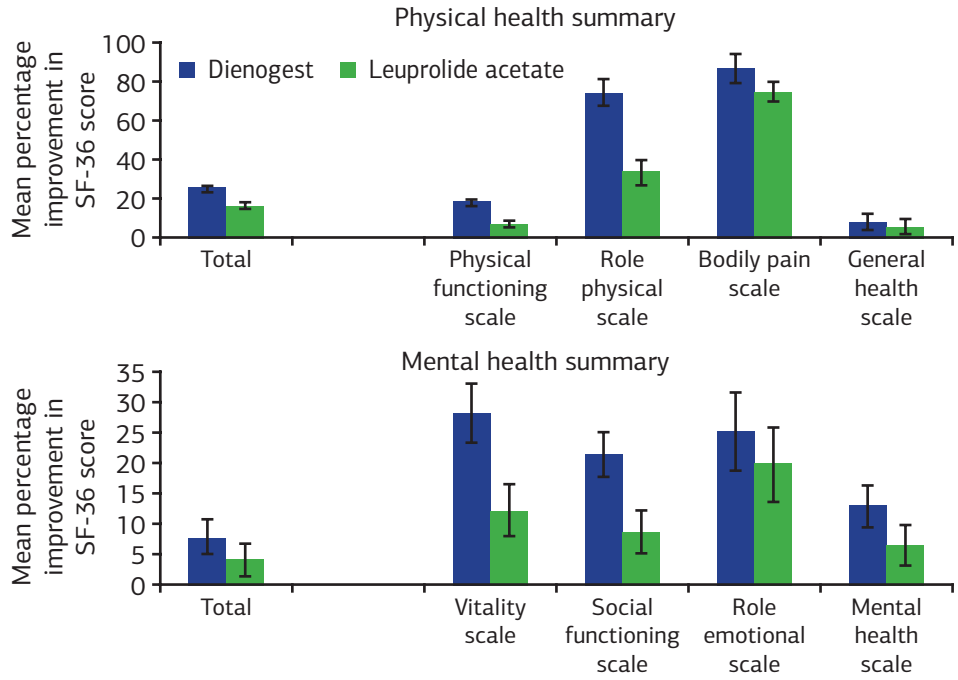
Therefore, dienogest was observed to be as effective as leuprolide for treating endometriosis symptoms, with specific quality-of-life benefits and a favorable safety profile.[17]

Figure 9. Visual analog scale (VAS) responder rates at study end



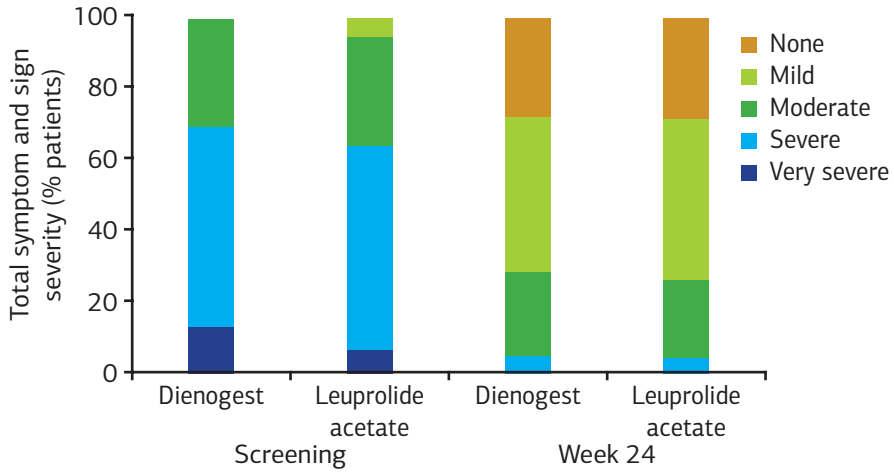
Responder analyses based on percentages of patients fulfilling response criteria of different strictness. p values for non-inferiority: [a]p=0.0005; [b]p=0.0044; [c]p=0.0002; [d]p=0.0014; [e]p=0.0009; [f]p<0.0001

Figure 10. Short Form-36 (SF-36) Health Survey quality-of-life (QoL) scores at study end[17]



Another study showed that Dienogest 2 mg/day orally had equivalent efficacy to depot leuprolide at standard dose in relieving the pain associated with

Figure 11. Total symptom and sign severity score profile (BandB) at baseline and Week 24 in the dienogest and Leuprolide acetate groups (PPS)[18]



BandB, Biberoglu and Behrman; LA, leuprolide acetate; PPS, per protocol

endometriosis, and offered advantages in safety and tolerability. Women with endometriosis were randomized to treatment with dienogest (2 mg/day, orally) or leuprolide (3.75 mg, depot i.m. injection, every 4 weeks) for 24 weeks.[18]

- Both dienogest and leuprolide were associated with substantial reductions in VAS score between baseline and Week 24.
- In the per protocol set, compared to baseline, 96.7% of women in the dienogest group and 95.8% of women in the leuprolide group experienced an improvement in pelvic pain after 24 weeks (P for non-inferiority, 0.0001).
- The improvement in Quality of life, assessed by the SF-36 Health Survey, showed a more pronounced benefit in the dienogest than leuprolide group, although it improved in both treatment groups.
- Women treated with dienogest less frequently experienced events representing other hypoestrogenic symptoms (such as hot flushes, vaginal dryness, and decreased libido and sleep disorder) than women treated with leuprolide.
- The intensity of pelvic symptoms and physical findings, summarized by the BandB total symptom and sign severity score profile, decreased similarly in the two treatment groups between screening and Week 24 (Figure 11).
- Whereas 12.2% of women in the dienogest group and 6.3% of women in the leuprolide group had very severe symptoms at screening, none had this symptom grade at final visit.

- Dienogest is reported to be as effective as leuprolide for relief of endometriosis-related pelvic pain. It led to more pronounced absolute improvements in quality of life including both the physical health and the mental health as compared with leuprolide.

Safety and tolerability of dienogest

A pooled analysis of four randomized, controlled, European trials was conducted to evaluate the safety and tolerability data to confirm and further characterize the safety profile of dienogest in the treatment of endometriosis. The pooled analysis confirmed that:[19]

- Dienogest 2 mg was well tolerated, with a favorable safety profile extending over a period up to 65 weeks in women with endometriosis.
- Common adverse drug reactions reported were headache, breast discomfort, depressed mood, and acne, each occurring in <10% of women, and were generally of mild-to-moderate intensity and associated with low discontinuation rates.
- The bleeding pattern associated with dienogest 2 mg was well tolerated, and only two women (0.6%) reported bleeding events as the primary reason for premature discontinuation.
- Laboratory and vital sign assessments indicated no safety concerns for dienogest.
- Estradiol levels were maintained within the low-physiological range, in support of previous evidence indicating that dienogest 2 mg demonstrates therapeutic efficacy without inducing estradiol deficiency.

Therefore, dienogest was observed to be well-tolerated therapy with a favorable safety profile and was suitable for long-term use. The equivalent efficacy of to the highest current treatment standards, its progressive improvement in pain during continued use and favourable safety profile makes it a promising approach for the treatment of endometriosis.[19]

- Guidelines from the World Endometriosis Society have recommended dienogest as an empirical treatment option for women without laparoscopic confirmation and as a suitable adjuvant therapy following endometriosis surgery.[19]
- Dienogest is well-tolerated with a favorable safety profile and is suitable for long-term use for the treatment of endometriosis.

Guidelines from the World Endometriosis Society have recommended dienogest as an empirical treatment option for women without laparoscopic confirmation and as a suitable adjuvant therapy following endometriosis surgery.

Dienogest is well-tolerated with a favorable safety profile and is suitable for long-term use for the treatment of endometriosis.

Maintenance therapy with dienogest following GnRH agonist treatment

Treatment with a GnRH-agonist followed by long-term dienogest therapy maintains the relief of endometriosis-associated pelvic pain achieved with GnRH-agonist therapy for at least 12 months. Patients were administered GnRH-agonist for 4-6 months and then dienogest (1 mg/day) for 12 months (Group 1). The dose of dienogest was increased to 1.5 or 2 mg/day when a patient had uncontrollable uterine bleeding [n=15 (39%)]. Another group was administered only dienogest (2 mg/day) for 12 months (Group 2).[20]

- GnRH-agonist significantly reduced the VAS score for pelvic pain, and alleviation was maintained during the 12-month therapy with dienogest.
- There was no significant difference in pain reduction between both groups.
- The pictorial blood loss assessment chart score during the first 6 months on dienogest was significantly smaller in Group 1 than in Group 2.
- Long-term dienogest therapy maintains the relief of endometriosis-associated pelvic pain achieved with GnRH-agonist therapy for at least 12 months. This regimen reduces the amount of irregular uterine bleeding that often occurs during the early phase of dienogest therapy.

Dienogest in the treatment of adolescents with clinically suspected endometriosis[21]

The treatment with dienogest for 52 weeks in adolescents (12 to younger than 18 years) with suspected endometriosis substantially reduced the endometriosis-associated pain.[21]

- Mean endometriosis-associated pelvic pain at baseline assessed using a VAS was 64.3 mm (SD, 19.1 mm). By week 4, the VAS score decreased to 36.8 mm (SD, 26.1 mm) and by week 48 to the lowest mean value of 9.0 mm (SD, 13.9 mm).
- The proportion of responders (≥30% reduction in VAS score from baseline) was 81.0% (81 of 100 patients) at week 24.
- BandB scores showed increased proportions of patients without endometriosis symptoms between baseline and EOT: pelvic pain (from 9.1% to 71.2%; n=110), dysmenorrhea (3.6% to 78.8%; n=110), and dyspareunia (9.1% to 23.1%; n=21).

Long-term dienogest therapy maintains the relief of endometriosis-associated pelvic pain achieved with GnRH-agonist therapy for at least 12 months. This regimen reduces the amount of irregular uterine bleeding that often occurs during the early phase of dienogest therapy.

Treatment with dienogest for 52 weeks in adolescents (12 to younger than 18 years) with suspected endometriosis substantially reduced the endometriosis-associated pain.

- At the end of dienogest treatment (EOT; defined as at 52 weeks or premature study discontinuation), the mean relative change in BMD from baseline was -1.2% (SD, 2.3%; n = 103). In the subgroup with decreased BMD at EOT (n = 60), follow-up at 6 months showed partial recovery in lumbar BMD (mean change from baseline: -2.3% at EOT, -0.6% 6 months after EOT).

Therefore, dienogest once daily in adolescents for 52 weeks was associated with a decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation. Since bone mass is critical during adolescence, the physician would need to weigh the benefits of dienogest 2 mg against potential risks in individual adolescent patients.[21]

- In adolescents with clinically suspected endometriosis, dienogest was effective in reducing the mean endometriosis-associated pelvic pain. Dienogest was also associated with a decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation.
- The VISADO study emphasizes that the the benefits of dienogest 2 mg needs to be weighed against potential risks in individual patients, since bone growth is critical during the adolescence period.

In adolescents with clinically suspected endometriosis, dienogest was effective in reducing the mean endometriosis-associated pelvic pain. Dienogest was also associated with a decrease in lumbar spine BMD, followed by partial recovery after treatment discontinuation.

The VISADO study emphasizes that the benefits of dienogest 2 mg needs to be weighed against potential risks in individual patients, since bone growth is critical during the adolescence period.

Guideline recommendations for the use of Dienogest

ESHRE 2014

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

FOGSI 2017

- Dienogest at the dose of 2 mg/day is as effective as GnRH agonist but with much less side effects [Evidence level-A]
- Dienogest may be useful in long-term treatment of symptomatic adenomyosis [Evidence level B].

Levonorgestrel-releasing intrauterine system (LNG-IUS)

In women with moderate to severe dysmenorrhea receiving operative laparoscopy for endometriosis, recurrence of dysmenorrhea was lower in the group with a LNG-IUS postoperatively than in the control group receiving expectant management.[20]

- A statistically significant reduction in the recurrence of painful periods in the LNG-IUD group compared with expectant management (RR; 0.22, 95% CI; 0.08 to 0.60, 95 women, I(2) = 0%, moderate strength of evidence).
- The proportion of women who were satisfied with their treatment was also higher in the LNG-IUD group (RR; 1.21, 95% CI: 0.80 to 1.82, 95 women, I(2) = 0%).
- The number of women reporting a change in menstruation was significantly higher in the LNG-IUD group (RR; 37.80, 95% CI: 5.40 to 264.60, 95 women, I(2) = 0%)
- In one trial, women receiving LNG-IUD noted lower pain scores compared with women receiving GnRH-agonists (MD -0.16, 95% CI: -2.02 to 1.70, 40 women)
- Postoperative LNG-IUD use reduces the recurrence of painful periods in women with endometriosis.

As per the ESHRE guideline

- In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a LNG-IUS for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia.

FOGSI 2017

- LNG-IUS is effective for endometriosis associated pelvic pain and is comparable to GnRH with less side effects [Evidence level A].

Postoperative LNG-IUD use reduces the recurrence of painful periods in women with endometriosis.

ESHRE Guideline

In women operated on for endometriosis, clinicians are recommended to prescribe postoperative use of a LNG-IUS for at least 18–24 months, as one of the options for the secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia.

FOGSI 2017

LNG-IUS is effective for endometriosis associated pelvic pain and is comparable to GnRH with less side effects [Evidence level A].

AIs are shown to have a promising effect on pain associated with endometriosis.

ESHRE (European Society of Human Reproduction and Embryology) guidelines recommend concomitant use of AIs and oral contraceptives, progestogens, or aGnRHs in patients with pain associated with drug-resistant and surgery-resistant recto-vaginal endometriosi.

AIs are the 2nd line of therapy and can be prescribed in combination with oral progestagens to reduce EAPP as well as to reduce the size of endometrial lesions.

AIs can also be prescribed in patients with pain associated with drug-resistant and surgery, resistant recto-vaginal endometriosis.

Anastrazole [1mg] and Letrozole [2.5mg] can be given daily for 12 weeks with Progesterone add-back therapy (Evidence level B).

Aromatase inhibitors

- Aromatase inhibitors (AIs) decreased pain and improved quality of life when used in combination with gestagens or oral contraceptives in patients with endometriosis.
- Combination treatment with letrozole and norethisterone acetate was also associated with less severe side effects and fewer discontinuations than concomitant treatment with letrozole and a GnRH agonist, triptorelin.[23]
- AIs decreased pain, reduced the size of extrauterine endometrial lesions, and improved patients' quality of life when used in combination with gestagens, oral contraceptives, or GnRHs.
- AIs are shown to have a promising effect on pain associated with endometriosis.[24]

Selective progesterone receptor modulator

- Selective progesterone receptor modulator (SPRMs) is progesterone receptor (PR) ligands with specific clinical effects: agonists, antagonist, or agonist-antagonist combination on progesterone target tissues *in vivo*.
- ESHRE (European Society of Human Reproduction and Embryology) guidelines recommend concomitant use of AIs and oral contraceptives, progestogens, or a GnRHs in patients with pain associated with drug-resistant and surgery-resistant recto-vaginal endometriosis[25]
- AIs are the 2nd line of therapy and can be prescribed in combination with oral progestagens to reduce EAPP as well as to reduce the size of endometrial lesions.
- AIs can also be prescribed in patients with pain associated with drug-resistant and surgery, resistant recto-vaginal endometriosis.
- Anastrazole [1mg] and Letrozole [2.5mg] can be given daily for 12 weeks with Progesterone add-back therapy (Evidence level B).
- The ideal SPRM triggers antiproliferative effects on the endometrium and breast, but retains the protective effects of estrogen on bone and cardiovascular system. SPRM administration results in reduced endometrial thickness, loss of mitotic activity, and increased stromal density.[26]
- Administration of ulipristal acetate (doses 10, 50 or 100 mg) in the mid-luteal phase inhibits endometrial maturation, decreases endometrial thickness, and induces endometrial atrophy.[26]

Other newer therapies for the treatment of endometriosis[26]

Selective estrogen receptor modulator

- The selective estrogen receptor modulator (SERMs) are agents that have the effect of estrogen antagonists on the target organ, and the agonistic effects on bones and blood vessels
- There are three types of SERM: triphenylethylene (tamoxifen), benzothiophene (raloxifen), and steroid.
- Newer generation SERM, bazedoxifen, is being extensively studied for endometriosis therapy. The decrease in the size of lesions and reduced expression of various genes involved in tissue proliferation are significantly found after the administration of bazedoxifen 3 mg/kg/day.
- Bazedoxifen administration alone (3 mg/kg/day) or bazedoxifen-conjugated-estrogen combination led to lesion size reduction and decreased ER expression.

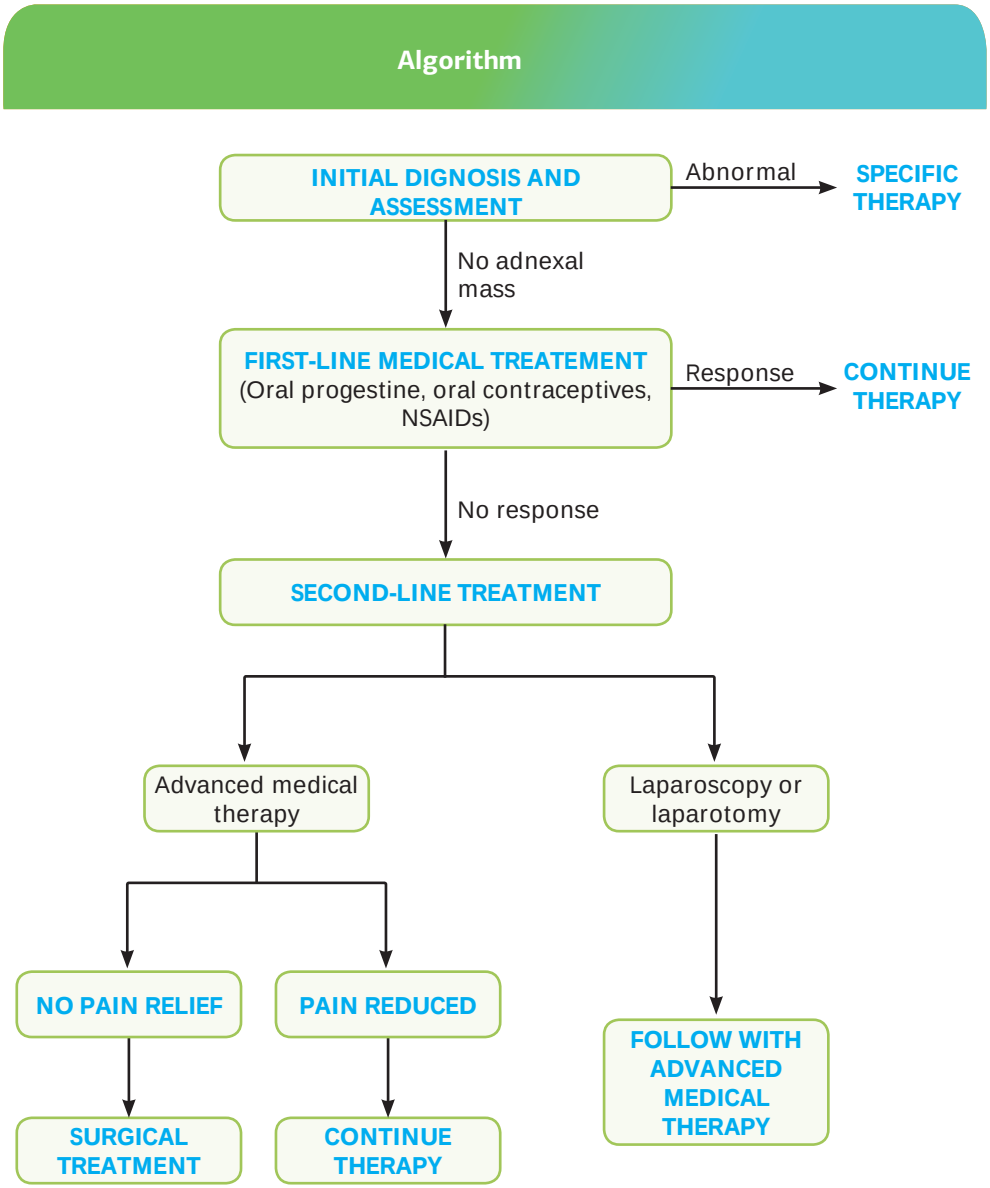
Anti-TNF-α

- TNF-α has a major role in the pathogenesis and survival of endometriosis lesions. Thus, targeting this molecule is a rational approach to treat endometriosis.
- Drugs classified as anti-TNF-α are either monoclonal antibodies (infliximab) or soluble TNF-α receptors (etanercept, TNF recombinant human protein bindings).
- In vitro studies have shown that regression of lesion size, as well as decreased expression of inflammatory cytokines after anti-TNF-α administration.

High-intensity focused ultrasound (HIFU)

- HIFU can be performed with the guidance of ultrasound (USgHIFU) or magnetic resonance imaging. The physical basis of HIFU technique is by focusing the ultrasonic wave so that high intensity acoustic energy will be absorbed and then converted into heat at a designed focal point, resulting in thermal coagulation.
- Abnormal tissue ablation with USgHIFU in the case of adenomyosis provides good safety and effectiveness as well as significant improvement of clinical symptoms
- HIFU has also been proven effective for ablation of endometriotic lesions. In a study, cyclic pain was found to disappear in all patients after 3–31 months (mean 18.7 months).

Medical management algorithm[26,27]



Case discussion

TREATING ENDOMETRIOSIS IN A WOMAN REFUSING SURGERY

Case presentation

A 38-year-old woman presented to the clinic with severe pelvic pain along with heavy menstrual bleeding that she has been experiencing over the past 5 years. The patient would take two to three days off from work each month due to her menstrual pain. Recently, she had started having deep pain after sexual intercourse. The patient is a mother of two and the pain has affected her quality of life and work she complains. Radiographic evaluation indicated the presence of endometriosis (Figure below).

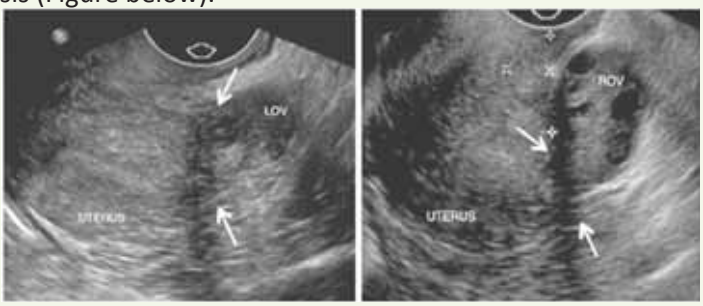


Figure. Hypoechoic endometriotic implant causing left ovarian (LOV) fixation to the uterine fundus. Right ovary (ROV) adherent to uterine fundus (white arrows). Endometriotic tissue fills the retrocervical space

Past history

The woman was diagnosed with dysmenorrhea and was receiving diclofenac 50 mg thrice daily for menstrual pain along with hormonal contraception. She had been anemic for the past several months.

Diagnosis

Endometriosis

Intervention

- The patient underwent ablation of the endometrium, which would help with the heavy menstrual bleeding. However, patient declined laparoscopic surgery for excision of ovarian endometriomas.
- The patient was given dienogest 2 mg/day to reduce endometriotic lesions.

Follow-up

- After 7 weeks of extended therapy with dienogest 2 mg/day, patient reported improvement in pelvic pain and normalization of menstruation.
- The patient was suggested to continue the therapy up to 24 weeks, after which she was asked to come for a follow-up visit.

Reference

Andres Mde P, Lopes LA, Baracat EC, et al. Dienogest in the treatment of endometriosis: Systematic review. Arch Gynecol Obstet. 2015; 292(3):523–9.

References

1. Burney RO, Giudice LC et al. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012; 98(3):1–14.
2. Bedaiwy MA. Evidence-based long-term management of endometriosis: Medical therapy and treatment of infertility. Middle East Fertility Society Journal. 2011; 16:236–39.
3. Management of women with endometriosis. Guideline of the European Society of Human Reproduction and Embryology. 2013.
4. FOGSI. Good clinical practice recommendations on endometriosis.2016.
5. Strowitzki T, Faustmann T, Gerlinger C, Seitz C. Dienogest in the treatment of endometriosis-associated pelvic pain: A 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol. 2010; 151(2):193–98.
6. Ota Y, Andou M, Yanai S et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. JEPPD. 2015; 7(2): 63–67
7. Nanthakumar MP, Arumugam SC et al. Adolescent endometriosis. Int J Reprod Contracept Obstet Gynecol. 2017; 6(8):3213–218.
8. Rafique S, Decherney AH et al.Medical management of endometriosis. Clin Obstet Gynecol. 2017; 60(3):485–96.
9. Gezer A, Oral E. Progestin therapy in endometriosis. Womens Health (Lond). 2015; 11(5):643–52.
10. Kim ML, Seong SJ. Clinical applications of levonorgestrel-releasing intrauterine system to gynecologic diseases. Obstet Gynecol Sci. 2013; 56(2):67–75.
11. Pavone ME, Bulun SE. Aromatase inhibitors for the treatment of endometriosis: A review. Fertil Steril. 2012 Dec; 98(6): 1370–379.
12. 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.
13. Köhler G, Faustmann TA, Gerlinger C, et al. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4mg of dienogest daily for endometriosis. Int J Gynaecol Obstet. 2010; 108(1):21–5.
14. 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.
15. Momoeda M, Harada T, Terakawa N et al. Long-term use of dienogest for the treatment of endometriosis. J Obstet Gynaecol Res. 2009; 35(6):1069–76
16. Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet. 2015; 292(3):523–9.
17. Strowitzki T, Marr J, Gerlinger C, et al. Detailed analysis of a randomized, multicenter, comparative trial of dienogest versus leuprolide acetate in endometriosis. Int J Gynaecol Obstet. 2012; 117(3):228–33.
18. Strowitzki T, Marr J, Gerlinger C, et al. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: A 24-week, randomized, multicentre, open-label trial. Hum Reprod. 2010; 25(3):633–41.
19. 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.
20. Kitawaki J, Kusuki I, Yamanaka K, Suganuma I. Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain. Eur J Obstet Gynecol Reprod Biol. 2011;157(2):212–6.
21. 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):560–67.
22. Abou-Setta AM, Houston B, Al-Inany HG, et al. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database Syst Rev. 2013; (1):CD005072.
23. Ferrero S, Gillott DJ, Venturini PL, et al. Use of aromatase inhibitors to treat endometriosis-related pain symptoms: A systematic review. Reprod Biol Endocrinol. 2011; 9:89
24. Ferrero S, Venturini PL, Gillott DJ, et al. Letrozole and norethisterone acetate versus letrozole and triptorelin in the treatment of endometriosis related pain symptoms: A randomized controlled trial. Reprod Biol Endocrinol. 2011; 9:88
25. Słopień R, Męczekalski B. Aromatase inhibitors in the treatment of endometriosis. Prz Menopauzalny. 2016; 15(1): 43–47.
26. Suardika A, Astawa Pemayun TG. New insights on the pathogenesis of endometriosis and novel non-surgical therapies. J Turk Ger Gynecol Assoc. 2018; 19(3):158–64.
27. American College of Obstetricians and Gynecologists. Practice bulletin no. 114: Management of endometriosis. Obstet Gynecol. 2010; 116(1):223–36.

Supported by

Bayer Zydus Pharma