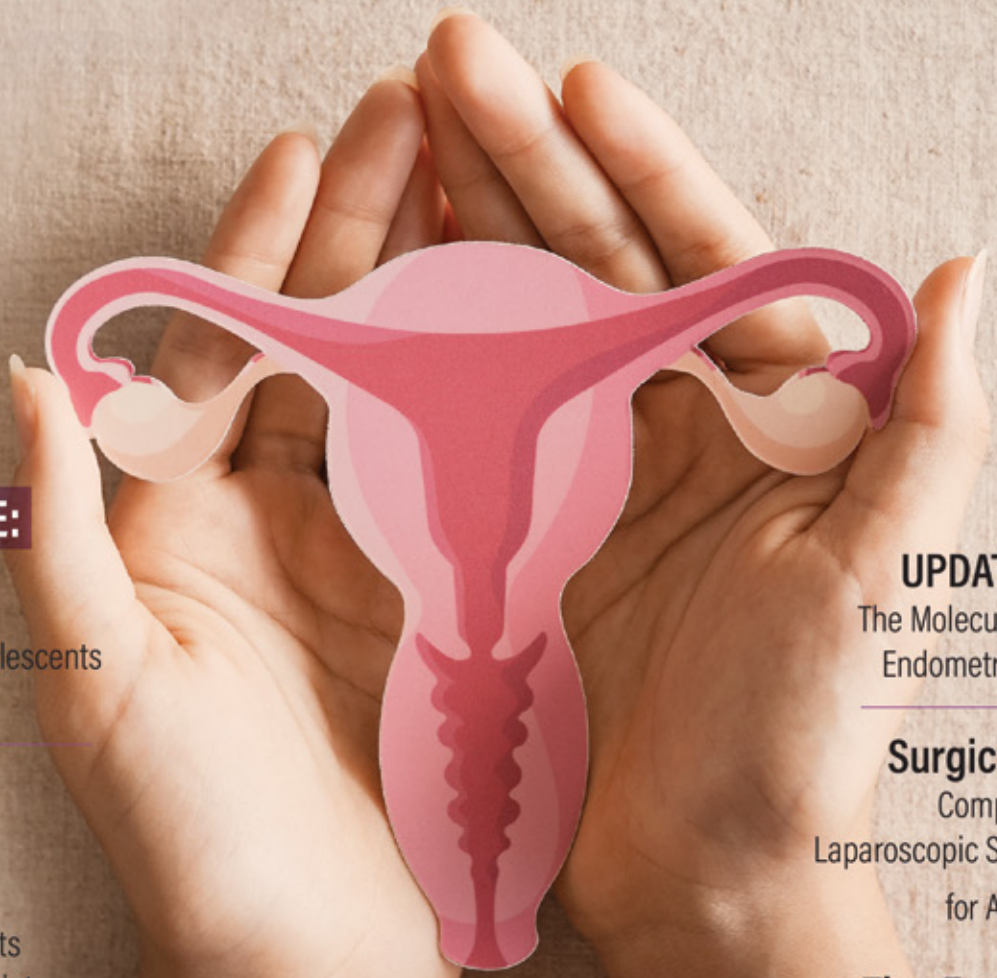
Volume 2: 2025

Endometriosis update



IN THIS ISSUE:

A publication of Endometriosis Society of India

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Dear Colleagues,

Endometriosis remains one of the most enigmatic and burdensome gynecologic conditions, affecting an estimated 10% of women and individuals assigned female at birth during their reproductive years. Despite its prevalence, diagnostic delays, underfunding, and therapeutic challenges persist, underscoring a pressing need for ongoing research, education, and advocacy.

This issue of the Endometriosis Update underscores both the complexity and diversity of endometriosis as a disease, from the new molecule Elagolix a future for endometriosis management to the profound impact on quality of life. Advances in non-invasive diagnostics and therapeutics, such as emerging biomarker panels and imaging innovations, may soon shift the paradigm away from diagnostic laparoscopy.

Surgical advances continue to provide relief to many; however, outcomes remain variable, and recurrence is common. Articles in this issue examine how laparoscopic surgical techniques, patient selection, and perioperative care strategies are evolving to meet these challenges. Perhaps most importantly, this issue recognises the need to address endometriosis in adolescents. We emphasise that scientific progress must be measured not only in biomarkers and surgical metrics, but in lived experience and long-term well-being.

We hope this issue contributes to a growing movement: one that no longer accepts diagnostic delays, dismisses chronic pain, or tolerates fragmented care. Instead, we must continue to champion a collaborative, patient-centred, and scientifically rigorous approach to understanding and managing endometriosis.

As always, we thank our contributors, reviewers, and readers for advancing this mission.

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Screening of Peri-Adolescents for Endometriosis

INTRODUCTION

What is the peri-adolescent phase?[1]

It is an emerging terminology extending from 9 to 21 years, as most of the features of adolescence are appearing earlier over decades, including menarche. The impact of some adolescent problems persists even beyond the age of 19 years.

Why is this phase important to us?

Because these girls are the 'Future of the Nation', experiencing an unstable psychological phase, and thereby needing meticulous care.

Hence, 'Prevention/protection' should be offered in three areas: Physical, Mental, and Environmental. In this context, the author focuses on physical problems where prevention, screening, or protection is the need of the hour. Two important problems are Endometriosis and Cervical Cancer. This write-up addresses only the Endometriosis aspect, as more and more cases of pre-menarcheal Endometriosis are being detected.[2]

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Endometriosis is a non-curable, lifelong disease with no known specific causative factor.

Unlike cancer, there is no pre-endometriotic stage, and as of now, no validated biomarker or test for mass screening—including saliva or mRNA tests—is available.

The incidence is rising progressively and may be up to 65-70% in the adolescent population, marking this issue as a global epidemic[3]. Although some schools of thought believe that there is no difference in prognosis between early and late symptomatic detection (once diagnosis is confirmed before treatment initiation), the author's view is contrary. He advocates the earliest suspicion, detection and initiation of treatment, followed by lifelong supervision (at least up to 30 years) to prevent various adverse impacts on life.[4]

1. PROBABLE CAUSATIVE FACTORS

Peri-adolescent Endometriosis is probably not usually seen due to retrograde menstruation, as the occurrence of pre-teen/premenarchial Endometriosis has been documented[5]. Other associated factors may include coelomic metaplasia, embryonic Müllerian rests, iatrogenic implantation, and vascular or lymphatic metastasis.

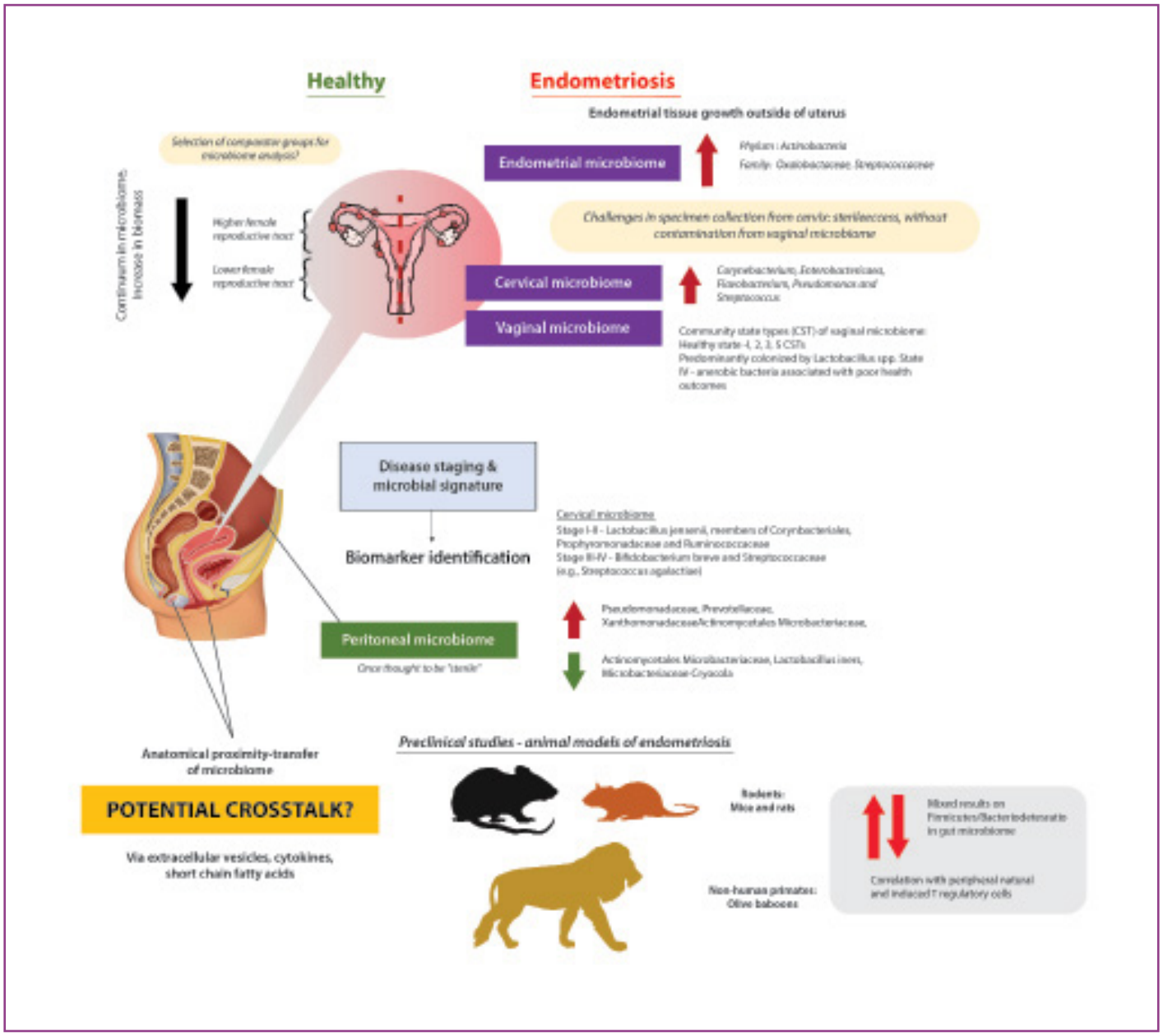
However, genetics and epigenetics, and the role of endometrial stem/progenitor cells, are special areas of aetiopathogenesis, although no

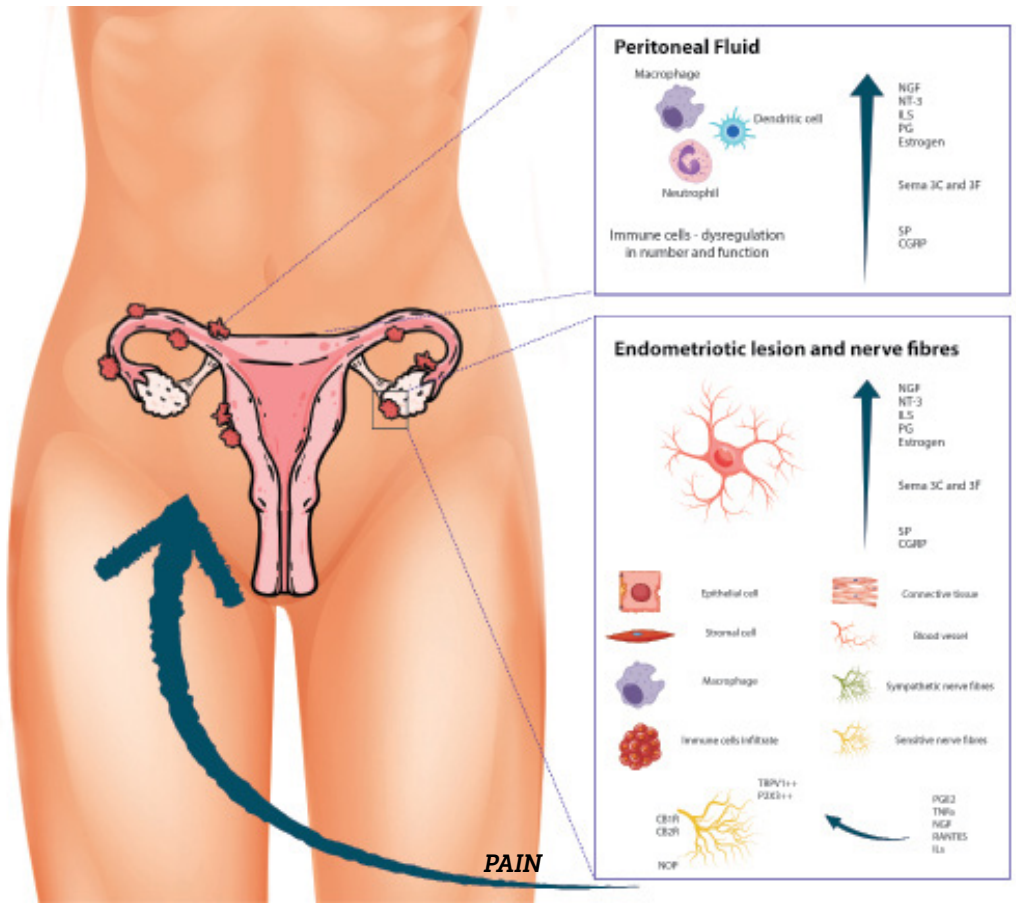
single factor can explain all types of Endometriosis. The mutation of the cancer related KRAS[7] gene is under extensive investigation.

For peri-adolescent Endometriosis, the role of NUB (Neonatal Uterine Bleeding) appears to be important, as the shedding of endometrial stem/progenitor cells into the peritoneal cavity occurs during NUB. These intra-peritoneal cells are disproportionate compared to external vaginal bleeding in NUB and remain viable for many years. Subsequent secretion of E2 and VEGF at menarche results in angiogenesis, leading to premature florid hemorrhagic lesions and endometrioma.

Thus, the pathogenesis may differ between adolescent and adult Endometriosis[8]. However, the "how" remains unknown. The role of the gut microbiome may also be significant in this age group, as diagrammatically represented.

Furthermore, concepts of pain site, extent, and variability have evolved, with neurogenesis and neuropathic, nociceptive, and nociplastic components—via peripheral, central, and cross-sensitization pathways—offering insights into this complex issue.[9]





Peripheral , Central & Cross Sensitization in Endo

REMINISCENCE AND HISTORICAL PERSPECTIVE

The author has been involved in Endometriosis awareness programs for the past 14 years. In 2010, adolescents in schools, along with their teachers and guardians, had never heard of a disease called Endometriosis, although they were aware of ovarian cysts, such as in PCOS. This scenario remained unchanged even in 2025.

Under the umbrella of the Endometriosis Society India, the awareness program has continued, expanding from urban centers to remote rural areas—not only in West Bengal but also in other states of Northern India—through collaborations with various NGOs, the BSF, and others. Festive seasons were also utilized, and young individuals—both boys and girls (especially the Endo-Warriors, most of whom were adolescent Endometriosis sufferers)—took an active role in raising general public awareness about this lifelong, non-curable, and distressing disease. Though not cancerous, it can often be more distressing than cancer, without being fatal.

All forms of media have been employed—not only during Endometriosis Awareness Month (March) but throughout the year. However, in 2018, the author concluded that "Only awareness is NOT ENOUGH." Simultaneous screening with registration of every suspected case, followed by periodic monitoring based on severity, is essential. Until we address the following two areas, meaningful outcomes will remain out of reach:

i) The failure to study the problem in a systematic manner

ii) The tendency to advise sporadically without structured follow-up

Thus, a modified approach was initiated based on the following key observations:

1. The incidence of dysmenorrhea and chronic pelvic pain (CPP) is progressively increasing.
2. These symptoms are mostly ignored by parents and school teachers.
3. Suffering girls are often compelled to accept this as a normal part of life.
4. Most cases are detected very late, with an onset-to-detection interval (O-D Interval) of 8-12 years.
5. The disease progresses at a rate exceeding 10% per year, depending on geographical variation in India.
6. It is prevalent not only in urban

Ten years ago, the late Prof. B.N. Chakraborty—fondly remembered as 'The Then Living Legend' and our revered mentor—taught us about the vital role of awareness and screening in peri-adolescents.

He emphasized three key principles: "Prediction and Prevention," "Catch them Early," and "Strike at the Root." He believed that Endometriosis should be approached as a clinical diagnosis, much like PCOS.

One cherished memory remains etched in time—Sir BNC, PDM, and the author together conducted a live telecast of this program, which was aired for the first and last time and later re-telecast in multiple languages across the globe.

populations but may be equally or more prevalent in rural areas.

7. Transgender and gender-expansive individuals are also affected.

SCREENING OBJECTIVES

A) Objectives:

1. **Immediate Objective:**

To suspect and provisionally diagnose the disease using non-invasive approaches, thereby avoiding the typical diagnostic delay of 8-12 years in Endometriosis.

2. **Thereafter, the Lifetime Plan Should Aim to:**
    i. Avoid various complicated surgical procedures
    ii. Promote conception
    ii. Maintain optimum quality of life (QOL)

B) Materials and Methodology

An attempt was made to detect asymptomatic Endo-Adeno complex.

RELEVANT APPROACHES

Three relevant approaches were undertaken:

1. Periodic School Visits for students in Classes VII to XII throughout the year.
2. Involvement of General Practitioners (GPs) and Paramedics.
3. Inclusion of General Laparoscopic Surgeons and Imaging Specialists.

NGOs, social welfare organizations, and Endo-Warriors also played a crucial role.

Awareness-Cum-Screening Program in Schools

Among the three approaches, the school-based awareness and screening program proved to be the as the most impactful. The steps included:

- Prior distribution of the Endo-Survey Form
- Basic lecture session (duration: 40 minutes)
- Q&A session lasting nearly 1 hour
- Collection of Endo-Survey Forms
- Scrutiny of the completed forms (details provided below)
- On another scheduled date: clinical check-up and advice

The Endo-Survey Form is a structured questionnaire, which continues to be updated regularly to ensure relevance and accuracy.

Endometriosis Society India: Dr P K Mitra (WA:9830042832)

Endo Survey Form for Adolescents/ E-mail: souvik86@yahoo.co.in/endosocindia@gmail.com

Please put tick mark & write something - if necessary

Clinical Diagnosis - might be possible

1) Name ..... Code No
2) Age ..... Student/Unmarried/Married
3) Address ..... State..... Urban/Semirural/Rural

   3A) Family History: (From Mother): Endo in 1st degree relative, H/O NUB
4) Menstrual History ..... Age of Onset ..... Regular/Irregular ..... Bleeding ..... Days ..... Mild/Moderate / Severe ..... Number of Pads used ..... 3 or more per day
5) Pain During Menstruation ..... Yes/No ..... If yes ..... When it starts ..... Before/During/After/Persists throughout the month/Irregular Vague pain ..... How Long the Pain Persists ..... VAS: 7+/-2
6) Do you feel any other problem ..... Difficulty in passing stool /Urine with/without bleeding from Rectum/Urinary Passage or back pain before/during/after Menses?
7) Is your pain during menses gradually increases with time? Yes/No
8) Do you take any medicine/pain killer for Menstrual Pain? Yes/No/Sometimes. From where you get the medicine - Doctor's prescription / Over the counter/ Friends/ Relatives
9) If yes - what medicine you are taking?
10) Have you consulted any doctor/Female disease specialist? Yes/No
11) Have you done any test for the pain like Ultrasonography? Yes/No-

    If yes - what was the report?
12) Did you have any Hormone Therapy for your Pain-Yes/No

    If yes --- Continuously / Cyclically

    If Continuous Therapy- Are you free from symptom during the treatment phase ..... Yes/No
13) Are you sexually active? Yes/No
14) Do you have white discharge? If yes - Bad smell/Itching/Staining of undergarments- Yes/No
15) For Persistent Menstrual Pain - Do you have to skip school/ Social activities/ affect your studies/ Extracurricular activities-sports/dance etc.--Yes/No / To some extent
16) Is the menstrual pain affecting your mental balance? Yes/No

    If Yes - What type? Depression/ Irritability/ Anger/Social Isolation
17) What is your future plan regarding Marriage & Child birth?

    ----- Within 25 yrs./30 yrs./35 yrs./ Until I am self sufficient
18) Write in detail on the back page/separately on anything.....
19) Miscellaneous Health Issues - H/O General/Medical/Surgical -Rx -Details

Digital Endo-Survey Form: PKM -2024

- The link... for the Endo-Survey cum Screening is: https://docs.google.com/ forms/d/e/1FAIpQLScW-jhnl1xtk6qPHLdeed19gPmlX4f3WHBOMdGSwhSjKMSDAQ/viewform?usp=sf.link
- ESI is trying to make it a 'Widespread National Program'
- Monitored by trained Class Teacher, Social Workers & 'Endo Warriors'- Remote supervision of a Gynecologist

Symptom-Based Grading (G1-G5)

After thorough scrutiny, students were categorized using a symptom-based grading scale as follows:

- G1: No or mild vague menstrual pain - Control Group
- G2: Progressive Dysmenorrhea (PD) (VAS score 7.5 ± 2.1)
- G3: Chronic Pelvic Pain (CPP)
- G4: PD & CPP causing incapacitation of normal activities
- G5: PD/CPP with associated bowel or urological symptoms

Initially, 4,286 students were deemed eligible after the scrutiny of Endo-Survey forms. Parental consent was mandatory for participation. This is an ongoing study, conducted in phases. Each participant was assigned a unique registration code.

Although 4,286 were recruited after obtaining proper consent, only 3,352 participated in the current study phase (January-March 2024). The dropout rate was relatively high in

this phase. However, the subsequent phases—April to June 2024 and July to September 2024—saw a decline in dropouts, with zero dropouts in the final phase.

The pre-treatment data were tabulated as follows:

Group				
Grade 1	No Menstrual Pain	Mild Vague Pain	670 (20%):	CONTROL
2	Progressive Dysmenorrhea (PD)	PD	1344 (40%)	40%
3	Chronic Pelvic Pain(CPP)	CPP	736 (22%)	22%
4	PD & CPP causing incapacitation of Normal Activities	PD + CPP <<< Normal Life	402(12%)	12%
5	as CPP/PD +Bowel/ Urologic symptoms-		204(6.1%)	6.1%
		Total	3352	

Grade-wise Management Protocol

- G1 - Control (670): No treatment
- G2 - 1,344 students: Given analgesics/NSAIDs for 3 months
  - Only 10% became asymptomatic or showed slight improvement
  - The remaining 90% showed no improvement and were reassessed. The reclassification results showed:
    - **31% - G3:** Total = 375 + 736 = N = 1,111
    - **22% - G4:** Total = 85 + 402 = N = 487
    - **8% - G5:** Total = 183 + 204 = N = 367

Total (Reclassified): N = 2,482

All these students were placed on trial drug therapy. A continuous low-dose oral contraceptive pill (OCP) was administered for 3-6 months, after excluding basic contraindications. The outcomes were monitored in all N = 2,482 participants.

Results and Analysis

(Post-Treatment Trial)

Interesting observations were made during the first 12 months of the ongoing trial:

i) 70% (1,737 students) became amenorrhoeic and experienced partial to complete relief.

A provisional diagnosis of Endometriosis could be assumed in G2, G3, and G4 cases that became asymptomatic within 3 months (N = 1,737). These participants were advised to continue the same treatment for an additional 3 months and were later shifted to the long-cycle OCP (84/7 regimen).

ii) The remaining 30% showed no relief with combined oral contraceptive pills (COCPs). To evaluate these cases further, the Clinical Global Impression-Improvement (CGI-I) Scale was used. This scale consists of a single question:

"How are your symptoms (pain and others) now compared with how they were before treatment?"

Responses were rated using the following seven options:

1. Much better
2. Better
3. Somewhat better
4. No change
5. Somewhat worse
6. Worse
7. Worst

No Relief: 745 participants (30%)—mostly from G4 and G5—did not respond to treatment.

Plan:

Ultrasonography (USG) was conducted using one or more of the following modalities:

- Transabdominal
- Transperineal
- Transrectal

Note: Transabdominal sonography (TAS) was performed in all cases.

Results:

1. 660 out of 745 showed no apparent abnormality.
2. In the remaining 85 participants, the following were detected:
   - EOMA (Endometrioma) in 36 participants (Grade 4)
   - Adenomyosis in 33 participants (Grade 4 and 5)
   - Rectovaginal (RV Endometriosis in 25 participants (Grade 5)
3. All were placed on Dienogest 2 mg/day or given a single injection of DMPA. These cases were referred to a tertiary center for detailed review with high-resolution USG (HR-USG), MRI, and potential laparoscopy.

Final Evaluation

Conclusion from the current phase: Good coordination between NGOs, class teachers, Endo-Warriors, and gynaecologists is the backbone of the Endometriosis screening protocol.

Who played the most vital role?

The Endo-Warriors and NGOs. They are the future of mass awareness and screening programs. Their contributions included:

1. **Youths and Class Teachers**
   Trained to conduct peri-adolescent school visit programs under the remote supervision of a gynaecologist (ESI Member).
2. **NGOs**
   Encouraged to operate across districts, covering 10 or more schools. Their outreach to the

grassroots level proved pivotal.

3. **Friends and Colleagues**

   Many got inspired and joined the movement.

4. (Note: Point 4 is missing in the original content.)

5. **The Entire Brigade**

   Built a bridge between the sufferers and the gynaecologists.

6. **Adolescent Endometriosis Survivors**

   Volunteered and led the project, acting as frontline warriors.

Statistical Interpretation : 1st Approach

- P-Value: P< 0.05
- Sensitivity: 91%

  Specificity: 82%
- Confidence Level (CL)-95%
- SD Ratio: 2
- Others:
- Specificity: PL (Positive Likely hood) 86%
- Sensitivity of 98.1% and NL (negative likelihood ratio) <0.03
- Post-test probability rates - 77.2%

SECOND APPROACH: TWO KEY COMPONENTS

1. Endometriosis Awareness Training

Targeted general practitioners (GPs), paramedics, social workers, and even village health workers. Though a challenging task, it was found to be highly effective.

2. Waiting Room Screening

Implemented in GP clinics using a simplified Endometriosis Screening Form. This ensured timely referrals. Additionally, posters in local languages describing symptoms had a significant impact.

THIRD APPROACH: ASYMPTOMATIC ENDOMETRIOSIS DETECTION

Involvement of General Laparoscopic Surgeons and Imaging Specialists was requested to observe and report pelvic findings while performing non-gynecological procedures.

Although current guidelines recommend no intervention for asymptomatic Endometriosis, recognition and recording were considered vital by the author.

A Stage IV Endometriosis does not develop in a day—it evolves, often leading to frozen pelvis, colorectal, or ureteric involvement.

OUTCOME OF THE PROJECT

1. Targeted adolescent screening is of utmost importance. A provisional diagnosis could be made in over 70% of participants in G2-G5.
2. Early initiation of treatment resulted in a substantial reduction in suffering and a notable decrease in the Onset-to-Detection (O-D) Interval.
3. Among the control group (G1), 65% progressed to G2 within 9-11 months, indicating auto-progression when left untreated.
4. Involvement of general practitioners (GPs), who cater to large populations, is a crucial step toward widespread Endometriosis screening.
5. Imaging specialists and general laparoscopic surgeons play a valuable role in identifying and managing endometriosis cases.
6. Endo-Warriors represent the future of sustained awareness and screening programs.

Togetherness is essential to fight against Endometriosis.

APPROPRIATE DIAGNOSIS AND DIFFERENTIAL EVALUATION

When painful symptoms persist, differential diagnosis becomes imperative.

A) Gynecological Causes:

- Primary Dysmenorrhea (No organic disease)
- Secondary Dysmenorrhea (Due to organic disease), including:
  - Endometriosis
  - Adenomyosis
  - Pelvic Inflammatory Disease (PID)
  - Congenital obstructive lesions (e.g., Hematocolpos)
  - Hematosalpinx
  - Vulvodynia
  - Complicated pregnancy

B) Non-Gynecological Causes:

- Gastrointestinal disease
- Urinary tract disease
- Musculoskeletal syndromes
- Visceral hyperalgesia
- Neurological problems
- Psychiatric comorbidities

A MULTIDISCIPLINARY DIAGNOSTIC APPROACH

A **multidisciplinary diagnostic approach** should be considered to accurately assess suspected cases.

Preferred: Noninvasive Diagnostic Methods

A noninvasive diagnostic approach remains the preferred strategy for evaluating suspected Endometriosis.

A) History - Structured Questionnaire

The following parameters should be recorded:

1. Age at menarche
2. Characteristics of menstrual period, including duration of bleeding
3. Interval between menstrual cycles
4. Assessment of menstrual flow (GRADE 1, strong recommendation)
5. Associated symptoms, such as pelvic pain
6. Timing of onset, severity of pain, and impact on daily activities
7. Other symptoms such as nausea, diarrhea, and fatigue
8. VAS (Visual Analog Scale) for pain scoring

B) Clinical Examination

Includes:

- P/A (Per Abdominal)
- P/V (Per Vaginal) - if appropriate
- P/R (Per Rectal)

C) Laboratory Evaluation

A comprehensive panel should be conducted, including:

- CBC, CRP, and metabolic panel
- Plasma levels of LH, Progesterone (P), Estradiol (E2), Prolactin (PRL), CA-125, CA 19-9
- Urine analysis (R/E & C/S)
- Urine or blood for βhCG
- Testing for sexually transmitted infections (STIs)

D) Imaging

- Ultrasound (USG): Transrectal (TRS), Transvaginal (TVS), or Transperineal
- MRI

E) Endoscopy

- Upper and Lower Gastrointestinal Endoscopy

F) Laparoscopy (Controversial in asymptomatic adolescents)

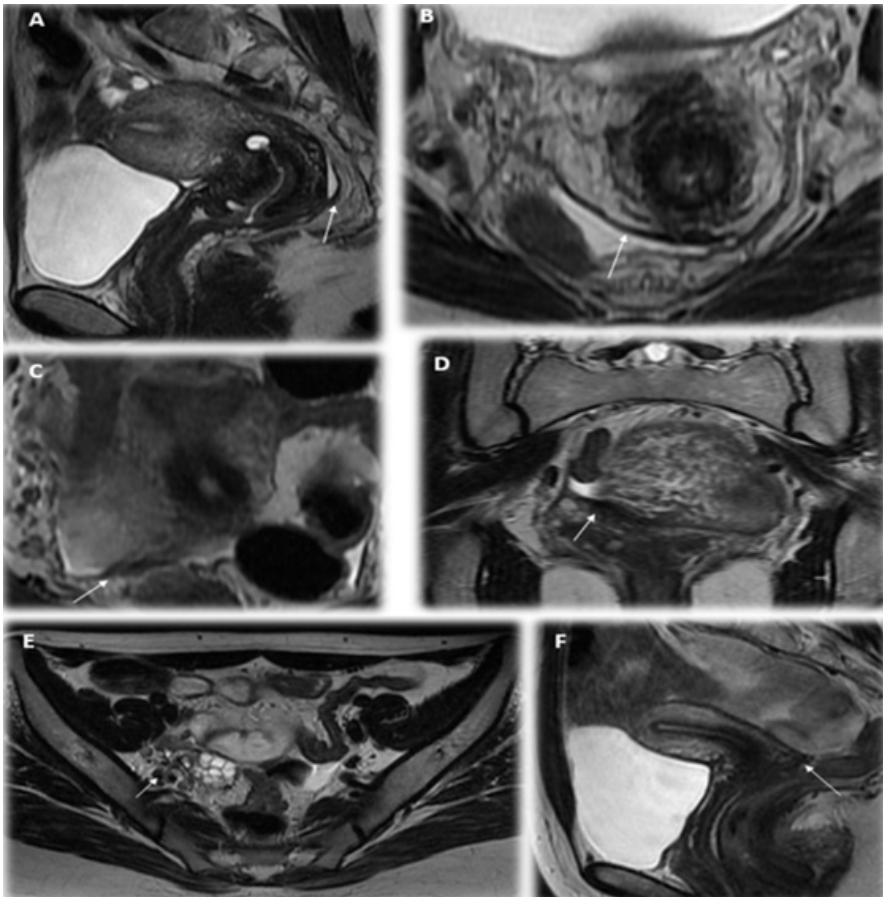
CONSULTATION WITH SPECIALISTS

Referral to the following specialists may be necessary:

1. Gastroenterologist
2. Urologist
3. Psychiatrist

MRI Signs of Endometriosis in Adolescents

MRI findings in adolescents with peritoneal Endometriosis (PE) include:



- (A) Thickening of the peritoneum and partial obliteration of the pouch of Douglas
- (B) Thickened Douglas space peritoneum, free fluid, and a low-intensity signal at the uterosacral ligament (T2VI Ax)
- (C) Thickening of pelvic peritoneum and uterosacral ligament with ovarian fixation (right side) - T2VI Ax
- (D) Thickened pelvic peritoneum and right uterosacral ligament - T2WI Cor
- (E) Asymmetry in the sacro-uterine ligament projection and right ovarian fixation - T2VI Ax
- (F) Small nodules (up to 0.3 cm) - T2VI Cor

Diagnostic accuracy: 81% (X^2 = 19.54, $p < 0.001$)

Laparoscopic Observations

Among the diagnosed PE cases:

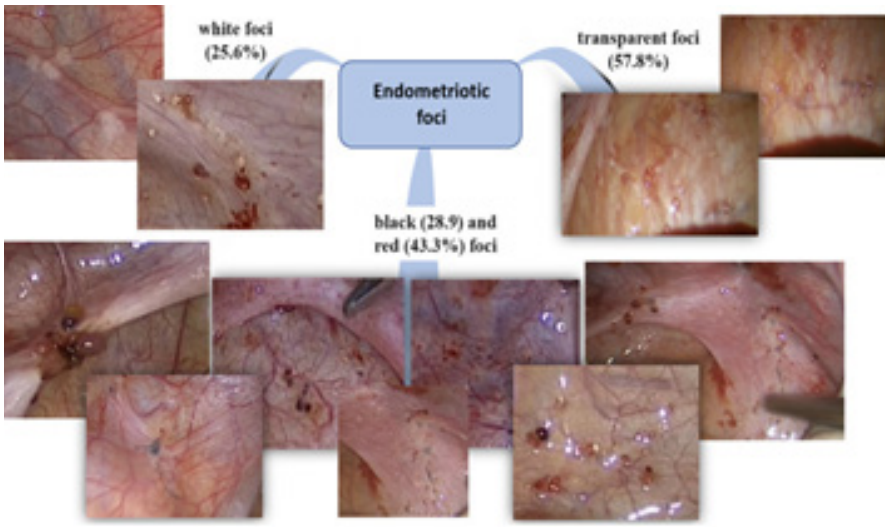
- **Stage I:** 64.4% (rASRM score 3.1 ± 1.3)
- **Stage II:** 27.8% (score 8.4 ± 3.1)
- **Stage III:** 7.8% (score 24.5 ± 7.5)

Lesions were predominantly found in the uterosacral ligaments (84.4%) and pouch of Douglas (66.7%).

Clear, red, and white vesicular foci were observed in:

- 57.8% - Clear
- 43.3% - Red
- 25.6% - White

These findings correlated significantly with VAS pain scores (r = 0.32, p = 0.007).



Norethindrone acetate 15 mg/ day (considered most effective).

IV) Subcutaneous implant of etonogestrel.

V) Progestin-only therapy (note: monitor for bone mineral density [BMD] changes).

VI) GnRH agonists with add-back therapy (e.g., norethisterone [NE], Tibolone, Calcium + Vitamin D) + Dienogest.

VII) GnRH antagonists - Oral: Elagolix 150 mg.

VIII) Levonorgestrel intrauterine system (LNG-IUS).

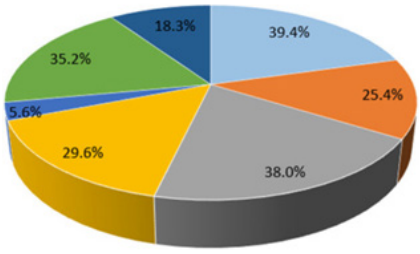
IS THERE A ROLE FOR SURGICAL MANAGEMENT?

A different approach is necessary compared to adults.

Surgery is indicated only when adolescent Endometriosis is refractory to all forms of medical therapy.

However, the recurrence rate remains high—approximately 40-50% over 5 years—particularly when estrogen (E2) levels rise, necessitating

LAPAROSCOPIC % OF THE LOCATIONS ADOLESCENT ENDO

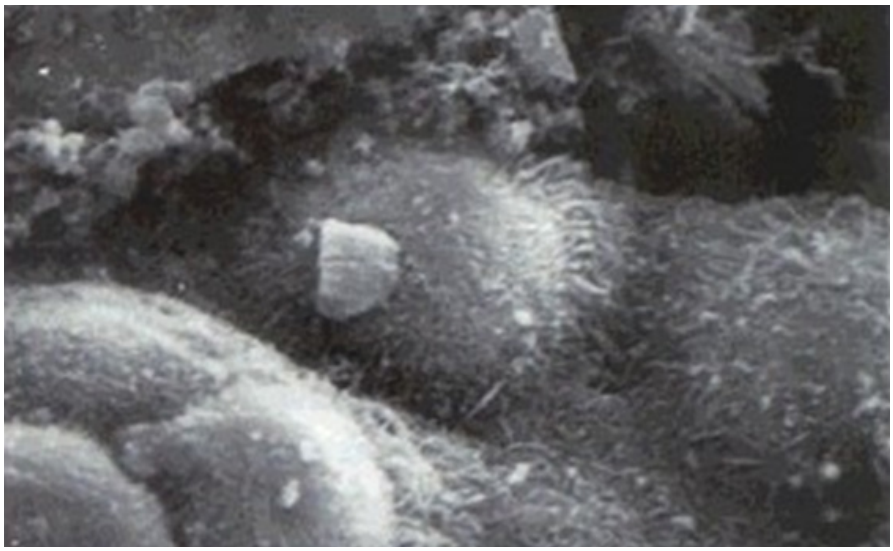


- Uterosacral ligament
- Peritoneum and tissue of the Douglas pouch
- Parametrial tissue
- Paraovarian tissue
- Retrocervical area and cervix
- Endometrial implants on the ovaries
- Posterior leaf of broad ligament

Ref- Endometriosis in Adolescents: Diagnostics, Clinical and Laparoscopic Features,J Clin Med. 2023 Feb; Published online 2023 Feb 20. doi: 10.3390/jcm12041678, PMCID: PMC9962715,PMID: 3683621412(4): 1678.Elena P. Khashchenko,1, Elena V. Uvarova,1,2 Timur Kh. Fatkhudinov,1,3 Vladimir D. Chuprynin,1 Aleksandra V. Asaturova,1 Elena A. Kulabukhova,1 Mikhail Yu. Vysokikh,1,4 Elvina Z. Allakhverdieva,5 Maria N. Alekseeva,5 Leila V. Adamyan, Writing - original draft,1 and Gennady T. Sukhikh[1,2]*

NORMAL LOOKING PERITONEUM SHOWING ENDOMETRIOSIS

(SEM Image - Dr. P.K. Mitra, 2009)



5. MANAGEMENT OPTIONS

I) Continuous oral combined oral contraceptive pills (COCP), followed by long-cycle OCP.

II) Vaginal continuous monthly hormonal ring - NuvaRing.

III) Oral: Dienogest 2 mg/day ±

aggressive follow-up.

Thus, medical therapy is mandatory even after surgical intervention.

There is no single best treatment for adolescent Endometriosis. Therapy must be personalized to the patient's profile to ensure optimal quality of life (QOL).

6. PRIMARY PREVENTION STRATEGIES

I) Promote widespread awareness about the disease.

II) Implement lifestyle modifications, including:

Lifestyle Risk Factors:

- Sedentary habits, such as constant cellphone or laptop use, have significant negative impacts.
- Cellphone addiction has been associated with various effects:
  - Electromagnetic wave (EMW) exposure affecting ovaries/testes
  - Premature aging and facial wrinkles
  - At least 22 documented side effects related to mobile phone use

Smoking and Alcohol

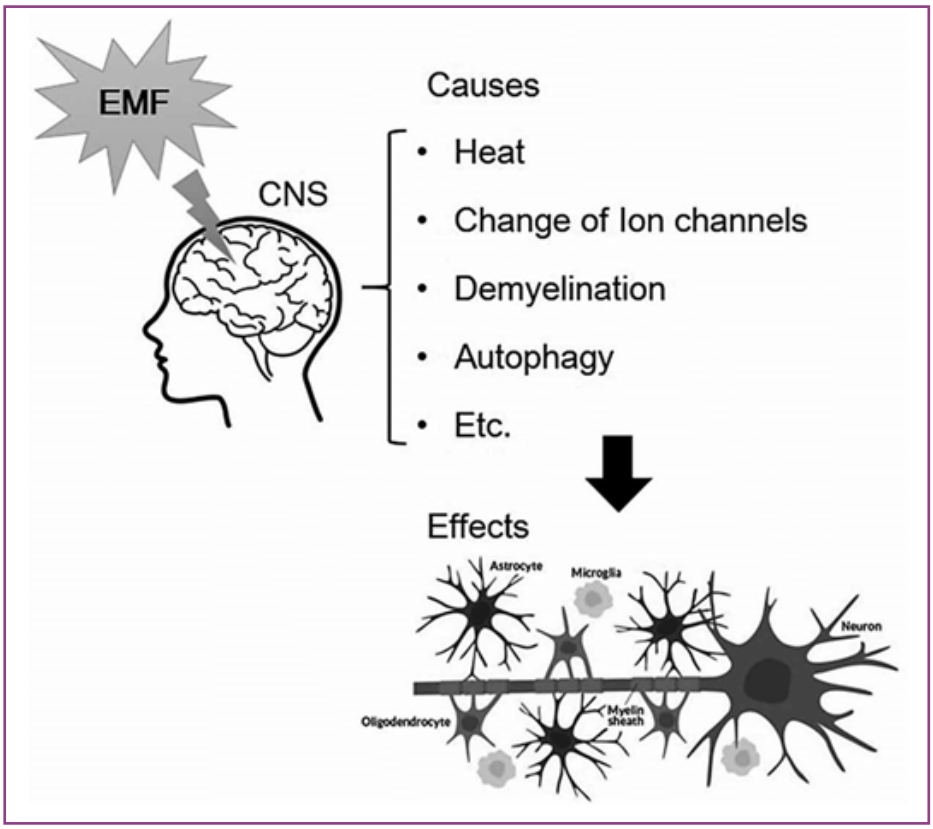
- As of 2014, smoking was thought to have an inverse relationship with Endometriosis.
- By 2024, updated findings suggest it directly aggravates the condition.

Moreover, literature reports a significant association between moderate or regular alcohol intake and worsening of Endometriosis.

(Reference: Sci Rep. 2022; 12:19122. Published online: Nov 9, 2022. doi: 10.1038/s41598-022-21173-9. PMID: 36352037)

7. HOME REMEDIES

Several lifestyle and home-based interventions may help manage symptoms:



1. **Heat Therapy**

   Taking a warm bath, or placing a heating pad/hot water bottle on the lower abdomen helps relax pelvic muscles and reduce cramping pain.

2. **Pelvic Massage**

   May relieve endometriosis-related pain. Manipulation of the pelvis and lower back improves blood flow and may ease discomfort from scar tissue

3. **Over-the-Counter Pain Relievers**

   Nonsteroidal anti-inflammatory drugs (NSAIDs) can help reduce inflammation and alleviate cramps and pelvic pain. **(Consult a healthcare provider before use.)**

4. **Dietary Changes**

   Reducing intake of gluten, dairy, sugar, and red meat has been associated with symptomatic relief in some patients.

5. **Rest**

   Practicing deep breathing, taking mindful breaks, walking, or listening to music can help reduce stress. Sufficient sleep is also crucial, as poor sleep can disrupt hormonal balance, increase inflammation, and worsen pain.

6. **Herbal Supplements**

   Turmeric, due to its anti-inflammatory properties, is being explored for its potential benefits in endometriosis. *(Further evidence needed.)*

7. **Omega-3 Fatty Acids**

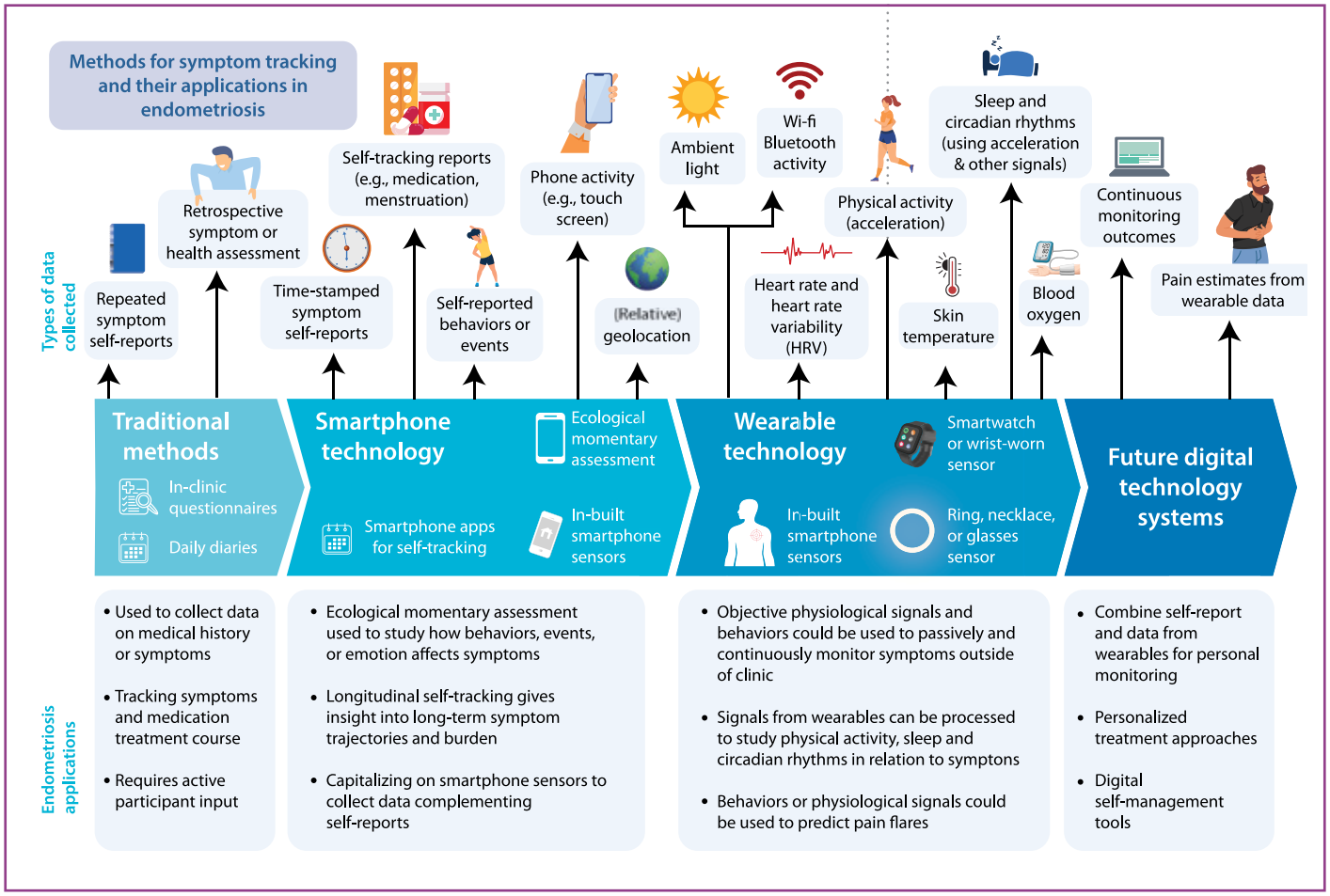
   May reduce inflammation and improve pain-related symptoms.

8. **CBD Oil (Cannabidiol)**

   Emerging as a potential pain-relief agent. Consult a physician for use in adolescents.

9. **Light Exercise**

   Regular physical activity stimulates the release of endorphins ("feel-good hormones"), which can alleviate pain.



FINAL SUMMARY

Widespread awareness, especially among rural population, is key.

Early suspicion, followed by timely detection and initiation of treatment, can lead to:

1. Significant reduction in the O-D interval (8-10 vital years)
2. Avoidance of extensive surgeries and their associated complications
3. Improved quality of life (QOL) from adolescence onwards

REFERENCES

1. Periadolescence. Last updated: April 29, 2024. Source: American Academy of Pediatrics. (Copyright © 2019)
2. Endometriosis. Last reviewed: October 2020
3. Endometriosis has been a silent epidemic. Here's how research is changing it. Dr. Christine Metz, Head of Medicinal Biochemistry & Co-Director, ROSE Study, Northwell Health
4. Endometriosis: The Importance of Early Diagnosis - Top Doctors UK (Nov 5, 2024)
5. Epigenetic Dysregulation in Endometriosis. NIH. PubMed - Marquardt RM, 2023.

   J Pathol Clin Res. 2023 Jul;9(4):302-312. doi:10.1002/cjp2.317
6. KRAS Mutations and Endometriosis Burden of Disease - NIH, 2023
7. Pathogenesis of Endometriosis: The Origin of Pain. NIH. Gruber TM, 2021. PMC8226491
8. Questionnaire-Based Screening in Adolescents. NIH. Chapron C, 2024
9. Silent Endometriosis: Missed Symptoms and Diagnosis. Healthline. Oct 16, 2024

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Emerging Non-Invasive Therapeutics for Endometriosis

INTRODUCTION

Endometriosis is among the most common gynaecological diseases, characterised by the presence of endometrium-like epithelium and/or stroma outside the endometrium and myometrium [1]. Although endometriosis is a leading cause of infertility, there are not many conclusive studies on the pathophysiology and etiology of the disease.

Given its high prevalence in countries like India and the well-known diagnostic delay, surgical intervention is considered appropriate, especially for later stages of the disease. However, surgery is often associated with complications, and the recurrence rate is considered to be more than 20% in 2 years and 40-50% in 5 years after treatment [2].

Thus, the development of novel strategies, especially non-invasive therapeutics, is needed to provide more treatment options with minimal complications. This review highlights the latest preclinical studies on biomolecules such as recombinant proteins, immunomodulators, stem cells, and RNA/gene therapies (mRNA, miRNA), which hold high potential as future therapeutic and diagnostic molecules (Figure 1).

RECOMBINANT PROTEINS

Recombinant proteins are exogenous proteins produced from living organisms or their components, used for the treatment or prevention of diseases in humans or animals. Monoclonal antibodies (mAbs) constitute a special class of recombinant proteins [3].

Recombinant human tumor necrosis factor binding protein-1 (r-hTBP-1) was among the first recombinant proteins studied in an in vivo experimental model of endometriosis. The study revealed that r-hTBP-1 is effective in reducing the size of endometriotic-like foci, particularly at later sacrifice time points, with a significant 64% reduction compared to control animals [4].

A recent study targeting the inflammatory molecule interleukin (IL-37), a natural suppressor of inflammation, indicated that recombinant human IL-37 (rhIL-37) could suppress the development of endometriosis by increasing the Th1/Th2 (T helper cells) ratio [5].

CELL THERAPY

Cell therapy is a promising area for treating endometriosis. This vast branch of therapeutic methods involves estrogen receptor activity, angiogenesis, fibrosis, and stem cells in endometriotic foci.

Defective endometrial stromal fibroblast (EMSF) function, particularly abnormal responses to hormones like progesterone, plays a critical role in the pathogenesis of various endometrial disorders, including endometriosis and endometrial cancer.

A recent study demonstrated the differentiation of human induced pluripotent stem cells (hiPSCs) to EMSF under molecularly defined embryoid body culture conditions using specific hormonal treatments. The differentiation occurred through activation of the WNT/CTNNB1 pathway, and these hiPSC-derived tissues show potential for iPSC-based endometrial regeneration [6].

Adipose tissue is a rich source of multipotent adipose-derived stem cells (ADSCs). ADSCs demonstrate effects on tissue regeneration and immune regulation. Studies have shown that ADSCs isolated from lipoaspirate and their conditioned medium (ADSC-CM) inhibit endometriosis development and improve pregnancy outcomes in mice[7].

Gene Therapy

Gene therapy for endometriosis focuses on suppressing vascularisation in endometrial lesions. Anti-VEGFA (vascular endothelial growth factor-A) siRNA delivery into endometrial implants in a rat model resulted in 55-60% inhibition of lesion growth and nearly a two-fold decrease in VEGFA gene expression compared to untreated implants [8].

Endostatin, a 20 kDa C-terminal fragment of type XVIII collagen, has shown therapeutic potential. Intralesional injection of a lipofectamine-endostatin-pBud plasmid in a rat autotransplantation model increased endostatin mRNA and protein levels, reduced MMP-2 levels, and effectively treated endometriosis [9].

NON-CODING RNAS (MICRORNAS)

As endometriosis continues to rise in severity and prevalence, identifying its etiopathogenic mechanisms remains a critical goal in modern medicine. MicroRNAs (miRNAs) play significant roles in disease pathogenesis alongside proteins. These small, non-coding RNAs (approximately 21-22 nucleotides long) regulate gene expression post-transcriptionally by targeting mRNA for degradation or translational repression[10].

This regulation occurs in both physiological conditions (e.g., cell growth, development, differentiation, proliferation, apoptosis) and pathological states (e.g., cancer, inflammation)[11].

Studies have shown differential expression of specific miRNAs in endometriotic lesions, including:

miR-1, miR-29c, miR-34c, miR-100, miR-125, miR-135, miR-141, miR-145, miR-148, miR-183, miR-194, miR-196b, miR-200a, miR-200b, miR-200c, miR-202, miR-365, miR-375.

In our own studies, we detected high expression of miR-148 in endometrial tissue with fibroids compared to healthy myometrium (Figure 2B). Additionally, immunofluorescent staining of primary endothelial cells from the same samples showed high expression of vimentin and mucin-1, suggesting their potential use as biomarkers for uterine disorders (Figure 2A).

Conclusion

Emerging preclinical studies support the efficacy of stem cells (hiPSCs), recombinant proteins, and miRNA-based therapeutics in modulating disease progression and symptoms in both endometriosis and uterine fibroids.

For dysregulated miRNAs, anti-miRNAs and mimics may be used to regulate their expression and target specific pathological pathways in endometriosis, offering promising avenues for personalised and precision therapy.

The development of nanoparticle-based delivery systems further enhances RNA therapeutic stability and bioavailability, overcoming challenges of delivery.

Endometriosis and related uterine disorders require a multidisciplinary management approach. While surgical and medical therapies remain foundational, ongoing innovations continue to improve outcomes and quality of life.

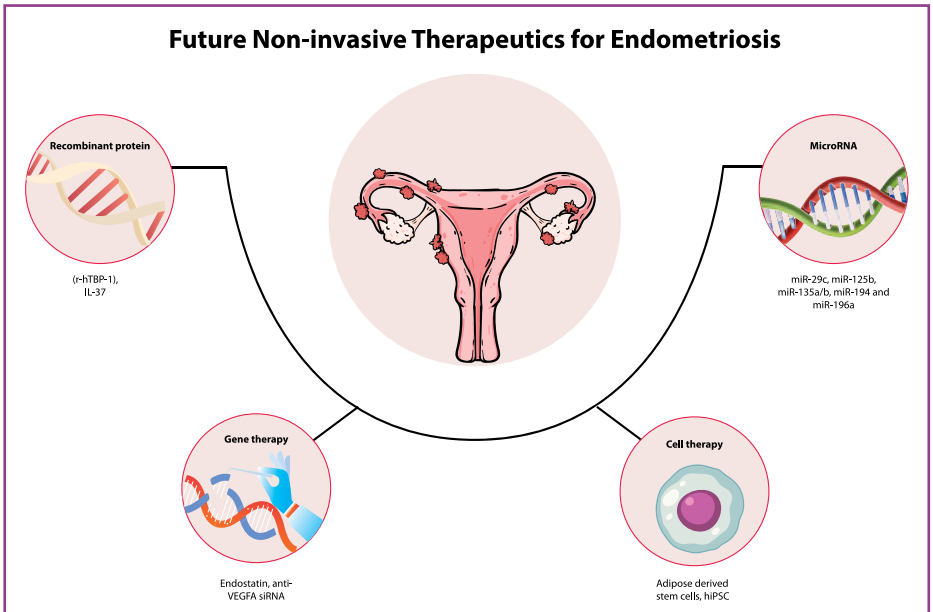

Figure 1: Schematic representation of the four categories of novel biologics considered for the therapy of endometriosis.

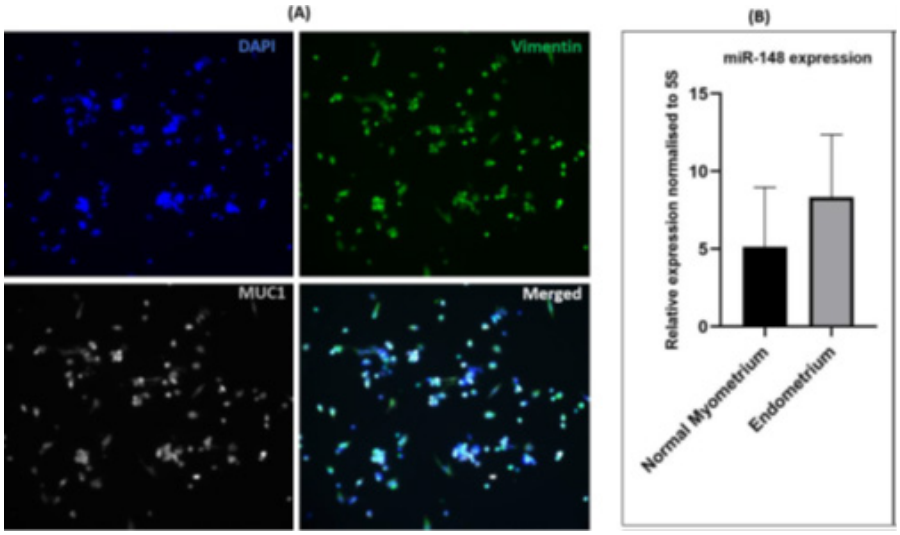

Figure 2:

(A) Immunofluorescent staining of primary endothelial cells: nuclei (blue), vimentin (green), mucin-1 (grey).

(B) qRT-PCR for miR-148 showing high expression in endometrium (Preliminary data from our ongoing study).

The evolving field of biological therapeutics holds immense promise, enabling tailored interventions and advancing the field of gynecological precision medicine. Continued research and clinical trials are essential to validate the safety and efficacy of these strategies for integration into clinical practice.

REFERENCES:

1. International working group of AAGL, ESGE, ESHRE and WES; Tomassetti C, Johnson NP, Petrozza J, Abrao MS, Einarsson JI, Horne AW, Lee TTM, Missmer S, Vermeulen N, Zondervan KT, Grimbizis G, De Wilde RL. An International Terminology for Endometriosis, 2021. J Minim Invasive Gynecol. 2021 Nov;28(11):1849-1859.
2. Huang SJ, Huang CY, Huang YH, Cheng JH, Yu YC, Lai JC, Hung YP, Chang CC, Shiu LY. A novel therapeutic approach for endometriosis using adipose-derived stem cell-derived conditioned medium-A new hope for endometriotic patients in improving fertility. Front Endocrinol (Lausanne). 2023 May 24;14:1158527.
3. Kamionka M. Engineering of therapeutic proteins production in Escherichia coli. Curr Pharm Biotechnol. 2011 Feb 1;12(2):268-74.
4. D'Antonio M, Martelli F, Peano S, Papoian R, Borrelli F. Ability of recombinant human TNF binding protein-1 (r-hTBP-1) to inhibit the development of experimentally-induced endometriosis in rats. J Reprod Immunol. 2000 Oct-Nov;48(2):81-98.
5. Li L, Liao Z, Ye M, Jiang J. Recombinant human IL-37 inhibited endometriosis development in a mouse model through increasing Th1/Th2 ratio by inducing the maturation of dendritic cells. Reprod Biol Endocrinol. 2021 Aug 24;19(1):128.
6. Miyazaki K, Dyson MT, Coon V JS, Furukawa Y, Yilmaz BD, Maruyama T, Bulun SE. Generation of Progesterone-Responsive Endometrial Stromal Fibroblasts from Human Induced Pluripotent Stem Cells: Role of the WNT/CTNNB1 Pathway. Stem Cell Reports. 2018 Nov 13;11(5):1136-1155.
7. EHuang SJ, Huang CY, Huang YH, Cheng JH, Yu YC, Lai JC, Hung YP, Chang CC, Shiu LY. A novel therapeutic approach for endometriosis using adipose-derived stem cell-derived conditioned medium-A new hope for endometriotic patients in improving fertility. Front Endocrinol (Lausanne). 2023 May 24;14:1158527.
8. Egorova A, Petrosyan M, Maretina M, Balashova N, Polyanskih L, Baranov V, Kiselev A. Anti-angiogenic treatment of endometriosis via anti-VEGFA siRNA delivery by means of peptide-based carrier in a rat subcutaneous model. Gene Ther. 2018 Dec;25(8):548-555.
9. Zhang TT, Fang XL, Gang J. Endostatin gene therapy for endometriosis in rats. J Int Med Res. 2012;40(5):1840-9.
10. Ambros V. The functions of animal microRNAs. Nature. 2004 Sep 16;431(7006):350-5. doi: 10.1038/nature02871. PMID: 15372042.
11. Begum MIA, Chuan L, Hong ST, Chae HS. The Pathological Role of miRNAs in Endometriosis. Biomedicines. 2023 Nov 17;11(11):3087.

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ELAGOLIX – The Molecule of the Future for Endometriosis Management?

Endometriosis is an estrogen-dependent, inflammatory condition marked anatomically by the presence of extrauterine lesions containing endometrial glands and stroma. Affecting an estimated 6%-10% of women, endometriosis is one of the most common gynecologic conditions among reproductive-age women.

While not all women with endometriosis are symptomatic, endometriosis-associated pain and infertility are the clinical hallmarks of the disease—affecting not only women with endometriosis, but also their partners and families. The impact of endometriosis, particularly pain symptoms, has been shown to affect quality of life and a wide range of life domains including:

- Physical functioning
- Everyday activities and social life
- Education and work
- Sex and intimacy
- Intimate partnerships
- Mental health and emotional well-being

There is also a significant emotional impact of infertility, or even concern about possible infertility, on both the patient and their relationship with their partner.

Endometriosis-associated pelvic pain often manifests as:

- Dysmenorrhea
- Non-menstrual pelvic pain (NMPP)
- Dyspareunia
- Dyschezia
- Dysuria

These symptoms play a dominant role in the disruption of patients' daily lives. Endometriosis should also be considered when a woman presents with cyclical or non-cyclical symptoms such as:

- Painful rectal bleeding or haematuria
- Shoulder tip pain
- Catamenial pneumothorax
- Cyclical cough, haemoptysis, or chest pain
- Cyclical scar swelling and pain
- Fatigue
- Infertility

Broader Impacts

Endometriosis has a substantial impact on society through direct and indirect healthcare costs. These costs are comparable to those of other chronic diseases such as type 2 diabetes, rheumatoid arthritis, and Crohn's disease. Despite its burden, a diagnostic delay of 8-12 years is common from the onset of symptoms to a reliable diagnosis.

Table 1: Hormonal Therapies for Endometriosis			
Medication	Dose	Adverse Effects	Relative Cost
Combined Hormonal Contraceptives	Oral: 1 tablet daily, skip the placebo	Nausea, spotting, headache, mood changes, breast discomfort	Low
	Vaginal ring: 1 ring every 3 weeks		Low
	Transdermal patch: 1 patch weekly		Low
Progestins	Norethindrone: 0.35 mg, 1–3 oral tablets daily	Acne, spotting, mood changes, headache, weight gain, breast discomfort	Low
	Norethindrone acetate: 5 mg, 0.5–3 oral tablets daily	Moderate	Moderate
	Dienogest: 2 mg oral daily		Moderate
	Medroxyprogesterone acetate: Depot 150 mg IM every 6–8 weeks / Oral 10–12 mg/day		Low
Progestin Subdermal Implant	Etonorgestrel: 68 mg, implant every 3 years		Low
Levonorgestrel IUS	52 mg or 19.5 mg released over 5 years	Spotting, headache, breast discomfort, functional ovarian cysts	Low (amortized over 5 yrs)

Table 2: Second-Line Therapies			
Medication	Dose	Adverse Effects & special considerations	Relative cost
GnRH Agonists		Hot flushes, headache, depression, decreased BMD, vaginal dryness Adverse effects minimized with add-back hormone replacement therapy	
Leuprolide acetate	3.75 mg IM monthly / 11.25 mg IM every 3 months		High
Nafarelin acetate	200 µg nasal spray twice daily		High
Goserelin acetate	3.6 mg IM monthly		High
Triptorelin	3.75 mg IM monthly		High
GnRH Antagonists		Hot flushes, headache, depression, decreased BMD, vaginal dryness Adverse effects minimized with add back hormone replacement therapy	
Elagolix	150 mg oral once daily / 200 mg twice daily		High
Aromatase inhibitors		Hot flushes, decrease BMD and headaches Used in combination with other medication	
Letrozole	2.5mg, oral, daily		Moderate
Anastrozole	1mg, oral daily		Moderate

Current Therapeutic Approaches

Therapeutic options aim to:

- Improve pain symptoms and fertility prospects
- Suppress endogenous estrogen levels
- Induce pro-apoptotic and anti-inflammatory effects on endometriotic tissue
- Surgically remove or destroy endometriotic lesions
- Divide adhesions
- Manage chronic pain syndromes

A wide range of pharmaceutical agents is used to manage endometriosis-related pain, though few have formal approval for this indication by regulatory authorities.

Clinical Use of GnRH Antagonists: The Case for Elagolix

Many guidelines recommend treating endometriosis-associated pain with a combination of oral estrogen and progestin as first-line therapy. However, these hormonal contraceptives:

- Fail to relieve symptoms in ~25-33% of women
- Cause adverse effects such as mood changes, breast tenderness
- Increases thrombotic risk

If ineffective, next-line options include high-dose progestins or GnRH agonists, though these have limitations:

- Resistance to progesterone is common
- GnRH agonists are long-acting, irreversible in the short term, and require injections
- **Add-back therapy** is required to reduce hypoestrogenic side effects like hot flushes and BMD loss

Danazol is rarely used due to androgenic side effects (e.g., acne,

Table 3: Mechanism of Action of Drugs Used in Endometriosis	
Drug Category	Mechanism of Action
NSAIDs	Inhibit COX-1 and COX-2 to reduce prostaglandin formation
Combined Estrogen–Progestin Contraceptives	Inhibit FSH/LH, reduce proliferation, enhance apoptosis in endometrial tissue
Progestin-Only Preparations	Suppress FSH/LH, induce regression of endometrial lesions
Androgens	Act as anti-estrogens, inhibit steroid formation, suppress gonadotropin release
Aromatase Inhibitors	Inhibit conversion of androgens to estrogen
GnRH Agonists	Initially stimulate, then downregulate GnRH receptors, causing full suppression of E2
GnRH Antagonists	Competitively block GnRH receptors; dose-dependently suppress FSH, LH, without flare-up

hirsutism).

For many women, surgery may be preferred despite recurrence risks and similar long-term efficacy as medical therapy.

The Optimal Goal of Medical Therapy

- **Lower estrogen (E2) levels** sufficiently to induce amenorrhea and relieve symptoms
- **Maintain enough** E2 to prevent severe side effects (e.g., hot flushes, BMD loss)

Partial suppression of E2 within 30-60 pg/mL may be the ideal compromise between efficacy and tolerability.

GnRH Antagonists: A Modern Advancement

GnRH antagonists like Elagolix offer:

- Dose-dependent suppression of FSH/LH without flare-up effects
- Rapid onset of action
- Reversible suppression, enabling flexibility in treatment tailoring

Unlike GnRH agonists (which cause initial stimulation and full suppression of E2), antagonists like Elagolix:

- Avoid flare-up
- Provide quick relief
- Allow fine-tuning of hormonal suppression

ELAGOLIX: A Targeted Oral GnRH Antagonist

Elagolix is the first FDA-approved orally administered therapy for endometriosis-associated pain in over a decade. It:

- Partially suppresses estradiol, reducing hypoestrogenic side effects
- Shows rapid, dose-dependent E2 suppression
  - 150 mg daily → ~42 pg/mL E2
  - 200 mg twice daily → ~12 pg/mL E2

Clinical Benefits

- Reduces pelvic pain (dysmenorrhea, NMPP, dyspareunia)
- Improves quality of life
- Decreases reliance on analgesics
- Maintains benefits during 12 months of treatment

Elagolix Drug Profile

- **Chemical Name:** Sodium 4({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6-(trifluoromethyl) phenyl]methyl}]-4-methyl-2,6-dioxa-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino) butanoate
- **Class:** Non-peptide GnRH receptor antagonist
- **Mechanism:** Competitively inhibits GnRH receptors → suppresses LH/FSH → ↓ estradiol & progesterone
- **Reversibility:** Hormone levels return rapidly upon discontinuation

Key Clinical Trials

I. ELARIS EM-I and EM-II (Phase 3)

- Randomised, double-blind, placebo-controlled
- Participants: Surgically diagnosed moderate-severe endometriosis
- Dosing: 150 mg once daily / 200 mg twice daily for 6 months
- Results:
  - N = 872 (EM-I), 817 (EM-II)
  - Completion: 74.9% (EM-I), 77.4% (EM-II)
  - **Conclusion:** Dose-dependent reduction in dysmenorrhea and NMPP. Higher doses linked to greater BMD loss.

II. ELARIS EM-III and EM-IV (Extension Studies)

- Additional 6-month treatment + 1-year follow-up
- Same dosing continued
- Supplementation: Calcium (500-1000 mg) + Vitamin D (400 IU)
- **Conclusion:** Long-term efficacy and safety were consistent; no major new safety concerns observed.

Additional Clinical Evidence: PETAL Trials

III. Phase 2 Daisy PETAL Trial

- **Design:** Multicenter, double-blind, randomized
- **Participants:** 137 women (18-49 years) with endometriosis
- **Groups:** Elagolix 150 mg daily vs placebo

- **Results:**
  - Significant ≥30% pain reduction in Elagolix group
  - Improvement across dysmenorrhea, NMPP, and dyspareunia (measured via CPSSS)

IV. Phase 2 Lilac PETAL Trial

- **Design:** Randomized, double-blind, multicenter
- **Participants:** 155 women with endometriosis
- **Groups:** Placebo, Elagolix 150 mg, Elagolix 250 mg for 12 weeks
- Results:
  - Most significant improvements were seen in the 150 mg group
  - Safety and tolerability established

V. Phase 2 Tulip PETAL Trial

- Design: Randomized, double-blind, multicenter
- Participants: 174 women with laparoscopic diagnosis
- Groups: Elagolix 150 mg, 250 mg, Leuprolide Acetate (LA), placebo
- Outcome:
  - Elagolix and LA groups had greater pain reduction than placebo
  - LA showed a higher impact on the EHP-5 pain component
  - Statistically relevant comparisons between doses and LA

Patient Selection and Recommendations

Recommended for:

Premenopausal women with surgical or clinical diagnosis of endometriosis who:

- Have endometriosis-associated pain
- Do not respond to or tolerate first-line treatments (NSAIDs, CHCs, progestins)
- Have progestin-resistant disease
- Have prior adverse reactions to oral contraceptives

Table 4: Common Adverse Reactions (≥5% incidence):

Adverse Event	ELAGOLIX 150mg Once Daily N=475 (%)	ELAGOLIX 150mg Once Daily N=475 (%)	ELAGOLIX 150mg Once Daily N=475 (%)
Hot flushes	24	46	9
Headache	17	20	12
Nausea	11	16	13
Insomnia	6	9	3
Mood changes	6	5	3
Amenorrhea	4	7	<1
Depression symptoms	3	6	2
Anxiety	3	5	3
Arthralgia	3	5	3

May be Considered as First-Line Therapy:

- Severe endometriosis-related pain
- Dyspareunia
- History of intolerance to contraceptives (mood changes, bloating, breast tenderness)

Contraindications

- Pregnancy
- Known osteoporosis
- Severe hepatic impairment (Child-Pugh Class C)
- Concomitant use with strong OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil)

Use with Caution

- History of GnRH agonist/antagonist nonresponse
- Use with CYP3A inhibitors (e.g., rifampin, midazolam): restrict duration
- Monitor with digoxin
- Potential dose adjustments with statins (e.g., rosuvastatin)
- Avoid estrogen-containing contraceptives; use non-hormonal or progestin-only contraception

Adverse Events

Serious Adverse Events (EM-1 & EM-2 trials):

- Appendicitis (0.3%)
- Abdominal pain (0.2%)
- Back pain (0.2%)

Bone Mineral Density (BMD) Considerations

BMD Effects in Clinical Trials:

- **Elagolix 150 mg once daily (6 months):**

Table 5: Dosing and Administration

Recommended Dosage and Duration of Use Dosing Regimen	Maximum Treatment Duration	Coexisting Condition
Initiate treatment with Elagolix 150mg once daily	24months	None
Consider initiating treatment with Elagolix 200mg twice daily	6 months	Dyspareunia
Initiate treatment with Elagolix 150mg once daily. Use of 200mg twice daily is not recommended.	6 months	Moderate hepatic impairment(Child-Pugh Class B)

Table 6: Drug Interactions: Effects of ELAGOLIX on other Drugs Concomitant Drug		
Drug Interactions Effects of ELAGOLIX on other Drugs Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Concomitant Drug	Clinical Recommendation
Cardiac glycosides: Digoxin		Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating ELAGOLIX in patients who are taking digoxin. If ELAGOLIX is discontinued, increase monitoring of digoxin concentrations.
Benzodiazepines: Oral Midazolam		Consider increasing the dose of midazolam by no more than 2-fold and individualize midazolam therapy based on the patient's response.
Statins: Rosuvastatin	↓ Rosuvastatin	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
Proton Pump Inhibitors: Omeprazole	↓ Omeprazole	No dose adjustment needed for omeprazole 40mg once daily when co-administered with ELAGOLIX. When ELAGOLIX is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole.

Table 7: Comparison of Elagolix with Conventional treatment options		
Parameter	GnRH Agonists	Elagolix
Administration	Injection (IM/SC)	Oral tablet
Estradiol suppression	Complete, after flare-up	Dose-dependent, without flare-up
Onset of relief	Delayed (2–4 weeks)	Fast (within days)
Reversibility	Weeks to months	Within 48 hours of cessation
Breakthrough bleeding	Breakthrough bleeding	Breakthrough bleeding
Hormonal recovery post-treatment	Hormonal recovery post-treatment	Hormonal recovery post-treatment

OCPs/COCs vs. Elagolix		
Parameter	OCPs / COCs	Elagolix
Non-responder rate	~33%	More effective, especially in severe cases
Risk of thromboembolism	Present	Lower relative risk
Menstrual irregularities	Common	None reported
Onset of effect	After 2–3 cycles	Within 1 week
Progesterone resistance	May limit effectiveness	Effective in resistant cases
Regulatory status	Off-label use	Approved for moderate-to-severe pain

Mean lumbar spine BMD change: -0.3% to -0.7%

- **Elagolix 200 mg twice daily (6 months):**
  Mean BMD change: -2.5% to -2.6%

Follow-up:

- Partial BMD recovery observed at 12 months post-treatment in extension studies
- Long-term effects on bone health and fracture risk remain under investigation

Comparison to Other Therapies:

- BMD loss with Elagolix (150 mg) was similar to Depot Medroxyprogesterone Acetate (DMPA) in a head-to-head Phase 2 study
- BMD loss from Elagolix (any dose) is less than that observed with GnRH agonists (typically -3.2% to -4.3%)

Important Notes:

- Exclude pregnancy before starting therapy
- Initiate within 7 days of menstruation onset
- Take at the same time each day, with or without food
- Use the lowest effective dose, considering symptom severity and goals

Pregnancy and Contraception Guidance

- Ovulation may still occur on Elagolix
- Effective contraception is required during treatment and for 1 week after discontinuation
- Estrogen-containing contraceptives are NOT recommended
- Progestin-only options (oral or IUS) may be considered
- If pregnancy occurs, discontinue Elagolix immediately

Pregnancy Data:

- 49 pregnancies reported in trials
- 2 congenital malformations documented
- Data insufficient to draw definitive

Table 8: Oral GnRH Antagonists Compared			
Parameter	Elagolix	Linzagolix	Relugolix
Half-life	4–6 hours	15 hours	25 hours
Dosing in Phase 3 trials	150 mg OD / 200 mg BID	75 mg OD / 200 mg OD + ABT	40 mg OD + ABT
Add-back therapy (ABT) required	Not initially used	Yes (E2 1 mg / NETA 0.5 mg)	Yes (same combination)
Total treatment duration studied	Up to 12 months	Up to 52 weeks (ongoing)	Up to 104 weeks (ongoing)
Major Phase 3 study	ELARIS 1 & 2	EDELWEISS 1 & 2	Giudice et al. 2022

conclusions on teratogenic risk

Add-Back Therapy (Under Investigation)

- Add-back therapy aims to mitigate hypoestrogenic effects (hot flushes, lipid changes)
- Data from uterine fibroid trials using:
  - **Estradiol 0.5 mg / Norethindrone Acetate 0.1 mg**
  - **Estradiol 1 mg / Cyclical Progestogen 200 mg**
- Reduced hot flushes and lipid effects observed
- Ongoing trials are assessing similar add-back combinations in endometriosis patients

Guideline Recommendations

European Society of Human Reproduction and Embryology (ESHRE) Endometriosis Guideline Development Group 2022.

GnRH antagonists are prescribed as a second line(for example, if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile.

American Society for Reproductive Medicine(ASRM), French national college of obstetrician and gynaecologist (CNGOF),and World Endometriosis Society (WES) Guidelines.

These guidelines refer GnRH antagonist as a possible therapeutic option for endometriosis related pain.

Use of Elagolix in Uterine Fibroids

Elagolix is effective and safe for treating menorrhagia in women with uterine fibroids. However, it is reported to be associated with hypoestrogenism that can be alleviated by adding estradiol/ norethindrone acetate. This systematic review and meta-analysis aimed to determine the effectiveness of elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroid by comparing: elagolix versus placebo and elagolix versus estradiol/norethindrone acetate.

The Cochrane Central Register of Controlled Trials (CENTRAL 2021, Issue 3 of 12), MEDLINE databases (1980 to December week 1, 2020), and trial registries for relevant randomized clinical trials were used.

Four randomized controlled trials with 1949 premenopausal women from 323 locations were included.

Elagolix appeared to be effective in reducing heavy menstrual bleeding caused by uterine fibroid and combination with estradiol/ norethindrone acetate was able to alleviate the hypoestrogenism side effects in premenopausal women.

Conclusion

The efficacy and safety of Elagolix for managing endometriosis-associated pain have been validated across multiple Phase 2 and Phase 3 trials.

Its oral administration, reversible action, and dose-titratable suppression of estradiol allow for a patient-friendly, flexible therapeutic approach.

Compared to traditional GnRH agonists, Elagolix is associated with:

- Fewer hypoestrogenic adverse effects
- Rapid onset and offset
- Lower risk of flare reactions
- No need for injections

Elagolix bridges the treatment gap between first-line hormonal therapies and invasive surgery. Its potential for individualized therapy, along with evolving evidence supporting add-back regimens, positions it as a next-generation option in the modern management of endometriosis.

REFERENCES

1. Nicholas Leyland, BASc, MD, MHCM, FRCSC,1 Stephanie J. Estes, MD,2, Bruce A. Lessey, MD, PhD,3 Arnold P. Advincula, MD,4 and Hugh S. Taylor, MD5- A Clinician's Guide to the Treatment of Endometriosis with Elagolix. JOURNAL OF WOMEN'S HEALTH Volume 30, Number 4, 2021. DOI: 10.1089/jwh.2019.8096.
2. Guideline of European society of Human Reproduction and Embryology. 2022 ESHRE Endometriosis Guideline.
3. Elagolix Product Information.
4. Anna Maria Rzewuska, Monika Zybowska, Ilona Sajkiewicz, Izabela Spiechowicz, Klaudia Zak, Monika Abramiuk, Krzysztof Kułak and Rafał Tarkowski. Gonadotropin-Releasing Hormone Antagonists-A New Hope in Endometriosis Treatment?. J. Clin. Med. 2023, 12, 1008. https://doi.org/10.3390/jcm12031008.
5. Hugh S. Taylor, MD Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, New Haven, CT. Use of Elagolix in Gynaecology. JULY JOGC JUILLET 2018.
6. Herv´e Fernandez a,b,c, Aubert Agostini d, Hortense Baffet e, Nathalie Chabbert-Buffetf, Philippe Descamps g, Jean-Philippe Estrade h, G´eraldine Giraudet i, Claude Hocke j, Bruno Salle k, Florence Tremollieresl, Charles Chapron m. Update on the management of endometriosis-associated pain in France. Journal of Gynecology Obstetrics and Human Reproduction 52 (2023) 102664.
7. Juliawati Muhammad, Yusnita Yusof, Imran Ahmad and Mohd Noor Norhayati. Elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroid: a systematic review and meta-analysis. Muhammad et al. BMC Women's Health (2022) 22:14 https://doi.org/10.1186/s12905-022-01596-2

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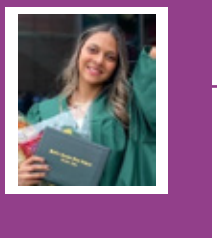

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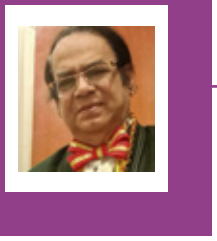

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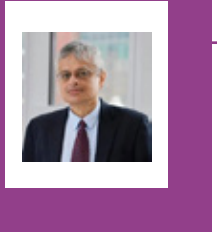

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The potential roles of anti-angiogenic agents and immune checkpoint inhibitors

INTRODUCTION

Endometriosis is a painful gynecological inflammatory disease that affects approximately 10% of women, with considerable healthcare costs ranging from $78-119 billion annually in the United States : 1. Debilitating chronic pelvic and abdominal pain is a major clinical feature of patients with endometriosis 2, 3, and current therapeutic agents such as nonsteroidal anti-inflammatory drugs, hormonal contraceptives, Gonadotropin-releasing hormone (GnRH) agonists or antagonists, progestin, and aromatase inhibitors are ineffective in a substantial proportion of patients 1,4. Furthermore, current treatments cause suppression of ovulation, which is detrimental for women with endometriosis who desire pregnancy, thereby highlighting the need for additional therapies with long-term benefits 4. In this brief review, we discuss the roles of anti-angiogenic agents and checkpoint immunomodulators in the treatment of endometriosis.

ANGIOGENESIS AND ENDOMETRIOSIS

Angiogenesis, the formation of new blood vessels, is a suitable target for endometriosis management (4-6). Similar to that in malignant tumors, the formation of adequate blood vessels is necessary for the development, growth, invasion, and recurrence of endometriotic lesions 4-6. Increased vascular density in early developing endometriotic lesions and increased concentrations of angiogenic growth factors are observed in the peritoneal fluid of patients with endometriosis, leading to the classification of endometriosis as an angiogenic disorder 6.

Vascular endothelial growth factor-A (VEGF-A), a cytokine from the vascular endothelial growth factor family, plays a critical role in several diseases, including endometriosis (4-6). VEGF-A promotes angiogenesis by acting through the vascular endothelial growth factor receptor (VEGFR-2) 7. Increased VEGF-A expression is observed in red and deep-infiltrating endometriotic lesions, and 80% of blood vessels in endometriotic lesions are immature and responsive to VEGF-A 5, 6.

Dopamine Agonists

Animal Studies

In a previous study, we demonstrated for the first time that the neurotransmitter dopamine can selectively inhibit VEGF-A-induced angiogenesis and its function by acting through its D2 receptor (DRD2) [7]. Based on this discovery, subsequent preclinical animal experiments demonstrated thatcabergoline, a DRD2 agonist, significantly decreases the number of active endometriotic lesions, cellularity, and vascularization in an experimental mouse model of endometriosis [8]. By activating DRD2 in eutopic and ectopic endometrium, cabergoline decreases VEGFR2 phosphorylation, which significantly inhibits VEGF-A function [8]. In another preclinical animal study, the effects of bromocriptine and cabergoline were examined in a rat model of endometriosis and their efficacy was compared using gonadotropin-releasing hormone (GnRH) agonists and controls. Rats were randomly divided into four study groups, and the mean surface area, histopathological glandular tissue and stromal tissue scores of the endometriosis lesions were analyzed and compared. The results indicate that DRD2 agonists are as effective as GnRH agonists in the regression of endometrial implants [9].

Clinical Studies

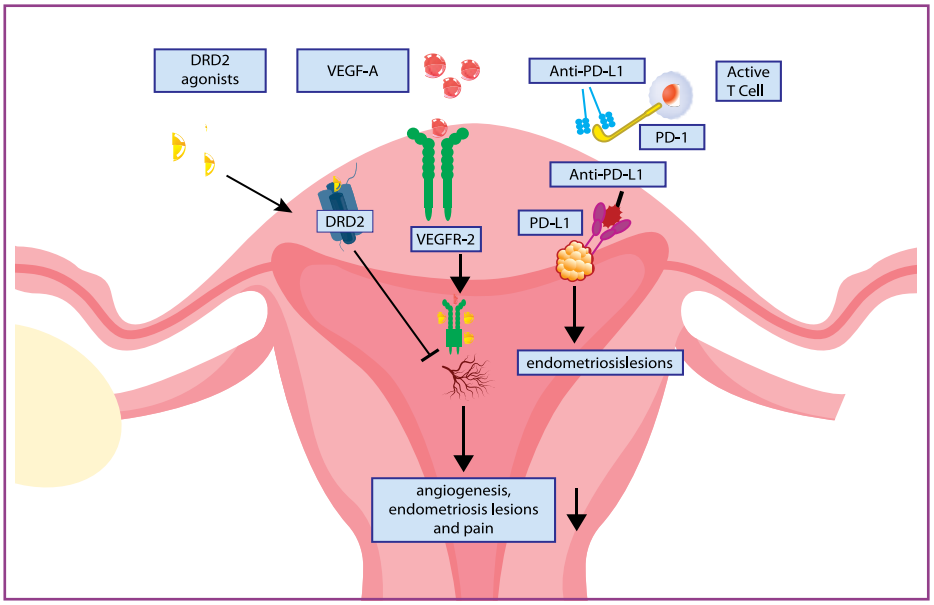
Two randomized controlled trials have been conducted to evaluate the efficacy of DRD2 agonists as an anti-angiogenic therapy for endometriosis. First, a prospective randomized trial compared the efficacy of cabergoline with that of triptorelin acetate, an agonist analog of gonadotropin-releasing hormone. The study included 140 patients with laparoscopically diagnosed endometriosis and unilateral endometriomas measuring <5 cm in diameter. Cabergoline shows

significant efficacy over luteinizing hormone-releasing hormone (LHRH) agonists in reducing the size of endometriomas 10. Similar results are observed in a more recent study that shows similar efficacy of cabergoline as that of GnRH agonists in reducing pain and endometrial implant size with minimal side effects. Another benefit of the dopamine agonists is the maintenance of a regular menstrual cycle, as 80% of women in the leuprolide group experienced amenorrhea after three doses 6, 11. A clinical trial (Clinical Trials.gov Identifier: NCT03928288) is currently underway to determine whether cabergoline is a useful adjunct to standard hormone therapy for reducing endometriosis-associated pelvic pain in adolescents and young women with surgically proven endometriosis.

Considering the association between the long-term use of ergot-derived dopamine agonists and valvular heart failure, further studies have been conducted with a non-ergot-derived selective DRD2 agonist, quinagolide, on endometriosis 6. A Phase 1 clinical program from Belgium has demonstrated that quinagolide is safe, with an efficacy comparable to that of cabergoline 6, 12. Additionally, two ongoing randomized clinical trials (Clinical-Trials.gov identifiers: NCT03749109 and NCT03692403) are evaluating the effect of quinagolide vaginal rings in reducing endometriotic lesions, particularly deep-infiltrating endometriosis and endometriomas. These studies are also investigating the efficacy of quinagolide vaginal rings in reducing endometriosis-related pain.

IMMUNE CHECKPOINTS AND ENDOMETRIOSIS

Several recent reports have demonstrated that the development of endometriosis is associated with altered systemic and local immunity, including functional disturbances in effector and antigen-presenting cells. One potential reason for the immune imbalance is the inappropriate expression of immune checkpoints. The programmed cell death protein 1/programmed death-ligand-1 (PD-1/PD-L1) pathway is one of the most studied immune checkpoints responsible for the negative regulation of T cell activity. Recent evidence suggests that the PD-1/PD-L1 pathway is important in the pathogenesis of endometriosis, making it a potential target for the treatment of this disorder [13].



CONCLUSION

Among several proangiogenic molecules, VEGF-A plays a vital role in the etiopathogenesis of endometriosis. As clinical trials indicated that DRD2 agonists are comparatively safe and can reduce endometriotic lesions and related pain, DRD2 agonists alone or in combination with currently approved drugs for endometriosis may be a suitable and effective treatment for this painful disease. Furthermore, because anti-PD-L1 and anti-PD-1 agents have shown improved efficacy when combined with anti-VEGF-A agents in some patients with cancer 14, it will be interesting to conduct studies to determine the effects of anti-PD-L1 or anti-PD-1 agents, either alone or in combination with anti-VEGF-A agents, for the treatment of endometriosis (Figure 1).

REFERENCES

1. Ellis K, Munro D, Clarke J. Endometriosis Is Undervalued: A Call to Action. Front Glob Womens Health. 2022; 3:902371.
2. Maddern J, Grundy L, Castro J, Brierley SM. Pain in Endometriosis. Front Cell Neurosci. 2020; 14:590823.
3. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell. 2021; 184:2807-2824.
4. Pellicer N, Galliano D, Herraiz S, Bagger YZ, Arce JC, Pellicer A. Use of dopamine agonists to target angiogenesis in women with endometriosis. Hum Reprod. 2021; 36:850-858.
5. Laschke MW, Menger MD. Anti-angiogenic treatment strategies for the therapy of endometriosis. Hum Reprod Update. 2012; 18:682-702.
6. Mikuš M, Vitale SG, Ćorić M, Zajec V, Ciebiera M, Carugno J, D'alterio MN, Herman M, Puževski T, Angioni S. State of the art, new treatment strategies, and emerging drugs for non-hormonal treatment of endometriosis: a systematic review of randomized control trials. Gynecol Endocrinol. 2022; 38:911-917.
7. Basu S, Nagy JA, Pal S, Vasile E, Eckelhoefer IA, Bliss VS, Manseau EJ, Dasgupta PS, Dvorak HF, Mukhopadhyay D. The neurotransmitter dopamine inhibits angiogenesis induced by vascular

permeability factor/vascular endothelial growth factor. Nat Med. 2001; 7:569-74.

8. Novella-Maestre E, Carda C, Noguera I, Ruiz-Saurí A, García-Velasco JA, Simón C, Pellicer A. Dopamine agonist administration causes a reduction in endometrial implants through modulation of angiogenesis in experimentally induced endometriosis. Hum Reprod. 2009; 24:1025-35.
9. Ercan CM, Kayaalp O, Cengiz M, Keskin U, Yumusak N, Aydogan U, Ide T, Ergun A. Comparison of efficacy of bromocriptine and cabergoline to GnRH agonist in a rat endometriosis model. Arch Gynecol Obstet. 2015; 291:1103-11.
10. Hamid AM, Madkour WA, Moawad A, Elzaher MA, Roberts MP. Does cabergoline help in decreasing endometrioma size compared to LHRH agonist? A prospective randomized study. Arch Gynecol Obstet. 2014; 290:677-82.
11. Category - adolescent gynaecology. BJOG: Int J Obstet Gynecol. 2021; 128:4-7.
12. Bagger Y, Arce J-C. Quinagolide vaginal ring for endometriosis: results from the clinical phase 1 program. Fertil Steril. 2020;114: e78.
13. Suszczyk D, Skiba W, Pawłowska-Łachut A, Dymanowska-Dyjak I, Włodarczyk K, Paduch R, Wertel I. Immune Checkpoints in Endometriosis-A New Insight in the Pathogenesis. Int J Mol Sci. 2024; 25:6266.
14. Kudo M. Scientific Rationale for Combined Immunotherapy with PD-1/PD-L1 Antibodies and VEGF Inhibitors in Advanced Hepatocellular Carcinoma. Cancers (Basel). 2020; 12:1089.

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Comparative Analysis of Laparoscopic Surgical Techniques for Adenomyomectomy:

Evaluating Intraoperative and Postoperative Outcomes and Reproductive Health

INTRODUCTION:

Adenomyosis presents significant challenges in gynecological practice, impacting women's reproductive health and quality of life. Laparoscopic adenomyomectomy has emerged as a promising surgical intervention for symptom relief and fertility preservation. However, the comparative effectiveness of different laparoscopic techniques remains unclear.

METHODOLOGY:

This retrospective study conducted at the Firm Hospital in Chennai over a five period (2019-2024) evaluated 30 patients undergoing laparoscopic adenomyomectomy using the wedge resection technique, T incision, and the four-petal technique. Inclusion criteria comprised a diagnosis of adenomyosis,confirmed by clinical evaluation and imaging, and undergoing one of the specified laparoscopic techniques. Intraoperative outcomes such as median operating time "and blood loss. Postoperative outcomes, including including pain reduction, menstrual health, reproductive outcomes, and surgical success, were assessed.

RESULTS:

The four-petal technique demonstrated superior pain management (VAS score: 1.67), resolving heavy menstrual bleeding (HMB) completely. Reproductive outcomes were similar among techniques, but the four-petal method showed a higher conception rate (33.3%). Statistical analysis confirmed significant differences in pain and bleeding reduction among techniques, favoring the four-petal approach.

DISCUSSION:

Our findings align with the existing literature, highlighting the advantages of the four-petal

technique in pain management and menstrual health improvement. The technique's potential fertility benefits underscore its effectiveness in addressing adenomyosis.

CONCLUSION:

The four-petal technique emerges as a preferred option for laparoscopic adenomyomectomy, offering superior pain management and potential fertility benefits. Individualized selection of technique based on patient-specific factors is crucial.

Keywords:

Adenomyosis, laparoscopic adenomyomectomy, postoperative outcomes, reproductive health.

INTRODUCTION:

Adenomyosis is a chronic gynecological condition characterized by the presence of endometrial tissue within the myometrium, the muscular layer of the uterine wall[1]. This ectopic endometrial tissue responds to hormonal changes, similar to the endometrial lining, often resulting in debilitating symptoms such as severe dysmenorrhea, chronic pelvic pain, menorrhagia, and infertility. [2,3] The condition significantly affects the quality of life for many women, leading to physical discomfort, emotional distress, and decreased reproductive potential. Despite its prevalence, adenomyosis remains underdiagnosed and often misunderstood, highlighting the need for effective diagnostic and therapeutic strategies [4,5].

The surgical management of adenomyosis has evolved with advancements in minimally invasive techniques, particularly laparoscopic surgery. [6] Laparoscopic adenomyomectomy, a procedure involving the excision of adenomyotic tissue, has gained prominence due to its minimally invasive nature, reduced postoperative pain, shorter hospital stays, and quicker recovery times compared to traditional open surgery. [7] However, the success and outcomes of laparoscopic adenomyomectomy can vary significantly based on the specific surgical technique employed.

This study on compares three distinct laparoscopic techniques for adenomyomectomy: the four-petal technique, wedge resection, and T incision. Each technique offers unique advantages and challenges in terms of exposure, resection, and postoperative outcomes. The four-petal technique is designed to maximize exposure to diffuse and focal adenomyosis, enabling extensive resection while preserving myometrial integrity. This method involves creating four flaps that are anchored to subendometrial tissue, ensuring adequate uterine wall thickness post-surgery. [8] Wedge resection, a more traditional approach, involves excising a wedge-shaped portion of the myometrium containing adenomyotic tissue. [9] The T incision technique entails creating a T-shaped incision in the myometrium to access and remove the adenomyotic tissue. [10]

Understanding the postoperative outcomes associated with these techniques is crucial for improving patient care. This study evaluates postoperative outcomes using the Visual Analog Scale (VAS) scores for pain and various reproductive health metrics. By investigating these outcomes, the research aims to determine which technique offers the best balance between effective adenomyosis resection, preservation of myometrial reserve, and overall patient satisfaction.

The rationale for this study stems from the need to optimize laparoscopic surgical approaches to adenomyomectomy. Despite the proven efficacy of laparoscopic methods, there is a lack of comparative data on the specific outcomes associated with different techniques. This research seeks to address this gap by providing a detailed analysis of postoperative pain, reproductive health, and other relevant clinical outcomes.

Ultimately, this comparative analysis aims to contribute valuable insights to the field of gynecological surgery, guiding clinicians in selecting the most effective laparoscopic technique for adenomyomectomy. The findings are expected to improve surgical management strategies for adenomyosis, enhancing patient outcomes and quality of life.

METHODOLOGY:

The primary purpose of this study is to evaluate the various laparoscopic surgical methods for adenomyomectomy and their postoperative outcomes, focusing on techniques such as wedge resection, T incision, and the four-petal technique. This research is a retrospective study conducted over a period of five years, from 2019 to 2024, at Firm Hospital in Chennai. The study involves 30 patients diagnosed with adenomyosis who underwent laparoscopic adenomyomectomy using one of the specified surgical methods at the Firm Hospital, Chennai. Inclusion criteria for the study include a diagnosis of adenomyosis confirmed through clinical evaluation and imaging techniques such as MRI or ultrasound, and undergoing one of the three laparoscopic surgical techniques (wedge resection, T incision, or four-petal technique).

The wedge resection technique involves excising a wedge-shaped portion of the myometrium containing adenomyotic tissue. The T incision method entails creating a T-shaped incision in the myometrium to access and remove the adenomyotic tissue. The four-petal technique maximizes exposure to both diffuse and focal adenomyosis,

involving the creation of four flaps that are anchored to subendometrial tissue, ensuring adequate uterine wall thickness post-surgery.

Data will be collected retrospectively from medical records and surgical videos, focusing on the following parameters: preoperative assessment and diagnosis of adenomyosis, detailed steps of each surgical technique documented through video footage, intraoperative and postoperative outcomes, including Visual Analog Scale (VAS) scores for pain and reproductive health metrics such as fertility rates and menstrual regularity.

The primary outcome measures include postoperative pain assessed using the VAS score post-surgery, and reproductive health evaluated based on patient reports of menstrual regularity, fertility rates, and any complications related to reproductive health.

Data will be analyzed using statistical software to compare the postoperative outcomes of the three surgical techniques. Descriptive statistics will be used to summarize patient demographics and clinical characteristics. Comparative analyses will be conducted using appropriate statistical tests (e.g., ANOVA, t-tests) to evaluate differences in VAS scores, reproductive health metrics, and overall surgical success between the three groups.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Firm Hospital. Informed consent was obtained from all patients involved in the study, ensuring adherence to ethical guidelines and patient confidentiality. By comparing the postoperative outcomes of these three laparoscopic techniques, this study aims to provide valuable insights into the most effective surgical approach for adenomyomectomy, ultimately improving patient care and clinical outcomes in the management of adenomyosis.

RESULTS:

The study analyzed 30 patients with adenomyosis who underwent laparoscopic adenomyomectomy using three different surgical techniques: wedge resection, T incision, and the four-petal technique. The study aimed to assess intraoperative outcomes such as median operating time and blood loss and, postoperative outcomes, including pain reduction, reproductive health, and overall surgical success.

Table 1 shows that most patients, approximately 73.3%, were between 31 and 40 years old, with smaller percentages in the 20-30 and 41-50 age groups, each accounting for 13.3% of the total population. Regarding the surgical techniques used, 40% of patients underwent wedge resection, while 30% underwent either the four-petal or T incision techniques. In terms of their desire to conceive after surgery, 40% of patients expressed a desire to conceive, whereas 60% did not. When it came to reproductive outcomes, 16.7% of patients conceived after the surgery, while 83.3% did not.

The descriptive statistics, as shown in Figure: A, that the average age of the patients was around 35.47 years. The median operative time for the procedures was approximately 69.93 minutes, with a range of 43 to 120 minutes . The average preoperative VAS (Visual Analog Scale) score, which measures pain, was 8.27, indicating a high level of pain before the surgery. The average preoperative heavy menstrual bleeding (HMB) score was 51.33, reflecting significant bleeding issues among the patients.

In Table 2, Postoperative outcomes varied significantly among the three surgical techniques. For postoperative pain (measured by VAS score), the four-petal technique resulted in the

Table 1: Demographic, Surgical, and Reproductive Characteristics of the Study Population

Variable	Frequency	Percent	Valid Percent	Cumulative Percent
AGE				
20 - 30 YEARS	4	13.3	13.3	13.3
31 - 40 YEARS	22	73.3	73.3	86.7
41 - 50 YEARS	4	13.3	13.3	100.0
Total	30	100.0	100.0	100.0
Surgery type				
WEDGE RESECTION	12	40.0	40.0	40.0
4 PETAL	9	30.0	30.0	70.0
T INCISION	9	30.0	30.0	100.0
Total	30	100.0	100.0	100.0
DESIRE TO CONCEIVE				
No	18	60.0	60.0	60.0
YES	12	40.0	40.0	100.0
Total	30	100.0	100.0	100.0
REPRODUCTIVE OUTCOME				
Conceived	5	16.7	16.7	16.7
Not conceived	25	83.3	83.3	100.0
Total	30	100.0	100.0	100.0

Table 2: Postoperative VAS Scores, Heavy Menstrual Bleeding, and Reproductive Outcomes by Surgical Technique									
Variable	Surgery Type	N	Mean	Std. Deviation	Std. Error	95% CI Lower Bound	95% CI Upper Bound	F	Sig.
POST-OP VAS SCORE	WEDGE RESECTION	12	5.17	1.337	.386	4.32	6.02	36.812	0.00
	4 PETAL	9	1.67	.500	.167	1.28	2.05		
	T INCISION	9	4.89	.782	.261	4.29	5.49		
	Total	30	4.03	1.847	.337	3.34	4.72		
POST-OP HMB	WEDGE RESECTION	12	17.50	22.613	6.528	3.13	31.87	5.761	0.00
	4 PETAL	9	0.00	.000	.000	.00	.00		
	T INCISION	9	32.22	25.874	8.625	12.33	52.11		
	Total	30	16.67	23.243	4.244	7.99	25.35		
REPRODUCTIVE OUTCOME	WEDGE RESECTION	12	1.92	.289	.083	1.73	2.10	1.281	0.294
	4 PETAL	9	1.67	.500	.167	1.28	2.05		
	T INCISION	9	1.89	.333	.111	1.63	2.15		
	Total	30	1.83	.379	.069	1.69	1.97		

Table 3: Reproductive Outcomes and Post-Conception Results by Surgical Technique			
SURGERY TYPE	REPRODUCTIVE OUTCOME		
	Conceived	Not Conceived	Post consumption outcome
WEDGE RESECTION	1 (8.3%)	11 (91.7%)	1= Abortion in first trimester
4 PETAL	3 (33.3%)	6 (66.7%)	1=Delivered by LSCS (Contraceptive period = 30 months) (IVF conception at FIRM) 1 – currently in second Trimester (C.P= 29 months 1- First trimester Abortion
T INCISION	1 (11.1%)	8 (88.9%)	1 = Abortion in first trimester

lowest average score (1.67), indicating the least amount of pain. In contrast, wedge resection and T incision had higher average scores of 5.17 and 4.89, respectively. The differences in pain reduction were statistically significant, with the four-petal technique showing a clear advantage. Regarding postoperative heavy menstrual bleeding, patients who underwent the four-petal technique experienced no postoperative heavy menstrual bleeding, which was a significant improvement compared to the other two techniques. Patients who had wedge resection had an average postoperative a PBAC score of 17.50, while those who underwent the T incision had the PBAC score of 32.22. Again, the four-petal technique proved to be the most effective in reducing menstrual bleeding. Reproductive outcomes did not show significant differences among the three techniques. On average, the reproductive outcome scores were similar across all groups, indicating that none of the methods had a clear advantage in terms of enhancing the likelihood of conception post-surgery.

However, in Table 3 the four-petal technique had the highest percentage of patients who conceived after surgery (33.3%), followed by the T incision (11.1%) and wedge resection (8.3%). The statistical analysis using ANOVA confirmed these findings. There were significant differences in postoperative pain and bleeding among the groups, but no significant differences in reproductive outcomes. The post-hoc analysis in table 4 further revealed that the four-petal technique significantly reduced pain and bleeding compared to the other methods. A detailed examination of the surgical techniques and their associated reproductive outcomes showed that the four-petal technique had a higher success rate for conception after surgery, with 33.3% of patients conceiving, compared to 11.1% for the T incision and 8.3% for wedge resection. However, the overall difference in reproductive outcomes among the techniques was not statistically significant.

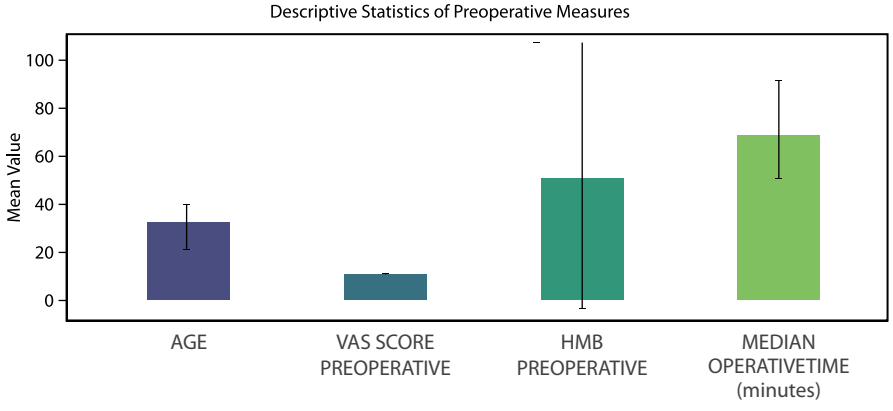
Graphs 2 and 3 that the 4-Petal Technique has the shortest median operative time (51.56 mins) with blood loss (245.5 ml). The T Incision has a moderate operative time (73.5 mins) and the lowest blood loss (226.2 ml). The Wedge technique has the longest operative time (81 mins) and moderate blood loss (248 ml). No significant mean difference in blood loss was

Table 4: Multiple Comparisons of Postoperative VAS Scores, HMB, and Reproductive Outcomes by Surgical Technique						
Dependent Variable	(I) surgery type	(J) surgery type	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval
POST-OP VAS SCORE	WEDGE RESECTION	4 PETAL	3.5	0.437	0.0	2.6 ,4.40
	WEDGE RESECTION	T INCISION	0.278	0.437	0.531	-0.62, 1.18
	4 PETAL	WEDGE RESECTION	-3.5	0.437	0.0	-4.4, -2.60
	4 PETAL	T INCISION	-3.222	0.468	0.0	-4.18, -2.26
	T INCISION	WEDGE RESECTION	-0.278	0.437	0.531	-1.18, 0.62
	T INCISION	4 PETAL	3.222	0.468	0.0	2.26, 4.18
POST- OP HMB	WEDGE RESECTION	4 PETAL	17.5	8.893	0.059	-0.75, 35.75
	WEDGE RESECTION	T INCISION	-14.722	8.893	0.109	-3.52, -32.97
	4 PETAL	WEDGE RESECTION	-17.5	8.893	0.059	-35.75, 0.75
	4 PETAL	T INCISION	-32.222	9.507	0.002	-51.73, -12.72
	T INCISION	WEDGE RESECTION	14.722	8.893	0.109	-3.52, 32.97
	T INCISION	4 PETAL	32.222	9.507	0.002	12.72, 51. 73
REPRODUCTIVE OUTCOME	WEDGE RESECTION	4 PETAL	0.25	0.166	0.143	-0.09, 0.59
	WEDGE RESECTION	T INCISION	0.028	0.166	0.868	-0.31, 0.37
	4 PETAL	WEDGE RESECTION	-0.25	0.166	0.143	-0.59, 0.09
	4 PETAL	T INCISION	-0.222	0.177	0.22	-0.59,0.14
	T INCISION	WEDGE RESECTION	-0.028	0.166	0.868	-0.37, 0.31
	T INCISION	4 PETAL	0.222	0.177	0.22	-0.14, 0.59

observed among the three surgical approaches.

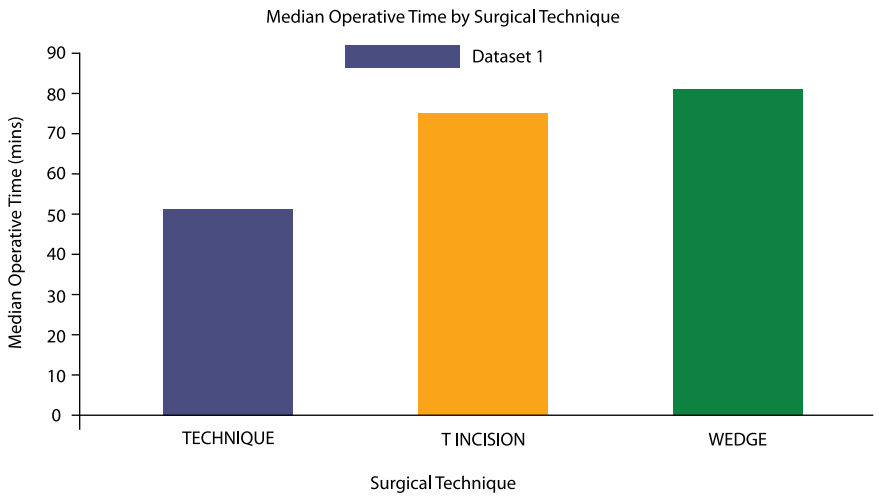
In summary, the four-petal technique demonstrated superior outcomes, including of shorter operating time, reducing postoperative pain and menstrual bleeding compared to wedge resection and T incision. While reproductive outcomes did not significantly differ among the three techniques, the four-petal technique had the highest percentage of patients who conceived post-surgery. This suggests that the four-petal technique may be the most beneficial for patients in terms of improving postoperative quality of life; however, all three techniques remain viable options ,depending on individual patient conditions and preferences.

Graph 1: The Graph Visually Represents The Descriptive Statistics Of The Preoperative Measures, Including The Mean Values And Standard Deviations For Age, VAS Preoperative Score, HMB Preoperative And Median Operative Time

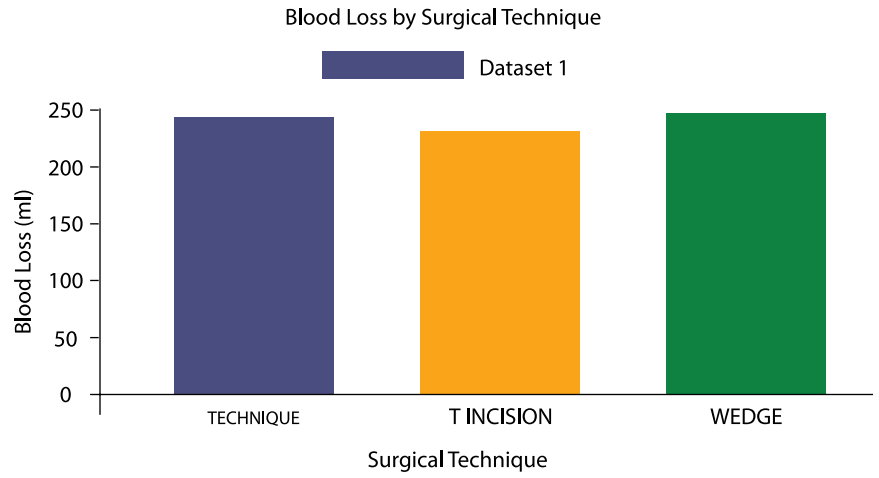


DISCUSSION:

Graph 2: Median Operative Time by Surgical Technique



Graph 3: Blood Loss by Surgical Technique



The results of this study provide a comprehensive evaluation of the intraoperative and postoperative outcomes associated with three different laparoscopic surgical techniques for adenomyomectomy: wedge resection, T incision, and the four-petal technique. This discussion delves into the implications of these findings, comparing them to existing literature, and highlighting the potential advantages and limitations of each method.

The analysis revealed significant differences in postoperative pain among the three surgical techniques. The four-petal technique demonstrated the lowest mean postoperative VAS score (1.67), indicating superior pain management compared to wedge resection (5.17) and T incision (4.89). This significant reduction in pain can be attributed to the meticulous and less invasive nature of the four-petal technique, which minimizes tissue trauma and enhances healing. The existing literature supports these findings. Stone et al. (2021) highlight the importance of standardized perioperative care for women undergoing minimally invasive gynecologic surgery. Their Enhanced Recovery After Surgery (ERAS) guideline serves as a comprehensive reference for optimizing care in this patient population. [11] Our study adds to this discourse by providing empirical evidence of the postoperative outcomes associated with different laparoscopic surgical techniques for adenomyomectomy. Potential benefits of specific laparoscopic approaches, such as wedge resection, 4-petal, and T-incision techniques, in terms of postoperative pain and reproductive health outcomes.

The four-petal technique also excelled in managing heavy menstrual bleeding (HMB). Postoperative mean PBAC scores for this technique were 35.7, indicating a complete resolution of heavy menstrual bleeding. Wedge resection and T incision had mean postoperative PBAC scores of 17.50 and 32.22, respectively. According to Hlinecka et al. (2022) they shed light shed light on the challenges faced by women with adenomyosis, including lower pregnancy rates and higher miscarriage rates compared to healthy individuals. Adenomyomectomy offers a potential solution for some of these patients, albeit with technical challenges, especially in severe diffuse cases. By comparing the clinical and reproductive outcomes of adenomyomectomy with intramural myomectomy, their study provides valuable insights into the efficacy of surgical interventions in improving fertility outcomes among this patient population. [12]

Additionally, Molotkov et al. (2023) emphasize the increasing incidence of adenomyosis among young patients yet to realize their reproductive potential. Their review underscores the importance of preserving uterine function in the surgical management of adenomyosis, aligning with the objectives of our study. By summarizing global experiences and highlighting technical considerations in surgical interventions for adenomyosis, their work provides

valuable guidance for clinicians navigating the complexities of managing this condition. [13]

Our study contributes to this discourse by specifically evaluating the four-petal technique's impact on menstrual health outcomes following adenomyomectomy. The observed improvements in menstrual health parameters among patients undergoing this technique underscore its potential as a viable surgical option for addressing both the symptomatic burden of adenomyosis and its implications for reproductive health.

While the differences in reproductive outcomes among the three techniques were not statistically significant, the four-petal technique showed a higher percentage of patients who conceived post-surgery (33.3%) compared to T incision (11.1%) and wedge resection (8.3%). This suggests a potential advantage of the four-petal technique in preserving and enhancing fertility. The thorough resection of adenomyotic tissue, combined with precise uterine reconstruction in the four-petal technique might facilitate better reproductive outcomes.

The superior outcomes associated with the four-petal technique suggest that it should be considered a preferred option for patients undergoing laparoscopic adenomyomectomy, particularly those who are concerned about postoperative pain and menstrual health. However, the choice of surgical technique should be individualized based on patient-specific factors, including the extent of adenomyosis, the patient's reproductive goals, and the surgeon's expertise.

The comparative analysis of laparoscopic surgical techniques for adenomyomectomy presented in our study sheds light on the efficacy of different approaches in improving postoperative outcomes and reproductive health. Our findings resonate with the growing body of literature addressing the challenges posed by adenomyosis and the need for effective surgical interventions to alleviate symptoms and preserve fertility.

Kuo et al. (2020) introduced the innovative four-petal method for performing laparoscopic adenomyomectomy, offering a systematic approach to address the unique challenges associated with this condition. By meticulously detailing the surgical technique and demonstrating its application in a patient with focal-type adenomyosis, their study provides valuable insights into optimizing surgical management strategies for adenomyosis. [14]

Givens et al. (2020) provided comprehensive insights into the clinical and pathophysiological aspects of adenomyosis, highlighting its impact on fertility and the challenges in its diagnosis and management. Their review underscores the importance of conservative surgical approaches, such as adenomyomectomy, for patients seeking uterine preservation while addressing symptomatic burden and fertility concerns. [15]

Furthermore, the systematic review by Mikos et al. (2020) and the retrospective comparative study by Ahn et al. (2021) offer additional perspectives on the surgical treatment of adenomyosis. Mikos et al. (2020) demonstrated that surgical excision of adenomyosis leads to significant improvements in pain, menorrhagia, and reduction of uterine volume, highlighting the efficacy of surgical interventions in controlling symptoms [16]. Ahn et al. (2021) compared laparoscopic-assisted adenomyomectomy with other surgical approaches, showing that laparoscopic-assisted surgery allows for maximal debulking of adenomyosis while retaining the advantages of the laparoscopic approach. [17]

Overall, our study contributes to the growing body of evidence supporting the efficacy of laparoscopic surgical techniques in managing adenomyosis. By optimizing surgical approaches and emphasizing uterine preservation, we aim to improve postoperative outcomes and reproductive health outcomes for patients with adenomyosis.

CONCLUSION:

This study compares three laparoscopic surgical techniques for adenomyomectomy—wedge resection, T incision, and the four-petal technique—highlighting the latter's significant advantages. The four-petal technique resulted in the lowest postoperative VAS scores, indicating superior pain management, and effectively resolved heavy menstrual bleeding in all patients. While reproductive outcomes were similar across techniques, the four-petal method showed a higher conception rate, suggesting potential fertility benefits and a highly effective effective option in treating adenomyosis and enhancing postoperative quality of life. Clinical practice should tailor the choice of technique to individual patient needs, considering the extent of adenomyosis, patient goals, and surgical expertise. This study provides valuable insights into the surgical management of adenomyosis, positioning the four-petal technique as a preferred approach, but emphasizes the need for larger, prospective studies to validate these findings and refine surgical strategies for improved patient outcomes.

ACKNOWLEDGMENT:

The authors would like to express sincere gratitude to all individuals who contributed to this study, including participants and healthcare

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professionals who assisted in data collection and analysis. Their invaluable support has been instrumental in the completion of this research.

Conflict of Interest:

The authors declare that there are no conflict of interest

REFERENCES

1. Gunther R, Walker C. Adenomyosis. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539868/.
2. Tsamantioti ES, Mahdy H. Endometriosis. [Updated 2023 Jan 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567777/.
3. Protopapas, A., Grimbizis, G., Athanasiou, S., & Loutradis, D. (2020). Adenomyosis: Disease, uterine aging process leading to symptoms, or both?. Facts, views & vision in ObGyn, 12(2), 91-104.
4. Dantkale, K. S., & Agrawal, M. (2024). A Comprehensive Review of the Diagnostic Landscape of Endometriosis: Assessing Tools, Uncovering Strengths, and Acknowledging Limitations. Cureus, 16(3), e56978. https://doi.org/10.7759/cureus.56978.
5. Taran, F. A., Stewart, E. A., & Brucker, S. (2013). Adenomyosis: Epidemiology, Risk Factors, Clinical Phenotype and Surgical and Interventional Alternatives to Hysterectomy. Geburtshilfe und Frauenheilkunde, 73(9), 924-931. . s.l. : https://doi.org/10.1055/s-0033-1350840.
6. Dessouky, R., Gamil, S. A., Nada, M. G., Mousa, R., & Libda, Y. (2019). Management of uterine adenomyosis: current trends and uterine artery embolization as a potential alternative to hysterectomy. Insights into imaging, 10(1), 48. s.l. : https://doi.org/10.1186/s13244-019-0732-8.
7. Kwack, J. Y., & Kwon, Y. S. (2017). Laparoscopic Surgery for Focal Adenomyosis. JSLS : Journal of the Society of Laparoendoscopic Surgeons, 21(2), e2017.00014. https://doi.org/10.4293/JSLS.2017.00014.
8. Kuo HH, Weng CH, Jaiswal A, et al. Performing laparoscopic adenomyomectomy with the four-petal method. Fertil Steril. 2020;114(6):1352-1354. doi:10.1016/j.fertnstert.2020.07.032.
9. Shu, S., Luo, X., Wang, Z., & Yao, Y. (2016). Fifteen cases clinical analysis of wedge-shaped resection of uterus treating adenomyosis-CONSORT. Medicine, 95(24), e3805. https://doi.org/10.1097/MD.0000000000003805.
10. Yoon, S. H., Lee, G. J., Cho, H. J., Kwon, H., Yun, B. S., Lee, C. H., Park, H. S., & Roh, J. W. (2023). Clinical efficacy of a novel method of fertility-preserving adenomyomectomy in infertile women with diffuse adenomyosis. Medicine, 102(13), e33266. . s.l. : https://doi.org/10.1097/MD.0000000000033266.
11. Stone R, Carey E, Fader AN, Fitzgerald J, Hammons L, Nensi A, Park AJ, Ricci S, Rosenfield R, Scheib S, Weston E. Enhanced recovery and surgical optimization protocol for minimally invasive gynecologic surgery: an AAGL white paper. s.l. : Journal of minimally invasive gynecology. 2021 Feb 1;28(2):179-203.
12. Hlinecka K, Mara M, Boudova B, Lisa Z, Richtarova A, Kuzel D. Comparison of clinical and reproductive outcomes between adenomyomectomy and myomectomy. Journal of Minimally Invasive Gynecology. 2022 Mar 1;29(3):392-400.
13. Molotkov AS, Yarmolinskaya MI, Tsypurdeeva AA, Shalina MA. Modern approaches to performing organ-preserving operations in adenomyosis. Journal of obstetrics and women's diseases. 2023 Jul 14;72(3):95-103.
14. Kuo HH, Weng CH, Jaiswal A, Wu KY, Wang CJ, Lee CL, Yen CF. Performing laparoscopic adenomyomectomy with the four-petal method. Fertility and Sterility. 2020 Dec 1;114(6):1352-4.
15. Givens MB, Lindheim SR, Goodman LR. New approaches in bloom: four-petal adenomyomectomy technique. Fertility and Sterility. 2020 Dec 1;114(6):1195-6.
16. Mikos T, Lioupis M, Anthoulakis C, Grimbizis GF. The outcome of fertility-sparing and nonfertility-sparing surgery for the treatment of adenomyosis. A systematic review and meta-analysis. Journal of Minimally Invasive Gynecology. 2020 Feb 1;27(2):309-31.
17. Ahn JW, You SG, Go EB, Lee SH, Kim JS, Cho HJ, Roh HJ. Minimally invasive adenomyomectomy via a laparoscopic-assisted approach compared to a laparoscopic or laparotomic approach. Taiwanese Journal of Obstetrics and Gynecology. 2021 Nov 1;60(6):1005-10.

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Study of endometriosis in women of reproductive age, laparoscopic management and its outcome

INTRODUCTION

Endometriosis is defined as a chronic and recurrent disease characterised by the presence and proliferation of endometrial glands and stroma outside the uterine cavity. It is responsible for varied and disabling symptoms and it also has an adverse impact on fertility. The incidence of endometriosis remains unknown because of the poor correlation between its presence and symptoms. The prevalence of endometriosis in reproductive women is around 10 % to 20% and endometriosis is the cause of infertility in 30% to70% of patients coming for infertility investigation.

The aetiology of endometriosis is complex and multifactorial. Even though it is benign in nature; the majority of women do not improve if left untreated. The most common symptoms of endometriosis are dysmenorrhoea, dyspareunia, pelvic pain and infertility. A large prospective study by Adamson et al, 1993 showed that laparoscopic surgery significantly increased the cumulative pregnancy rate which was confirmed by a further meta-analysis in 1994. The surgical modalities include laparoscopyand laparotomy. Medical hormone treatment has been unsuccessful in treating infertile women as it does not improve the fertility rate; but it hasaroleinprovidingsymptomaticreliefandsuppressingthe disease after laparoscopic surgery.5Laparoscopic surgery is widely used as a diagnostic and therapeutictool as it has quicker recovery time, shorter hospital stay, reduced physical and psychological stress, unlike laparotomy.

This study was done to find out the prevalence of endometriosis in the female population and to know the outcome after laparoscopic surgery.

METHODS:

The patients included in the study were in the age group 20 to 45 years with symptoms of dysmenorrhoea, dyspareunia, pelvic pain

and infertility. Pelvic examination was done and clinical findings of POD tenderness with nodular surface, restricted mobility of uterus or fixed retroverted uterus with adnexal mass either unilateral or bilateral were noted. These cases were subjected for pelvic ultrasound (USG) to look for altered pelvic anatomy and ovarian endometriomas. Diagnostic standard three-trocar laparoscopy was done under general anaesthesia, with a 10mm operating laparoscope inserted through an umbilical port and two 5mm sheaths inserted in the lower abdominal quadrants lateral to the inferior epigastric artery.

Disease staging was done using the Revised- American Fertility Society (R-AFS) classification score. Scores 1 to 5 were classified as stage 1 (minimal), scores from 6 to 15 were stage 2 (mild), scores 16 to 40 with mild adhesions were classified as stage 3 (moderate) and scores above 40 classified as stage 4 (severe). Ovarian endometriomas were a marker of severe disease

In the operative laparoscopy removal of lesions was done by:

1. Bipolar cauterisation and laparoscopic scissors.
2. The endometriomas were removed by cystectomy with maximum conservation of ovarian tissue.
3. Drainage and fulguration in very difficult cases.
4. Adhesiolysis for adhesions was done.
5. Chromopertubation was done to see tubal patency in all cases of infertility (45cases).

All the specimens retrieved were sent for histopathological (HPE) confirmation.

RESULTS

The prevalence of endometriosis (Table1) in women, who were included in the study, was found to be high (25%). The incidence of infertility was 22.5% (45) among the total cases (200) included in the study. In clinical examination, 37.5% (75 patients) were suspected to have endometriosis and subjected to pelvic ultrasound. USG pelvis revealed altered pelvic anatomy in some cases and ovarian endometriomas in 20 % (16 cases out of 75). Diagnostic/operative laparoscopy was done in 75 cases. Endometriosis was diagnosed in 50 cases, moderate to severe disease was seen in 25 cases and remaining 25 cases had minimal to mild disease. Pelvic endometriosis was the cause of infertility in 33 cases. There is increased prevalence of endometriosis in 20-30 years age group.

Table 1: The prevalence of endometriosis in various age groups.

Age group (years)	No. of patients	Prevalence (%)
20-30	25	50%
31-40	21	42%
41-45	04	8%

The prevalence of overall infertility (Table 2) was highest in the 20 to 30 years age group (78.78%). The prevalence of endometriosis was 73.33% in women suffering from infertility.

Table 2: Age wise distribution of infertility in endometriosis.

Age group (years)	Primary infertility	Secondary infertility	Prevalence (%)
20-30	20	06	78.78
31-40	02	05	21.22
41-45	nil	nil	nil

The maximum number of patients with endometriosis belongs to stage 3 (Table 3). The higher prevalence (75%) of infertility was observed in stage 3 and 4 diseases (25 out of 33 cases).

Table 3: Distribution of patients according to (R-AFS) classification and staging.

Stage of the disease	No. of patients	Prevalence of endometriosis in various stages (%)	No. of patients with infertility
Stage 1	12	24%	3
Stage 2	13	26%	5
Stage 3	15	30%	15
Stage 4	10	20%	10

A total of 16 cases had ovarian endometriomas indicating severe disease (Table 4). 10 cases had bilateral tubal block. Cystectomy was the major procedure done (Table 5).

Surgically treated cases were given leuprolide injection,
3.75 mg, intramuscularly, one dose immediately following laparoscopic surgery, before going for induction of ovulation, intrauterine insemination (IUI) or artificial reproduction technology (ART) by in-vitro fertilisation (IVF) in the follow up.

Table 4: Laparoscopic findings in women with endometriosis (50 cases).

Characteristic findings	No. of patients	Percentage
Site of endometriosis		
Ovary	16	32%
Unilateral	7	14%
Bilateral	9	18%
POD	5	10%
Posterior surface of uterus	3	6%
Uterosacral ligaments	2	4%
Adhesions(thick dense)		
Present	16	32%
Absent	34	82%
Chromopertubation (33 cases of infertility) due to endometriosis		
Unilateral patent tube	3	9.09%
Bilateral patent tubes	20	66.6%
Bilateral tubal block	10	30.30%

Table 5: The methods of laparoscopic procedures done.

Surgical procedure	Number of cases	Percentage
Cystectomy with/without adhesiolysis	12	24%
Chocolate cyst drainage with fulguration	04	08%
Adhesiolysis and remodelling of anatomy	09	18%
Bipolar cauterisation, scissor excision of deep lesions with cauterisation	25	50%

We had 25 cases in stage 3 and 4 out of which 5 patients conceived after treatment (Table 6).

Table 6: Table showing the success rate of pregnancy after laparoscopic surgery.

R-AFS stage	No. of patient	Pregnant	Percentage (%)
Stage 1	04	04	100
Stage 2	04	03	75
Stage 3	15	04	26.66
Stage 4	10	01	10

Table 7: Fertility rate as per R-AFS scoring.

R-AFS stages	Stage 1to2 (minimal to mild) [n=25]	Stage 3 (moderate) [n=15]	Stage 4 (severe) [n=10]
No of pregnancies (%)	07(28%)	04 (26.66%)	01(10%)
No of term pregnancy (%)	06 (85.71%)	04 (80%)	01(100%)

In fertile patients (17 patients) with endometriosis, Medroxyprogesterone acetate (MPA) injection, 150mg intramuscularly was given at 3 monthly interval for 3 doses and thereafter followed up for pain relief and suppression of the disease process. In these cases more than 80% of women got good relief from symptoms of pelvic pain and dysmenorrhoea. Four patients underwent TAH with BSO.

Out of the 33 cases of infertility due to endometriosis, 12 (36.36%) cases have conceived. Seven patients conceived naturally with clomiphene induction, in this one patient had spontaneous abortion. Two patients conceived by clomiphene and gonadotropin induction with IUI. Another three conceived by gonadotropin induction and ART by IVF in the nearby ART centre (one triplet and two twins).

Table 8: Comparison of pregnancy rates in various studies.

Author	No of infertile cases due to endometriosis	Stages of endometriosis as per R-AFS classification (operated)	Pregnancy rate (%)	Follow up period
Berrata al (1998)[24]	64	3 and 4	66.7%	2 years
Jones and Sutton (2002)[31]	39	2 and 3	39.5% (15)	1year
Elsheik et al (2003)[32]	151	1 to 4	53% (80)	2 years
Godinjak et al (2005)[25]	45	3 and 4	35% (15)	1 year
Fuchs et al (2007) [28]	34	1 to 4	65% (22)	8.5 months
Teksin Cirpan (2013)[33]	52	1 to 4	44% (23)	1 year
Hye Jun Lee et al (2013)[34]	43	1 to 4	41.9% (18)	1 year
Our study	33	1 to 4	37% (12)	2 years

DISCUSSION

Endometriosis remains a diagnostic as well as a therapeutic dilemma. It is considered as an enigma; hence it still intrigues researchers to addressing the cause and the management of the disease in every possible way. Endometriosis has a profound impact on quality of life, and developing a therapy that also improves fertility remains a challenge for gynaecologists. The exact mechanism by which it causes infertility is still unclear. The projected sequences of the causes of infertility in cases of endometriosis are by an altered peritoneal fluid composition as a result of hormonal, genetic and environmental factors. One of the accepted theories is increased levels of prostaglandins, proteases, and cytokines and vascular endothelial growth factor (VEGF) in the peritoneal fluid. These alterations adversely affect the mechanism of ovum pick up, sperm motility, embryo quality and poor tubal function. These altered peritoneal fluid composition and adhesions cause severe tubal dysfunction, the actual prevalence is difficult to quantify because of its very wide range in various studies across the world. In one of the studies, it has been shown that approximately 47% of women with infertility have endometriosis. In a study done by Tsuzi et al, the prevalence was 63%. In our study it is 73.33%. The diagnostic utility of USG in endometriosis is limited, but it can give corroborative evidences when there are ovarian endometriomas. Medical management accepts the basic principle of reducing inflammation, suppressing ovarian cycles and inhibiting the effect of oestrogen but its role in treatment of infertility is limited. Medical management can be used prior to surgery to decrease the size of endometriotic lesions and the extent of the operation. Conservative surgical procedures like adhesiolysis and removal of endometriotic cysts with post-operative medical therapy with OCP for more than a year can give longer duration of pain relief and delay the anatomical recurrence rates. The studies in the Table 8 include observational studies, randomized controlled studies and non-randomized studies. The pregnancy rate in our study was 36.36%. The fertility outcome was better with stage 1 and stage 2 disease (87.5%). The success rate in moderate to severe disease was 20%. It was better in patients who underwent cystectomy in severe disease. After surgical treatment, the pregnancy rate and live birth rate did improve.

The recent advances in operative laparoscopy have changed the view in the management of endometriosis with infertility. The laparoscopic treatment involves the identifying and removal of lesions by cauterization, fulguration or laser evaporation for minimal to mild disease, adhesiolysis, excision of deep lesions, cystectomy, drainage and coagulation for endometriomas of ovary (moderate to severe disease). A randomized controlled trial (RCT) was done by the Canadian collaborative study on endometriosis reveal a definite improvement in fertility rate. Based on a systematic review and meta-analysis, the ESHRE guideline has proposed that ablation of endometriotic lesions with adhesiolysis in minimal to mild endometriosis improves fertility. A more recent meta-analysis revealed that the pregnancy rate increases after laparoscopic ablation in women with stage 1 and 2 endometriosis. Laparoscopic cystectomy for ovarian endometrioma (size more than

3-4cm: stage 3 and 4) results in improvements in pregnancy rates as compared with cyst drainage and coagulation. In our study too we found a better outcome with cystectomy. The evidences from observational studies suggest that women who have stage 3 and 4 endometriosis without any other identifiable infertility factors may benefit from surgical treatment. A study by Charles Chaperon et al used surgical modality of treatment for endometriosis involving the uterosacral ligaments and obliteration of cul-de-sac. The overall intrauterine pregnancy rate, including births and abortions, was 50% (15 patients). 11 had spontaneous intra uterine pregnancy remaining 3 had induction of ovulation and one pregnancy occurred after IVF. 12 gave birth normally at term; one had an ectopic and remaining two had miscarriage. Fuchs F et al studied 64 patients with infertility in all stages by operative laparoscopy. 20 patients dropped out of study, 65% (22) patients became pregnant within 8.5 months. 89% with stage 1 and 2 and 56% with stage 3 and 4 got pregnant within one month post-surgery. They recommend complete surgical treatment for such patients to increase their chance of conceiving spontaneously or by ART. In a study by Sahu L et al, the fertility rate was 46%. In our study the fertility rate is (36.36%) comparatively lesser than other studies. The probable reason could be the higher prevalence of moderate to severe disease in infertile patients (75.75%) and many patients with severe disease were unwilling to undergo ART due to financial constraints. It is generally believed the prevalence of endometriosis is less common in India, but in our study in the Wayanad district of Kerala it was 25% of all the reproductive women studied. The most common site was in the pelvis with obliteration of cul-de-sac and ovarian endometriomas (Figure 1 and 2). The diagnosis can be well established in all cases by laparoscopy and HPE confirmation.

Figure 1: Showing powder burn red lesions (stage I).

Figure 2: Showing ovarian endometrioma, obliteration of cul-de sac with peritoneal adhesions (stage IV).

CONCLUSIONS

Patients with symptoms of dysmenorrhoea, dyspareunia, pelvic pain, infertility and clinical signs of cul-de-sac tenderness with nodular surface, restricted mobility of uterus or fixed retroverted uterus with adnexal mass along with USG findings should raise the suspicion of endometriosis in infertility patients. In infertile patients with stage III/IV endometriosis, surgical management can be recommended for better results in fertility rates. Patients with stage 1 and 2 disease also benefit after operative surgery. The diagnostic and therapeutic dilemma of endometriosis in infertility patients can be solved by laparoscopy. Laparoscopy remains the gold standard for diagnosing the disease; staging and surgically managing such cases. dilemma of endometriosis in infertility patients can be solved by laparoscopy. Laparoscopy remains the gold standard for diagnosing the disease; staging and surgically managing such cases.

Figure 1: Showing powder burn red lesions (stage I).

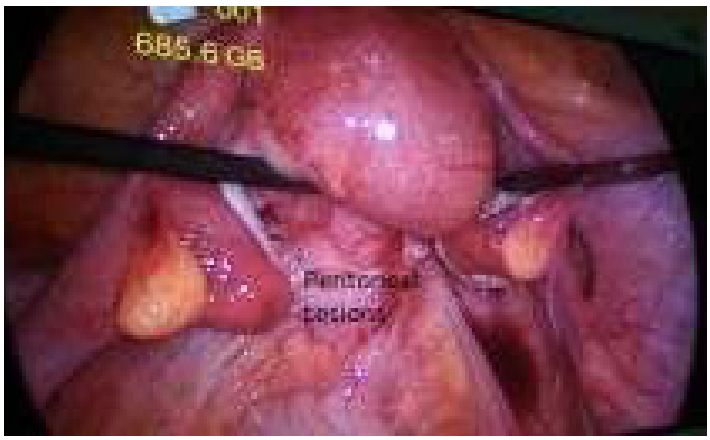
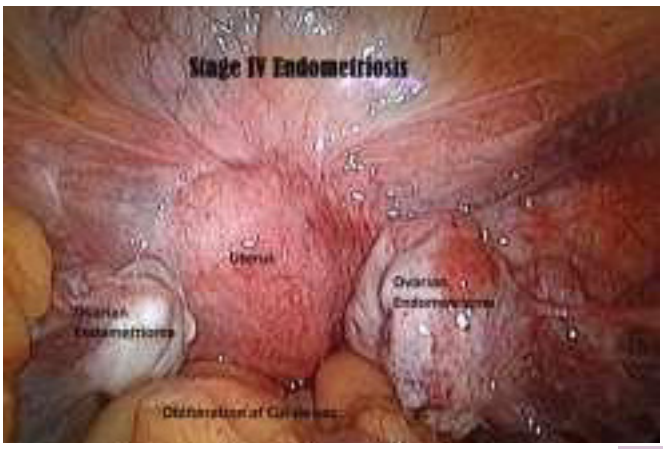


Figure 2: Showing ovarian endometrioma,obliteration of cul-de sac with peritoneal adhesions (stage IV).



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An update on endometriosis biomarkers

ARTICLE 1 :

Key Takeaways from the Article:

Endometriosis Overview:

Endometriosis is a chronic gynecologic disorder causing pelvic pain, infertility, and reduced quality of life. Diagnosis is often delayed by 8-10 years, resulting in a worsened severity and significant societal and economic burdens.

Current Diagnostic Challenges:

The gold standard for diagnosis is histological confirmation via tissue biopsy. Non-invasive diagnostic methods, such as biomarkers, are being explored to improve early detection and reduce costs.

Biomarkers for Endometriosis:

No single biomarker has been validated for the diagnosis of endometriosis Emerging biomarkers include inflammatory markers (e.g., IL-6, IL-8, TNF-α), angiogenesis-related markers (e.g., VEGF, leptin), immunologic markers (e.g., Th17, ANXA2), and epigenetic markers (e.g., SF-1, ER-β). MicroRNAs (miRNAs) show promise as biomarkers , but further research is needed due to variability among patients.

Imaging Techniques:

Transvaginal ultrasound (TVUS) is highly effective for diagnosing ovarian endometriomas. MRI is a second-line option, but is costly and has comparable accuracy to TVUS diagnosing deep endometriosis. Combining imaging with biomarkers may enhance diagnostic accuracy.

Research Limitations & Future Directions:

Studies on biomarkers often have small sample sizes and inconsistent methodologies, making comparisons difficult. Standardization of research methods is needed to validate biomarkers. Further investigation into serum biomarkers and miRNAs is necessary. Combining biomarkers with imaging and clinical predictors may lead to the development of non-invasive diagnostic panels for endometriosis.

Clinical Implications & Economic Impact:

Biomarkers may eventually help measure surgical outcomes and guide patient counseling and treatment selection. Endometriosis remains underdiagnosed and poorly treated, highlighting the need for innovative diagnostic approaches. Endometriosis imposes a significant economic burden, with studies showing billions in annual income loss due to work absences.

Conclusion:

Endometriosis is a complex and underdiagnosed condition.

While promising biomarkers and imaging techniques are emerging, further research and standardization are required to develop reliable, non-

LE KN, Nezhat C, Nezhat C, Benor A, Decherney A. Minerva Obstet Gynecol. 2024 Oct;76(5):458-469.doi: 10.23736/S2724 606X.23.05369-1. Epub 2024 Apr 10. PMID: 38602013.

invasive diagnostic methods.

ARTICLE 2

Bonocher CM, Montenegro ML, Rosa E Silva JC, Ferriani RA, Meola J. Endometriosis and physical exercises: a systematic review. Reprod Biol Endocrinol. 2014 Jan 6;12:4. doi: 10.1186/1477-7827-12-4. PMID: 24393293; PMCID: PMC3895811.

Key Takeaways from the Article

Objective of the Review:

The study aimed to assess the relationship between physical exercise and the prevalence and/or improvement of symptoms associated with endometriosis.

Potential Role of Physical Exercise:

Regular physical exercise may have protective effects against inflammatory diseases by increasing anti-inflammatory cytokines and reducing estrogen levels. Exercise could potentially reduce menstrual flow, ovarian stimulation, and estrogen action, which are factors associated with to endometriosis.

Findings from Selected Studies:

Six studies were reviewed; however their results were inconclusive and not directly comparable. Some studies suggested a protective effect of regular physical exercise against endometriosis, particularly when performed at high intensity or for longer durations. Pain associated with endometriosis may limit the ability of women to engage in physical exercise, potentially skewing results.

Limitations of Current Research & Recommendations for Future Research:

The reviewed studies were observational, lacked statistical significance, and did not include controlled or randomized trials. There is no definitive evidence to suggest that physical exercise prevents or alleviates endometriosis symptoms. Controlled and randomized studies are needed to determine the real role of physical exercise in preventing or treating endometriosis.

Experimental models could help clarify the impact of exercise intensity and duration on the disease.

Conclusion:

The available literature is inconclusive regarding the benefits of physical exercise for women with endometriosis. Further research is necessary to bridge the gap and provide evidence-based recommendations. This article highlights the potential of physical exercise as a therapeutic or preventive measure for endometriosis but emphasizes the need for more robust studies to confirm its efficacy.

Endometriosis Society India

[Established in 2003]

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