03 - ENDOMETRIOSIS

GYAN - VAHINI

FROM

FOGSI, FOOD DRUGS & MEDICOSURGICAL EQUIPMENT COMMITTEE

March - 2025

Message From Dr. Sunita Tandulwadkar

Dr. Sunita Tandulwadkar

President FOGSI-2025

Endometriosis is far more than a gynecological diagnosis—it is a deeply complex condition that challenges our understanding of chronic pelvic pain, infertility, and the psychosocial burden carried silently by countless women. As the President of FOGSI, I strongly believe that our role is not only to raise awareness but to ensure that cutting-edge science is translated into practical, accessible, and ethical care for every woman across India.

This special issue of the FDMSE E-Magazine stands as a testament to that commitment. It brings together a powerful spectrum of insights—from the latest pharmaceutical innovations and advances in hormonal and non-hormonal therapies to the growing role of medical nutrition, dietary interventions, and complementary approaches in improving quality of life. The evolution of diagnostic technologies, patient monitoring tools, and point-of-care devices are helping us reduce the long-standing delays in diagnosis—an essential step in timely intervention.

Surgical excellence too finds its place here, with a focus on fertility-preserving, minimally invasive techniques and state-of-the-art excision tools that offer precision with compassion. Importantly, this issue does not overlook the pillars of safe practice—offering clear discussions on ethical considerations, regulatory updates, and clinical trial data that ensure patient safety remains central to innovation.

FOGSI's strategic vision for 2025–2027 emphasizes building capacity among practitioners, expanding access to advanced therapies, and placing patient-centered outcomes at the heart of our efforts. Let us also advocate for stronger policies that include insurance coverage for proven therapies and integration of endometriosis counselling into reproductive health programs nationwide.

I extend my heartfelt gratitude to the FDMSE Committee and each contributor for shaping this landmark issue. Together, by bridging science with sensitivity and technology with empathy, we can transform the endometriosis journey from one of struggle to one of strength and healing.

Warm regards,
Dr. Sunita Tandulwadkar
President, FOGSI 2025

Message from Dr Abha Singh

Dr. Abha Singh
Vice President FOGSI-2025

Dear Fogsians, Warm Greetings!

It is with great pride, I welcome you to this edition of **Gyan Vahini** on **"Endometriosis"** which has been comprehensively curated by Dr Asha Jain and team members of FDMSE committee .

Endometriosis is no longer a niche sub-specialty topic; it is a public health issue. The breadth of subjects in this E- magazine ranging from nutrition science, complimentary medicine, clinical trials and pharmacological research reflects how multidisciplinary our response must be. For the practicing gynecologist these articles provide practical framework: when to escalate from medical to surgical therapy, how to integrate dietetic counselling and where to position emerging digital tools in long term follow-up.

The human dimension is equally important. Many women endure a decade of symptoms before receiving a definitive diagnosis. This delay is fueled by stigma, the normalization of menstrual pain and fragmented care pathways. I request every reader to initiate at least one awareness activity this month - host a school session to debunk myths about dysmenorrhea, publish a patient facing infographic on red flag symptoms or collaborate with pain specialists to create integrated clinics. These small, decentralized efforts, multiplied across FOGSI'S vast network, will accelerate cultural change and foster earlier help- seeking behavior.

From leadership stand point, we must also invest in the next generation. The pieces on educational resources for providers and imaging guidelines offer readymade curriculum for residency programs. Incorporating these modules in our patient care will ensure that tomorrows clinicians enter practice with a sharper diagnostic acumen and a holistic approach to management.

Let us harness the momentum of Endometriosis AWARENESS Month to build a healthcare ecosystem where no women's pain is dismissed and comprehensive evidence-based care is the standard for every woman.

Wishing all women pain free periods and happy reading to all.

Warm Regards,

Dr Abha Singh
Vice President North Zone Fogsi

Message from Dr Suvarna Khadilkar

Dr. Suvarna Khadilkar
Secretary General FOGSI-2025

I am happy that the **FDMSE** committee is releasing this March 2025 edition of **E- magazine** It focuses on endometriosis through a broad lens—capturing biomedical advances, lifestyle interventions, health system barriers, and the lived experiences of patients navigating a chronic, often invisible disease.
Our contributors dissect hormonal safety profiles, compare non hormonal analgesic protocols, and provide clarity on regulatory updates which will help everyday prescribing. What strikes me most is the emphasis on ethical decision making—a reminder that, while we pursue surgical precision and pharmacologic efficacy, we must safeguard informed consent, fertility aspirations, and mental health well being.

Together, we can shorten referral pathways and ensure that rural clinics are as well equipped as metropolitan centres to suspect, counsel, and initiate first line therapy.

Finally, data remain our guiding compass. I urge members to contribute de identified patient outcomes to multicentre registries highlighted herein. These datasets will not only refine our national guidelines but also bolster advocacy efforts for reimbursement of diagnostic laparoscopy and advanced imaging. By coupling robust evidence with grassroots dissemination, FOGSI will continue to drive equitable, ethical, and evidence based care for women with endometriosis.

With best and warm wishes,
Dr. Suvarna Khadilkar
Secretary General, FOGSI

Dr. Asha Jain
Chairperson
FOGSI FDMSE Committee

FOREWORD

At the outset, I extend my sincere gratitude to our dynamic FOGSI leadership—***President Dr Sunita Tandulwadkar, Secretary General Dr Suvarna Khadilkar, and VP-In-charge Dr Abha Singh***—whose constant encouragement powers every FDMSE Committee initiative.

Endometriosis Awareness Month reminds us that one in ten women still endure years of pain before a diagnosis. This special issue of the FOGSI-FDMSE E-Magazine aims to shorten that journey with concise, multidisciplinary guidance for earlier recognition and compassionate, personalised care.

My heartfelt thanks to our sixteen contributors whose expertise lights up these pages: ***Dr Jyothi G S, Dr Sonal Gupta, Dr V Nirusha Priya, Dr Sugandha Goel, Dr Sandhya Rani, Dr Prabhdeep Kaur, Dr Sreedevi Vellanki, Dr Ramani Devi, Dr Padmaja, Dr Okram Sarda Devi, Dr Meena Samant, Dr Sujaysri Sangita, Dr Monika Gupta, Dr Ishan Shah, Dr Neetha George, and Dr Ruche Bhargava***. Their articles span rapid imaging, minimally invasive surgery, fertility preservation, pain science, and psychosocial support—practical tools every clinician can apply tomorrow.

A special word of appreciation to ***Mr Bhupendra*,** whose creative layouts convert dense science into an inviting, reader-friendly experience.

Read, share, and act. Early listening, tailored therapy, and strong clinical networks can spare women needless pain and lost potential. Let's ensure no woman with endometriosis remains unheard.

Warm regards,
Dr Asha Jain
Chairperson, FOGSI FDMSE Committee (2025 – 2027)

"Know Your Numbers" is an ambitious health initiative.

- This project seeks to gather vital health data- Weight, Blood pressure, Blood Sugar Level with HbA1C, and Hemoglobin level -from women across India.
- By focusing on these key health indicators, the project aims to foster a proactive health management culture among women.
- The data collected will be instrumental in identifying prevalent health issues early and promoting interventions that can significantly reduce the incidence of che diseases.
- This initiative not only emphasizes the importance of regular health monitoring but also strives to empower women with the knowledge and tools needed to take charge of their health, ensuring they lead longer, healthier lives.
- Collect key health data: weight, blood pressure, blood sugar, HbA1C, and hemoglobin from women across India.
- Encourage proactive health management for early identification of prevalent health issues.
- Promote timely interventions to reduce chronic disease incidence.
- Empower women with knowledge and tools for better health and longevity.
- Gather vital health data: weight, blood pressure, blood sugar (HbA1C), and haemoglobin levels from women across India.
- Foster proactive health management among women.
- Identify prevalent health issues early and promote timely interventions.
- Reduce the incidence of chronic diseases through regular monitoring.
- Empower women with knowledge and tools for healthier, longer lives.

SURVEY FOR KNOW YOUR NUMBER (KYN) PROJECT

Do Teeke Zindagi Ke

As part of my upcoming tenure as the President of FOGSI, I am pleased to submit a proposal for a comprehensive training program on HPV vaccination, targeting 50,000 members of the Indian Medical Association (IMA). This initiative aligns with our shared goal of enhancing public health through preventive care, and I am confident that, with your support, we can make a significant impact in addressing cervical cancer awareness and prevention across India. 9-14 age group we will conduct the drive for increasing awareness of cervical cancer vaccination

Study on Understanding the Acceptance and Usage Patterns of Various Contraceptive Methods Among Women in India

Aims & Objectives

- To determine the prevalence of usage and type of contraceptives in various age groups across different demographic regions in India

- To identify whether contraception is used or not
- To identify the most commonly used contraception in men and women across India

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01

Latest Pharmaceutical Advancements in Endometriosis Treatment

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Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disorder characterized by the ectopic presence of endometrial-like tissue outside the uterus. This condition affects approximately 10% of reproductive-aged women and is a leading cause of chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility.

The exact etiology of endometriosis is not fully understood, but proposed mechanisms include retrograde menstruation, immune dysfunction, coelomic metaplasia, and stem cell involvement.

Traditionally, the management of endometriosis has included surgical excision and medical therapies aimed at suppressing ovarian function. While surgery remains an option, particularly in cases of severe pain or infertility, recurrence rates are high, and surgery alone is rarely curative. Existing pharmacologic treatments, including Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Combined Oral Contraceptives (COCs), progestins, and Gonadotropin- Releasing hormone (GnRH) analogs, offer symptom relief but often have limitations in terms of side effects, tolerability, and long-term safety.

Recent advancements in our understanding of the molecular mechanisms underlying endometriosis have paved the way for novel pharmaceutical approaches. These include next-generation GnRH antagonists, Selective Progesterone Receptor Modulators (SPRMs), estrogen receptor modulators, immune-targeting agents, and innovative drug delivery systems. Such therapies

aim not only to alleviate symptoms but also to target the disease process itself, potentially offering improved outcomes with fewer side effects.

This chapter will explore the latest pharmaceutical advancements in endometriosis treatment, focusing on emerging therapies, their mechanisms of action, clinical efficacy, and potential role in reshaping the management of this complex disease.

Approved Pharmaceutical Treatments for Endometriosis

1. GnRH Antagonists (Next-Generation)

GnRH antagonists have emerged as a significant advancement over traditional GnRH agonists by providing rapid suppression of gonadotropin secretion without the initial flare effect associated with agonists.

A. Elagolix

- **Approval**: FDA-approved (2018) for moderate-to-severe endometriosis-associated pain.
- **Mechanism of Action:**

Elagolix is an **oral GnRH antagonist** that **competitively inhibits GnRH receptors** in the pituitary gland.

This leads to a **dose-dependent suppression of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH)**, reducing ovarian estradiol production and endometriotic lesion activity.

Unlike GnRH agonists, **it does not induce an initial estrogen flare**, leading to a more immediate therapeutic effect.

- **Clinical Efficacy:**

Studies (EM-I and EM-II trials) demonstrated significant reductions in dysmenorrhea and non-menstrual pelvic pain.

- Higher doses: 200 mg twice daily, provided greater symptom relief but were associated with increased side effects.

Side Effects:

- Hypoestrogenic symptoms: Hot flashes, night sweats, headaches.
- Bone mineral density loss: dose-dependent; necessitating limiting the treatment duration.
- Mood disturbances: including depression and anxiety.

B. Relugolix

Approval: Approved in Japan for endometriosis; FDA-approved (2021) in combination with estradiol and norethindrone acetate for uterine fibroids (Myfembree®).

Mechanism of Action:

- Relugolix is a GnRH antagonist that suppresses ovarian estrogen production.
- Combined with Estradiol (E2) and Norethindrone Acetate (NETA) to mitigate bone loss and vasomotor symptoms.

Side Effects:

- Nausea, headache, and fatigue
- Venous Thromboembolism (VTE) risk due to estrogen component
- Menstrual changes

C. Linzagolix

- Approval: European Medicines Agency (2022) for uterine fibroids, under investigation for endometriosis

- Mechanism of Action:
- GnRH antagonist that provides flexible estrogen suppression, allowing partial suppression to minimize side effects.

Side Effects:
Similar to Elagolix: hot flashes, headache, decreased bone density

2. Progestins
A.Dienogest

- **Approval**: EMA-approved for endometriosis, available in some countries
- **Mechanism of Action:**

Suppresses Ovulation: Inhibits the release of gonadotropins (LH and FSH), preventing ovulation and reducing hormonal fluctuations.
Endometrial Atrophy: Reduces the size and activity of endometriotic lesions by mimicking progesterone's effects on the tissue.
Reduces Inflammation: Modulates the immune response to decrease the inflammatory process that contributes to endometriosis symptoms.

Side Effects:
Menstrual Irregularities: Spotting, breakthrough bleeding, or absence of periods.
Mood Changes: Possible mood swings or depressive symptoms.
Headaches: Some women may experience headaches or migraines.
Weight Gain or Bloating: Fluid retention and mild weight changes can occur.

B. Norethindrone Acetate

- **Approval**: FDA-approved for endometriosis treatment
- **Mechanism of Action:**

- Progestin that suppresses estrogen-driven endometrial proliferation and reduces inflammatory mediators.

Side Effects:

- Nausea, bloating, weight changes
- Androgenic effects: acne, hirsutism

3. Combined Hormonal Contraceptives (CHCs)

- **Examples:**
- Ethinyl estradiol + Drospirenone (Yaz)
- Ethinyl estradiol + Norethindrone (Loestrin)

Approval: Widely used off-label for endometriosis

Mechanism of Action:

- Suppresses ovulation and stabilizes endometrial tissue, reducing lesion growth and inflammation.

Side Effects:

- Nausea, breast tenderness, VTE risk

4. Aromatase Inhibitors (Used Off-Label)

Examples: Letrozole, Anastrozole

Mechanism of Action:

Inhibit aromatase enzyme, blocking estrogen synthesis in endometriotic lesions and systemically.

Side Effects:

- Joint pain, fatigue, osteoporosis with long-term use

Approved Pharmaceutical Treatments for Endometriosis

Drug	Class	Dose (Oral)	Duration	Consideration
Elagolix	GnRH antagonist	150 mg once daily (mild-moderate symptoms) OR 200 mg twice daily (severe symptoms)	24 months (150 mg) / 6 months (200 mg)	Higher dose associated with more bone loss
Relugolix + Estradiol + Norethin	GnRH antagonist+ Estrogen	40 mg Relugolix + 1 mg Estradiol + 0.5 mg	24 months	Add-back therapy reduces hypoestrogenic effects
drone e	progestin add-back therapy	Norethindrone once daily		
Linzagolix	GnRH antagonist	75 mg once daily (partial suppression) OR 200 mg once daily (full suppression)	Under investigation for endometriosis	Available in Europe for uterine fibroids
Dienogest	Progestin	2 mg once daily	Long-term use possible	Often used as monotherapy
Norethindrone Acetate	**Progestin**	5–15 mg once daily	Long-term use possible	Androgenic side effects at higher doses
Combined Hormonal Contraceptives (COCs)	**Estrogen-Progestin**	Standard low-dose COCs (e.g., Ethinyl Estradiol 20–35 mcg + Progestin)	Long-term	Used off-label for symptom control
Letrozole, Anastrozole (Off-label)	**Aromatase Inhibitors**	2.5 mg once daily (Letrozole) OR 1 mg once daily (Anastrozole)	Usually 6– 12 months	Combined with progestins or GnRH analogs to prevent ovarian stimulation

Non-Hormonal and Novel Approaches

Immune-Modulating Therapies

Monoclonal Antibodies Targeting Inflammatory Pathways:

- Anti-TNF agents (Infliximab, Adalimumab): Studied for their potential to reduce inflammation-driven progression.
- IL-6 Inhibitors (Tocilizumab) and JAK Inhibitors (Tofacitinib): Target cytokines involved in endometriosis-associated inflammation.

Neuromodulators and Pain-Targeted Therapies

- **Dienogest with Gabapentinoids:** Studies suggest that combining hormonal therapy with neuropathic pain modulators improves chronic pelvic pain management.
- **Cannabinoid-Based Therapies:** Under investigation for their potential role in modulating pain pathways in endometriosis.

Future Directions and Ongoing Clinical Trials

- **Gene Therapy and Epigenetic Modulators:** CRISPR and histone deacetylase inhibitors are being explored for modifying disease expression.
- **Personalized Medicine Approaches:** Pharmacogenomics to tailor treatment based on individual genetic profiles.

Conclusion

The landscape of endometriosis treatment is evolving with novel pharmaceutical advancements. The shift towards targeted, patient-specific therapies promises improved outcomes, reduced side effects, and better management of this chronic disease. Continued research is essential to refine these approaches and ensure accessibility for patients worldwide.

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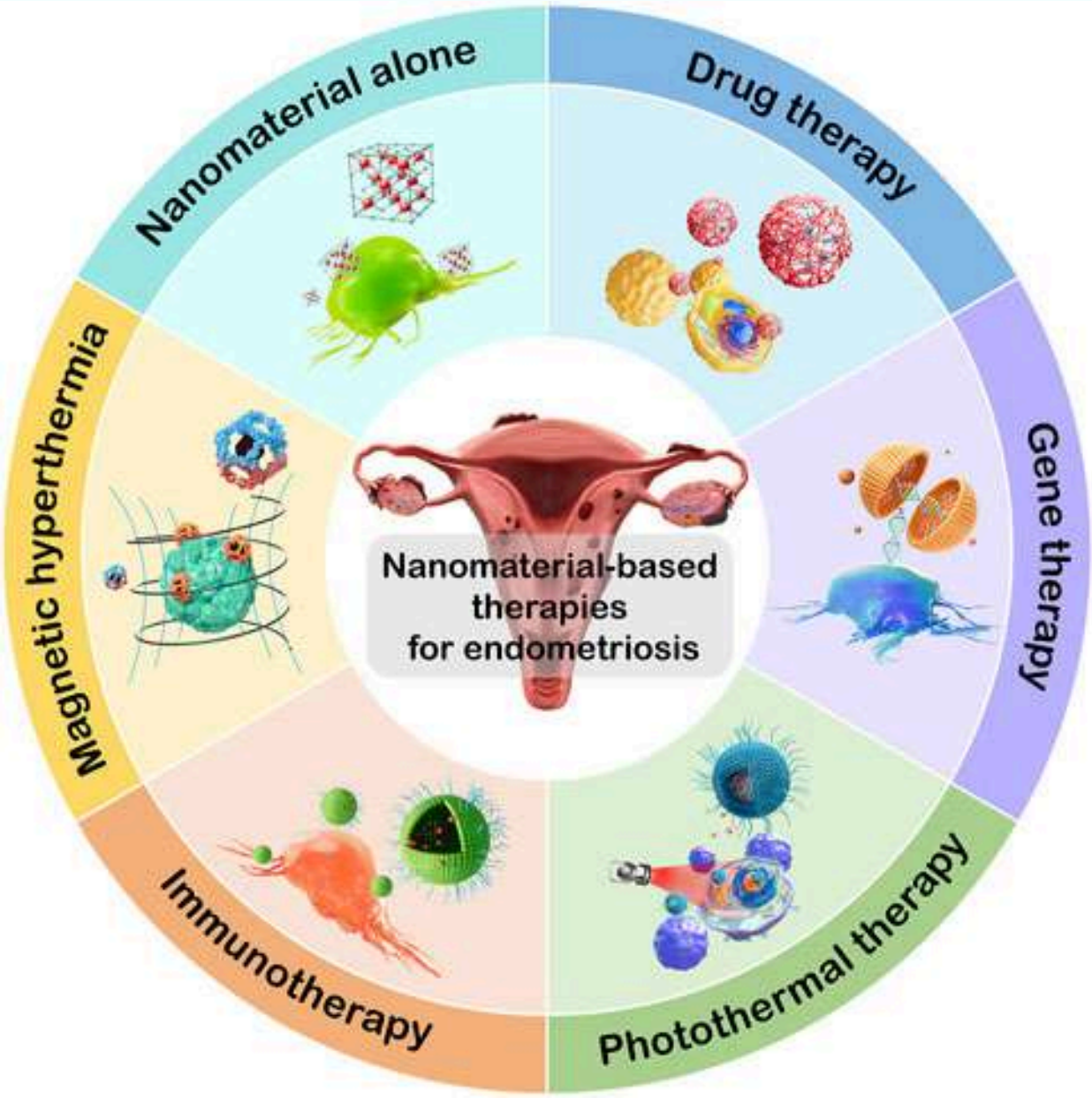
Nanomaterial alone
Drug therapy
Gene therapy
Photothermal therapy
Immunotherapy
Magnetic hyperthermia
Nanomaterial-based therapies for endometriosis

02

Dietary Recommendations in the Management of Endometriosis

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Abstract:
Endometriosis develops as a chronic inflammatory condition that depends on estrogen where tissue resembling the endometrium grows outside the uterus resulting in pelvic pain and reproductive complications. The standard treatment for endometriosis includes pharmacologic and surgical methods yet current research reveals dietary interventions can help lessen disease severity or reduce its progression. The article presents evidence-based nutritional recommendations for managing endometriosis supported by biochemical theory and clinical representation.

1. Introduction

Endometriosis affects nearly 10% of women of reproductive age worldwide (Zondervan et al., 2020), with far-reaching implications for quality of life, fertility and healthcare expenditures. While the aetiology is complex and multifactorial (e.g., genetic, hormonal, immunological), chronic inflammation and oxidative stress play a considerable role in the pathophysiology. Dietary approaches that target chronic inflammation, modulation of estrogen metabolism and immune function are beginning to receive increased interest in research and clinical practice, which may ultimately prove useful for women with endometriosis (Parazzini et al., 2017).

1.The Role of Diet in Pathophysiology

There are several ways or pathways in which diet can affect endometriosis, for instance:

•Nuanced effect on estrogen: Diet can influence the metabolism of estrogen with dietary fiber, gut microbiota, and hepatic metabolism and detoxification pathways,

•Inhibition of inflammation: Certain dietary components may enhance host production of inflammatory cytokines (e.g., IL-6, TNF-alpha), while other dietary components may inhibit the inflammatory process and related cytokine production,

• Reduction of oxidative stress: Antioxidant-rich diets can also lower reactive oxygen species (ROS) contributing to lesion proliferation,

• Modulation of immune function: omega-3 fatty acids, vitamin D, and the nutrition associated with intestinal microbiota can modulate immune function and alter host autoimmunity, both of which may impact the expression of endometriosis (Polak et al., 2021).

3. Evidence-Based Dietary Recommendations

3.1 Anti-inflammatory Diet

A diet rich in anti-inflammatory foods can reduce the inflammatory burden of endometriosis. In clinical research, women who ate high amounts of fruits, vegetables, and sources of omega-3 also had decreased pelvic pain and lesion size (Harris et al., 20201).

Recommended Foods:

•Fatty Fish (e.g., salmon, sardines): High in omega-3 polyunsaturated fatty acids that inhibit pro-inflammatory eicosanoids.

•Leafy greens or cruciferous vegetables: Contains sulforaphane and flavonoids with anti-inflammatory activity.

•Berries, turmeric, and ginger: Natural anti-inflammatories that down-regulate cytokine expression.

Limit:

•Red meat and processed foods: High amounts of arachidonic acid and saturated fats can promote prostaglandin synthesis.

•Sugar and refined carbohydrates: Promote insulin resistance and inflammation.

3.2 High-Fiber Diet

Fiber helps eliminate estrogen from the body via the fecal route by promoting each healthy gut microbiota and lowering levels of reabsorption through enterohepatic circulation (Fung et al., 2018).

Recommendations:

- 25-35 grams of dietary fiber from the following sources:
- Legumes (lentils, beans)
- Whole grains (quinoa, oats)
- Vegetables and fruits with skins

Clinical Tidbit:

Randomized control trial showed that women who consumed high-fiber diets had lower circulating estradiol: meaningful because lower circulating estradiol best for estrogen-related conditions, like endometriosis. (Yamamoto et al., 2019).

3.3 Omega-3 and Omega-6 Fatty Acid Balance

The Western diet typically has a significant omega-6 fatty acid (vegetable oils) excess that can promote inflammation. A lower omega-6/omega-3 ratio is more advisable for patients with endometriosis.

Recommendations:

- Increase omega-3s through fish oil supplements (1000-2000 mg/day EPA + DHA) or fatty fish
- Decrease sunflower, corn and soybean oil

Evidence:

Missmer et al. (2010) found a higher omega-3 intake was inversely associated with endometriosis risk and that trans fats increased the risk in case-control study.

3.4 Gluten-Free and Low-FODMAP Diets

While evidence continues to emerge, countless individuals who suffer with endometriosis report GI symptoms that mimic irritable bowel syndrome (IBS). Gluten and fermentable oligosaccharides (FODMAPs) may contribute to or worsen habitual GI symptoms

Clinical Relevance:

- According to a data mining study by Marziali et al. (2012), 75% of women with endometriosis, surveyed, reported symptom relief while eating gluten free for 12 months.
- Another pilot study of a low-FODMAP diet also reduced bloating and pain scores, in patients with IBS (Mancini et al., 2021).

Caution: Consideration of nutritional deficiencies when executing elimination diets should occur with the support of a dietitian.

3.5 Antioxidant-Rich Foods

Oxidative stress plays a role in the inflammation associated with endometriosis, and in the developing lesions associated with endometriosis. Antioxidants, such as vitamins A, C, E, and selenium, help control and deactivate ROS.

Sources include

- vitamin C - citrus fruits, strawberries, bell peppers
- vitamin E - nuts, seeds, spinach
- beta-carotene - carrots, sweet potatoes
- selenium - Brazil nuts, tuna, eggs

Evidence:

A study conducted by Santanam et al. (2013), indicated that daily supplementation with vitamins C and E (per 1000 body weight) reduced pelvic pain in endometriosis patients after 4 months.

3.6 Vitamin D Supplementation

Vitamin D has immunomodulatory and anti-inflammatory effects. Its deficiency is associated with the progression of endometrial lesions and pain severity.

Recommendations:

•For 25(OH)D serum levels maintain >30ng/ml.

•Supplement if vitamin D deficient with 1000–2000 IU/day.

Clinical Relevance:
Vitamin D affects the upregulation of regulatory T cells and downregulation of proinflammatory cytokines, which is crucial in mitigating endometriosis-related immune dysregulation (Vinci et al., 2020).

4**. Foods and Substances to Avoid**
Some foods and chemicals have been shown to worsen endometriosis through pro-estrogenic or inflammatory pathways:

- Alcohol: Increases estrogen; increases oxidative stress.
- Caffeine: In certain women has been linked with higher estrogen and worsening symptoms.
- Xenoestrogens (ex. BPA): Located in plastics; mimic estrogen and possibly exacerbate endometriosis.
- Trans fats: Thought to influence systemic inflammation and correlated with a greater risk of endometriosis.

5. Clinical Implications and Patient Counseling
Dietary changes are considered adjunct, or complementary, to therapy rather than therapy by themselves. Clinicians should help patients make evidence-based decisions, avoid overly stringent diets, and focus on sustainability. Diet plan personalization is also critical, this is where dietitians and nutritionists can help take everything into account based on the patient's symptoms, comorbidities, and culture.

Here's a patient-centered approach:
- Begin with an anti-inflammatory, high fiber food focus.
- Start slowly with eliminating foods and/or food groups in a controlled manner.
- Consistently assess symptom response and nutritional aspects of care.

1. Conclusion

Dietary intervention is an exciting adjunctive tool in the holistic management of endometriosis. Nutrition influences inflammation, estrogen metabolism, and oxidative stress, all of which facilitate improvements in the patient's outcome. While further large-scale RCTs are warranted, existing evidence demonstrates the benefits of incorporating anti-inflammatory, high-fiber, antioxidant, and sufficient omega-3 dietary patterns into usual care for endometriosis patients. By designing care teams that include gynecologists, specialist-dietitians and primary care providers, health care teams can offer maximal benefit to their patients.

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03

Role of Medical Devices in Endometriosis Diagnosis

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This chapter focusses on the role of imaging modalities in the diagnosis of endometriosis. It is well known that the gold standard for diagnosis of endometriosis is laparoscopy and tissue biopsy. However, in recent years, significant improvements have increased the possibility of depending solely on imaging itself prior to starting therapy. While imaging is unlikely to replace surgical diagnostics, an excellent correlation between imaging findings and eventual surgical diagnosis has been demonstrated.

The various imaging modalities available are

a. Transabdominal ultrasound
b. Transvaginal ultrasound
c. 3-D transvaginal ultrasound
d. Computerized Tomography (CT) scan
e. Magnetic resonance imaging (MRI) scan.

Transabdominal ultrasound is usually inadequate for pelvic imaging in women with gynecological complaints. Its role is limited in achieving accurate diagnosis in pelvic pathology. While easily identifiable problems like large ovarian endometriomas or bulky uteri with adenomyosis can be sufficiently imaged with abdominal ultrasound, detailed description of findings need transvaginal ultrasound.

Another modality which is not very suitable for evaluating suspected endometriosis is CT scan. This is continuation with the well-known fact that CT scan is better suited for bony pathology rather than deeper pelvic pathology. Hence, further discussion will be restricted to TVS and MRI.

Role/ importance of imaging

Largely, the role of imaging pertained to attaining a diagnosis. However, in recent years, it is possible to quantify the extent of the disease, it is possible to triage patients into those needing advanced laparoscopic procedures and those requiring only basic laparoscopic skills. This is especially important since the World Endometriosis Society suggests that outcomes of severe endometriosis are better when operated upon in centers of excellence. Hence, TVS serves as an ideal triage tool for the general gynecologist to help deciding path of referral. [1]

Methodology for performing TVS for endometriosis.

Standard steps in performing TVS are to be taken as is usual. (empty bladder, consent, lubricated condom to cover transvaginal probe, 5 MHz probe, etc).

One study suggested that the average duration of an excellent pelvic ultrasound was around 35 minutes.

A systematic approach should be followed while performing TVS for suspected endometriosis. A five-domain approach is suggested. [2]

These include objective assessment as listed below.

(1) Routine assessment of the uterus and ovaries;

(2) Assessment of site-specific tenderness (SST)

(3) Assessment for organ mobility (ovarian mobility and pouch-of-Douglas (POD) obliteration);

(4) Assessment of the anterior, posterior and lateral compartments of the pelvis for non-bowel DIE

(5) Assessment of the anterior wall of the bowel for DIE.

The common sonographic signs which are encountered in each of the domains are listed in table 1. These are found to have excellent correlation with the surgical phenotype

Table 1. Domains in systematic sonographic evaluation for endometriosis

Domain	Objective	Sonographic sign(s)	Predicted phenotype oF endometriosis
I	Routine assessment of uterus and adnexa	Myometrial cysts, streaky echogenic lines, thickened posterior myometrium, loss of endometrial/myometrial interface on 3D imaging. Thick-walled ovarian cysts with homogeneous low-level internal echoes. 'Ground glass' appearance	Adenomyosis Endometrioma
II	Tenderness-guided assessment	Site-specific tenderness	Possible peritoneal endometriosis
III	Assessment of organ mobility		
IIIa	Ovarian mobility	Ovarian immobility	Ovarian adhesions
IIb	Status of POD	Real-time dynamic sliding sign	POD obliteration/adhesions
IV	Assessment for non-bowel DIE Assessment of anterior, lateral and posterior pelvic compartments	Nodules: solid hypoechoic lesions rounded in shape Linear thickenings: hypoechoic linear thickening Plaques: hypoechoic lesions with irregular shape	Extraovarian non-bowel DIE
V	Assessment for bowel DIE	Non-compressible hypoechoic lesion on muscularis propria (may infiltrate mucosa layer)	Bowel DIE

The IDEA guidelines (International Deep Endometriosis Analysis) guidelines have provided systematic diagrammatic representation detailing the methods in which assessment of endometriosis should be done with TVS. [3] These are well illustrated in a review document [4] Figure 1 shows the various compartments which are to assessed systematically. Figures 2 and 3 show typical representative findings.

Figure 1. Systematic assessment components

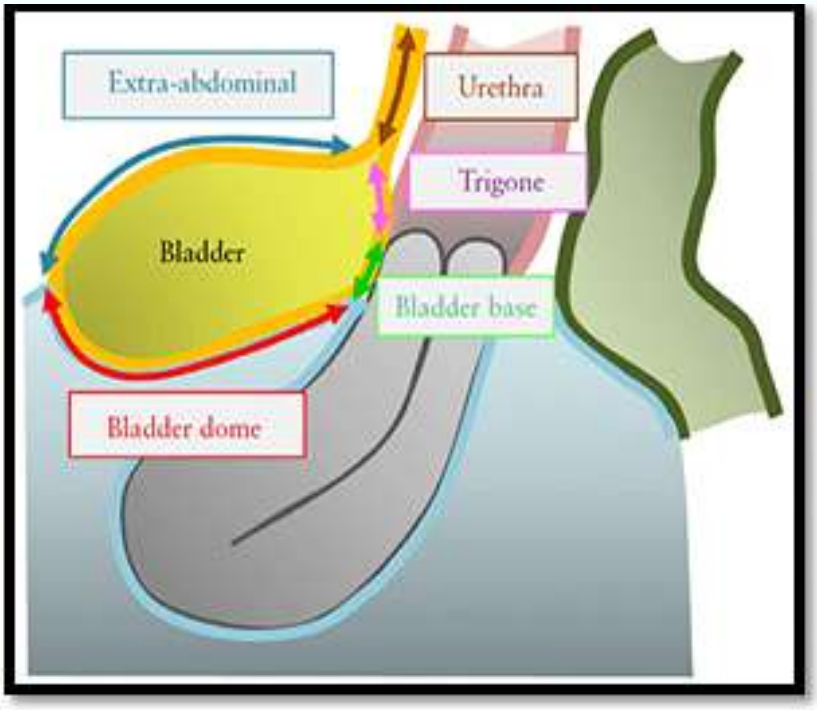


Figure 2. Diagrammatic explanation of typical posterior compartment lesion

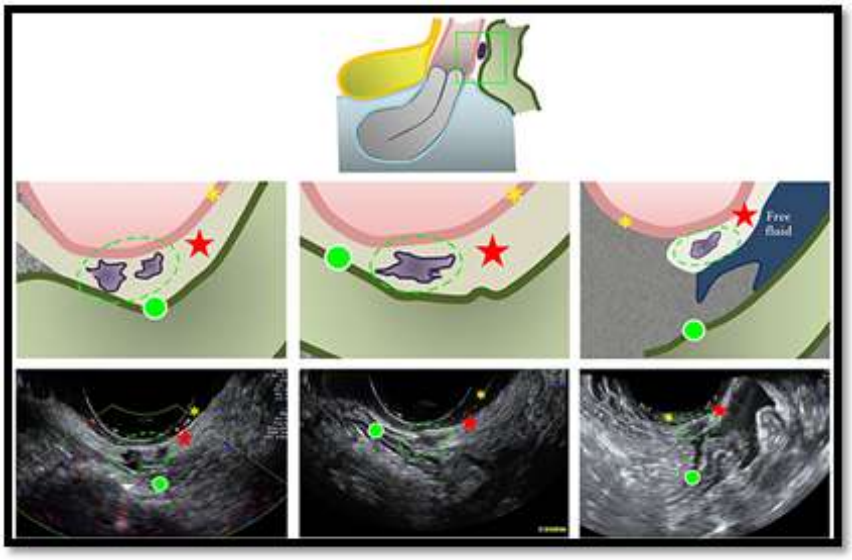
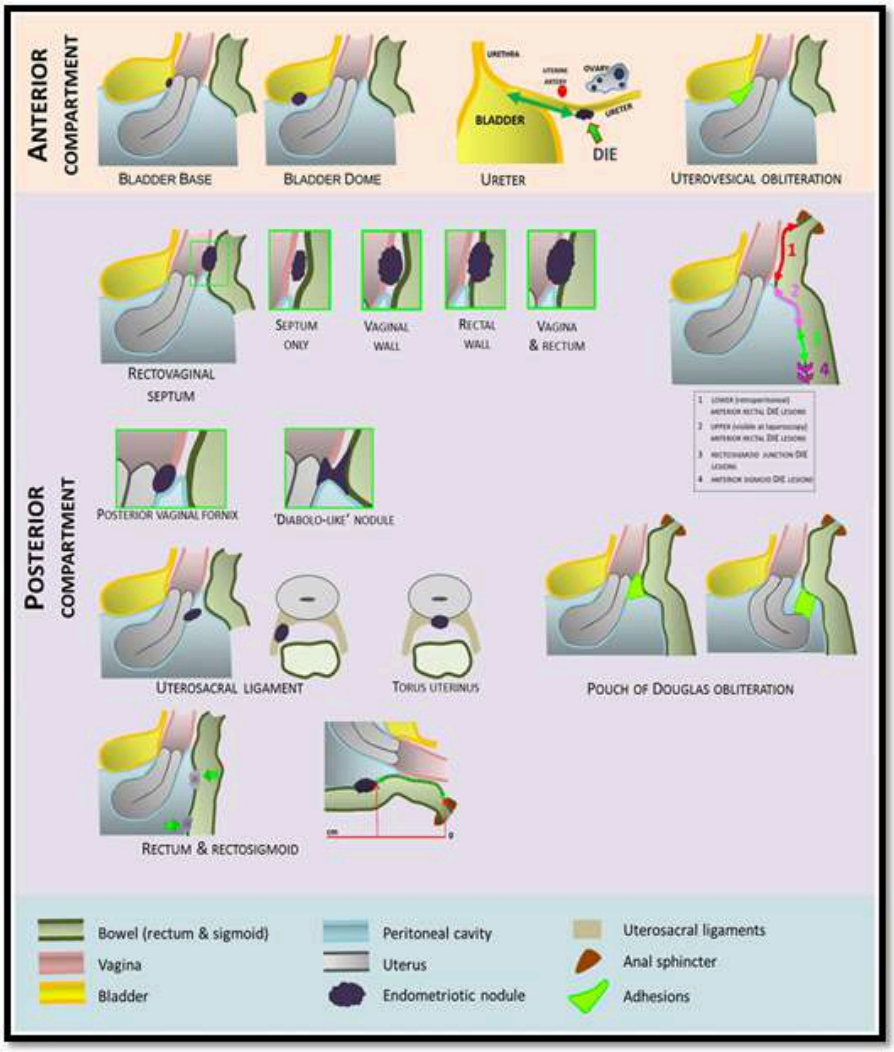


Figure 3. Summary diagrammatic representation of possible posterior and anterior compartment lesions.



Role of MRI in endometriosis diagnosis

MRI is used to support the TVS diagnosis of endometriosis.

Technical guidance: 1.5 Tesla or 3 Tesla scanner with high resolution phased array coils with Turbo spin echo T2W sequences for the pelvis and T1W sequences with and without fat saturation are recommended. Some recommendations include instillation of intravaginal and intrarectal gels to help clearer demarcation of peritoneal recesses. Table 2 summarizes common MRI findings and their diagnostic correlations.

MRI finding	Possible diagnostic correlation
T2 hypointense regions with attached nodular thickening and anatomical distortion	Adhesions
Tiny T1hyperintensities in superficial plane	Superficial endometriotic lesions with active bleeding
Thick-walled blood-filled tumors with uniform high signal strength in T1W sequence. Either Hyperintense or hypointense in T2W sequences. Presence of layered look (shading sign) – possibly due to cyclic bleeding and hemosiderin deposition.	Endometriotic ovarian cysts
Dark patches within the cysts in T2W sequences.	Chocolate cysts
Plaque-like lesions with uneven, spiculated appearance and MRI intensity comparable to that of pelvic muscles Densely packed endometrial glands/ stroma with fibro-muscular and inflammation responses	Deep Endometriotic nodules.
Hypointense thickening of the USL ligament with regular or irregular borders	Uterosacral/rectal endometriosis
Solid or plaque-like intestinal wall thickening and disappearance of the visceral fat barrier between the rectosigmoid and the uterine wall or adnexa	Bowel endometriosis
"Mushroom cap" sign ·Gills of the mushroom - retractile T2 hypointense growth of the muscular stratum · Cap of the mushroom cap - fine layer of T2 hyperintense submucosa and mucosa	Bowel endometriosis
Collapsing Ovaries in the Douglas pouch ("Kissing ovaries")	Pelvic adhesions
Lesions extend from the retro-cervical space to the anterior rectum	Obliteration of the Douglas pouch

Table 3 summarizes the accuracy parameters of MRI for different lesions.

Lesion	Sensitivity	Specificity
Endometrioma	95%	91%
Uterosacral endometriosis	85%	80%
Bowel endometriosis	83%	88%
Pouch of douglas obliteration	89%	94%

Figure 4. MRI image showing posterior involvement (displayed better with vaginal gel insertion)

CONCLUSION

To summarize, TVS and MRI are undergoing rapid advances in their accuracy. Though they are unlikely to replace surgery as the best diagnostic modality, clinicians should understand the utility of these diagnostic tools in aiding their clinical and surgical decision making.

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04

Innovative Surgical Instruments for Endometriosis Excision

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Endometriosis is a chronic condition characterized by ectopic endometrial-like tissue growth, leading to pain, infertility, and significant impacts on quality of life. Laparoscopic surgery has emerged as the standard approach for endometriosis excision due to its minimally invasive nature. Recent advancements in surgical instruments and technologies have enhanced the precision and effectiveness of these procedures. This paper reviews traditional laparoscopic instruments, energy devices, and innovative technologies, including advanced bipolar devices, ultrasonic energy, laser technology, and robotic-assisted surgery. The benefits, challenges, and future directions of these innovations are also discussed.

Introduction

Endometriosis affects approximately 10% of reproductive-aged individuals, causing chronic pelvic pain, dyspareunia, dysmenorrhea, and infertility (1). Laparoscopic surgery has become the preferred method for diagnosing and excising endometriotic lesions due to its reduced morbidity and faster recovery times. However, traditional surgical tools pose limitations in precision and thermal damage. The integration of novel technlogies, such as advanced energy devices and robotic-assisted systems, has significantly improved surgical outcomes. This paper explores the latest innovations in laparoscopic instruments and their impact on endometriosis surgery.

Traditional Laparoscopic Instruments

Laparoscopic surgery relies on specialized instruments designed for minimally invasive procedures. Key traditional instruments include:

Laparoscope: A thin, lighted instrument with a camera that provides visualization of the abdominal and pelvic cavities, minimizing the need for large incisions.

Needle Driver: Used for suturing, this instrument holds the suturing needle securely, facilitating precise stitching within the confined space of the abdomen.

Trocar: A pen-shaped instrument with a sharp tip used to create entry ports for other laparoscopic instruments.

Bowel Grasper: Allows surgeons to grasp and manipulate bowel tissue safely during surgery, essential for accessing and excising endometriotic lesions.

Energy Devices in Laparoscopic Surgery

Energy devices are integral to laparoscopic surgery, providing the means to cut and coagulate tissue effectively. Traditional energy sources include monopolar and bipolar devices:

Monopolar Devices: Commonly used for endometriosis resection, these instruments utilize a single electrode to deliver electrical current, effectively cutting tissue and achieving hemostasis.

Bipolar Devices: These instruments pass electrical current between two electrodes located at the tips of the forceps, reducing the risk of damage to adjacent tissues and providing precise coagulation.(4).

Innovative Surgical Instruments and Technologies

Recent advancements have introduced innovative instruments and technologies that enhance the precision and outcomes of laparoscopic surgery for endometriosis:

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Advanced Bipolar Devices

The LigaSure™ system enhances vessel sealing and tissue coagulation with minimal lateral thermal spread, improving safety and efficiency.

Ultrasonic Energy Devices

The Harmonic Scalpel employs ultrasonic vibrations to simultaneously cut and coagulate tissue. Compared to traditional electrosurgery, it reduces thermal damage, improving surgical precision (2).

Laser Technology

CO_2 laser systems, such as the DEKA SmartXide² TRIO, allow precise excision, coagulation, and vaporization of endometriotic lesions. These systems enable tailored treatment approaches, minimizing damage to surrounding tissues (5).

Robotic-Assisted Surgery

Robotic systems, such as the da Vinci Surgical System, provide surgeons with enhanced dexterity through articulated instruments and high-definition 3D visualization. These systems facilitate meticulous dissection, particularly in deep infiltrating endometriosis cases, improving surgical accuracy and reducing recurrence rates (3).

Benefits of Innovative Surgical Technologies

The integration of these advanced instruments into laparoscopic surgery offers several benefits:

Enhanced Precision: Advanced energy devices and robotic systems improve the accuracy of endometriosis excision, preserving surrounding healthy structures.

Reduced Thermal Damage: Ultrasonic and laser technologies minimize collateral thermal injury, promoting faster healing.

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Improved Visualization: High-definition cameras and 3D imaging provide surgeons with a clearer view of the surgical field, aiding in the identification and excision of lesions.

Minimally Invasive Approach: Smaller incisions, reduced postoperative pain, and shorter recovery times improve patient outcomes.

Considerations and Challenges

While these innovations have revolutionized laparoscopic surgery for endometriosis, certain considerations and challenges remain:

Surgeon Training: Proficiency with advanced instruments and technologies requires specialized training and experience to ensure optimal outcomes.(6)

Cost: The acquisition and maintenance of advanced surgical systems can be expensive, potentially impacting accessibility for some healthcare facilities and patients.

Patient Selection: Not all patients may be suitable candidates for certain advanced procedures; individualized assessment is essential.

Conclusion

The landscape of laparoscopic surgery for endometriosis excision has been significantly enhanced by the development and integration of innovative surgical instruments and technologies. These advancements have improved surgical precision, reduced recovery times, and enhanced patient outcomes. As technology continues to evolve, ongoing research and training will be vital to fully realize the potential of these innovations in the effective management of endometriosis.

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05

Treatment of Hormonal Therapy in Endometriosis and Safety Profile

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Endometriosis is an inflammatory entity with the presence of endometrial-like tissue outside the uterus, is a common clinical entity between women of reproductive age, with a prevalence of about 10%. Due to the variety of endometriosis-associated symptoms, a great variety of treatments have been implemented.

Womenwithendometriosis are confronted with one or both of two major problems: Endometriosis associated pain and infertility.

Endometriosis-associated pain includes dysmenorrhea, dyspareunia, dysuria, dyschezia, and nonmenstrual pelvic pain . Woman with endometriosis, the quality of life is to be included, although this was found in very limited study.

This chapter on the treatment of endometriosis-associated pain is subdivided into sections on empirical treatment, medical treatment, surgical treatment, pre- or postoperative medical treatment and non-medical management strategies. It has to be noted that endometriosis is a chronic and incurable disease in a significant number of women. Thetreatments described in this section can offer (partial, often only temporary) relief of pain symptoms, but symptoms often recur after discontinuation of therapy Analgesics and combination with other treatments to reduce endometriosis-associated pain (Brown et al., 2017)

It is recommended to offer women hormone treatment with combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists as one of the options to reduce endometriosis-associated pain Strongly recommended.

The GDGrecommends that clinicians take a shared decision-making approach and take individual preferences, side effects, individual efficacy, costs and availability into consideration when choosing hormone treatments for endometriosis associated pain.

It is recommended to prescribe women a combined hormonal contraceptive (oral, vaginal ring or transdermal) to reduce endometriosis-associated dyspareunia, dysmenorrhoea and non-menstrual pain (Brown et al., 2018;Jensen et al., 2018; Grandi et al., 2019)strongly recommended.

Womensuffering from endometriosis-associated dysmenorrhoea can be offered the continuous use of a combined hormonal contraceptive pill (Hee et al.2013;Zorbas et al., 2015; Muzii et al.,2016b) weakly recommended

It is recommended to prescribe women progestogens to reduce endometriosis associated pain is strongly recommended(Momoeda et al.,2009; Brown et al., 2012; Petraglia et al., 2012; Andreset al., 2015; Dragoman and Gaffield, 2016).

The GDGrecommends that clinicians take the different side effect profiles of progestogens into account when prescribing them. It is recommended to prescribe womenalevonorgestrel-releasing intrauterine (LNG-IUS) system or an etonogestrel-releasing subdermal implant to reduce endometriosis-associated pain strongly recommended (Lan et al., 2013. Margatho et al., 2020).\

It is recommended to prescribe women GnRH agonists to reduce endometriosis associated pain, although evidence is limited regarding dosage or duration of treatment strongly recommended (Brown et al., 2010; Tang et al., 2017).

The GDG recommends that GnRH agonists are prescribed as second-line (e.g. if hormonal contraceptives or progestogens have been ineffective) due to their side effect profile in general practice. Clinicians should consider prescribing combined hormonal add-back therapy alongside GnRH agonist therapy to prevent bone loss and hypo-oestrogenic symptoms strongly recommended (Wu et al., 2014; Sauerbrun-Cutler and Alvero, 2019).

Hormone therapy

Sometimes hormone medicine help ease or get rid of endometriosis pain. The rise and fall of hormones during the menstrual cycle causes endometriosis tissue to thicken, break down and bleed. Lab-made versions of hormones may slow the growth of this tissue and prevent new tissue from forming. Hormone therapy isn't a permanent fix for endometriosis. The symptoms could come back after stop treatment.

Therapies used to treat endometriosis include:

Hormonal contraceptives
Birth control pills, shots, patches and vaginal rings help control the hormones that stimulate endometriosis. Many have lighter and shorter menstrual flow when they use hormonal birth control. Using hormonal contraceptives may ease or get rid of pain in some cases. The chances of relief seem to go up if use birth control pills for a year or more with no breaks.

COMBINATION ESTROGEN/PROGESTIN CONTRACEPTIVES
Combination oral contraceptives are more effective than placebo at reducing dysmenorrhea in women with endometriosis. A double-blind, randomized

controlled trial of women with endometriosis demonstrated that low-dose combination oral contraceptives improved endometriosis pain compared with placebo.

Another study showed that combination oral contraceptives were less effective at six months compared with gonadotropin-releasing hormone (GnRH) analogues, although both significantly improved symptoms after 12 months. Combination oral contraceptives have significantly fewer adverse effects than GnRH analogues

Asmall, prospective, nonblinded, cohort study compared the ethinyl estradiol/etonogestrel vaginal ring (Nuvaring) with the norelgestromin/ethinyl estradiol transdermal patch (Ortho Evra) in patients with endometriosis.

Although continuous use of both treatments reduced pain, the ring was superior for dysmenorrhea. Patient satisfaction also seemed higher in patients using the ring. Continuous use of these treatments resulted in more breakthrough bleeding compared with cyclic use.

The combined oral contraceptive pill (COC) is a widespread contraceptive method which is also used widely from clinicians empirically in patients with dysmenorrhea. Most of the included guidelines propose combined oral contraceptives as a first empirical medical treatment in endometriosis associated pain before performing diagnostic laparoscopy although the reported level of evidence differs.

Ameta-analysis from Brown et al. showed that use of COCs in comparison with placebo is associated with relief of dysmenorrhoea, however in comparison with GnRHanalogue there were no superiority of treatment. Only CNGOF and WES refer the possibility of using COCs for downregulation before ART in patients with endometriosis. A Cochrane review underlines the limitation of the available data on the role of COC before IVF.

Progestin therapy

Progestin is a lab-made version of a hormone that plays a role in the menstrual cycle and pregnancy. A variety of progestin treatments can stop menstrual periods and the growth of endometriosis tissue which may relieve symptoms. A contraceptive rod placed under the skin of the arm (Nexplanon), birth control shots (Depo-Provera) or a progestin-only birth control pill.

PROGESTERONE-ONLYCONTRACEPTIVES

Medroxyprogesterone (oral, Provera) or depot injection [Depo-Provera]) may improve symptoms of endometriosis compared with placebo.

Trials comparing a lower-dose depot medroxyprogesterone (Depo-subQ Provera) with the GnRH analogue leuprolide (Lupron) showed comparable improvement in pain

Both trials indicated that depot medroxyprogesterone resulted in less bone loss and hypoestrogenic adverse effects than leuprolide. Depot medroxyprogesterone labels include U.S. Food and Drug Administration boxed warnings for bone loss.

Asmall study showed that the etonogestrel subdermal implant (Implanon) was as effective as depot medroxyprogesterone for endometriosis pain.

Progestin therapies include a tiny device placed in the uterus that releases levonorgestrel (Mirena, Skyla, others).

Small nonrandomized studies have shown a possible improvement in endometriosis pain with the levonorgestrel-releasing intrauterine system (Mirena).

GONADOTROPIN-RELEASING HORMONE ANALOGUES

Gonadotropin-releasing hormone (Gn-RH) agonists and antagonists.

These medicines block the menstrual cycle and lower estrogen levels.This causes endometriosis tissue to shrink. These medicines create an artificial menopause. Taking a low dose of estrogen or progestin along with Gn-RH agonists and antagonists may ease menopausal side effects. Those include hot flashes, vaginal dryness and bone loss. Menstrual periods and the ability to get pregnant return when stop taking the medicine.

If NSAIDs and hormonal contraceptives are ineffective, the next step is treatment with a GnRH analogue such as leuprolide or goserelin (Zoladex). GnRH analogue therapy downregulates the pituitary resulting in “medical menopause.

It has been shown to improve pain in women with endometriosis.However, the therapy causes adverse effects, such as hot flashes, night sweats, and possible bone loss. In many women. To mitigate the menopausal symptoms, reinitiating hormone therapy with low-dose estrogen and progestin is common.

Gonadotropin Releasing Hormones (GnRH) agonists

GnRH agonists use in endometriosis patients is reserved for patients with persistent endometriosis and not willing for surgical treatment or unfit for surgery

Leuprolide
All patients given leuprolide acetate depot at 3.75 mg, 1 ampule intramuscularly every 28 days and treatment had a planned duration of 6 months.

Follow-up evaluations were set every 2 months during the treatment phase and every 3 months thereafter until the completion of 1 year after discontinuation of medical therapy. At each follow-up visit pain symptoms were recorded, and clinical

exploration, transvaginal ultrasonography, and transrectal ultrasonography were performed.

Buserelin -

Buserelin Acetate in the treatment of pelvic pain associated with minimal and mild endometriosis. Buserelin, a gonadotropin-releasing hormone (GnRH) agonist, is used to treat endometriosis by suppressing estrogen production, which can help reduce pain and the growth of endometrial tissue outside the uterus.

Buserelin (brand name Suprecur®) is an injection for hormone treatment for womenfor endometriosis Buserelin injections these are usually administered just underneath the surface of the skin sub cutaneous route.

Nasal Spray of Bruserlin There is another brand of buserelin nasal spray available. The patient should trained

howmanytimes a day to usethe spray, and whether use the spray in one or both nostrils. This will depend upon how the patient will use it. Each time you open a new bottle of nasal spray and attach the nebuliser to the bottle of solution and then 'prime' the spray. Pumping the spray about six or seven times until there a fine mist. Priming the spray in this way, fills the nebuliser and tests that the spray is working correctly.

Grocerlin

Brand name Zoladex

Goserelin is a hormone similar to the one normally released from the hypothalamus gland in the brain. Goserelin prevents the growth of tissue associated with endometriosis in adult women during treatment and for up to 6 months after treatment is discontinued.

Suppressing estrogen can thin the bones or slow their growth. This is a problem for adult women whose bones are no longer growing like the bones of children. This is why goserelin is used only for up to 6 months in adult women treated for endometriosis.

Subcutaneous injection Grocerlin

Implant of Grocerlin

Whengiven regularly as an implant, goserelin works every day to decrease the amount of estrogen and testosterone in the blood

Oral GnRH antagonists

It reduce estrogen levels in a dose-dependent manner, which can help alleviate endometriosis-associated pain, including dysmenorrhea and nonmenstrual pelvic pain. These drugs are dose dependent in oestrogen suppression action

Advantages of oral GnRH antagonists: Oral administration: They are taken orally, making them more convenient than injectable GnRH agonists. No initial flare-up: Unlike GnRH agonists, they do not cause an initial flare-up of endometriosis symptoms. Rapid return of menstruation: Menstruation can resume quickly after discontinuation of the medication

Examples of oral GnRH antagonists:

Elagolix: Approved by the FDA for the management of moderate-to-severe pain associated with endometriosis. This is known as miracle drug for endometriosis.

Relugolix: Another oral GnRH antagonist that has shown efficacy in reducing endometriosis-associated pain.

The new tablet, known as relugolix combination therapy or Ryeqo, has been approved by the National Institute for Health and Care Excellence (NICE) (13th March 2025). The treatment, called relugolix–estradiol–norethisterone (also known as relugolix combination therapy or Ryeqo), works by blocking specific hormones that contribute to endometriosis, while also providing necessary hormone replacement in a single daily tablet.

This is known as Best pill for endometriosis.

Linzagolix: Currently being evaluated in clinical trials for endometriosis-associated pain.

DANAZOL: Danazol, an androgen, is effective in the treatment of pelvic pain associated with endometriosis. The drug has several U.S. Food and Drug Administration boxed warnings, including the risk of thrombosis and teratogenicity for

Medical treatment of endometriosis
Danazol

Danazol is an androgenic drug, that was used for the treatment of endometriosis related pain for more than 40 years. Because of the hyperandrogenic side effects

(weight gain, acne, hirsutisms, breast atrophy and virilisation), low dose vaginal administration has been proposed. As far as the use of danazol in treatment of endometriosis pain is concerned, ACOG is the only guideline which still propose the above medication as a possible first line therapy.

WES, ESHRE and SOGC are critical because of the side effects and WES recommends to use it only in women who have already had a well-tolerated treatment with danazol before. S2k and ASRM do not have an official recommendation.According to ESHRE and NICE guidelines, danazol for infertile patients should not be recommended while according to WES there is not enough evidence. However, androgenic adverse effects, such as acne, hirsutism, and male pattern baldness, often limit its use.

Progestines

All eight guidelines recommend progestins as first-line medical treatment for pain in endometriosis. There are different types and ways of administration of progestins on the treatment of endometriosis.

Dienogest : DNG is 19-nortestosterone derivative.

Dienogest (a new selective progestin that is not yet available in the United States) with GnRH analogues also showed comparable improvement in pain.

A fourth generation orally active progestogen with a high specificity for the progesterone receptor (PR) . The most common used dosage 2 mg per day. causes only a minimal reduction of the estrogen levels, thus, none hypoestrogenic side effect is described. WES and S2k recommend dienogest prior to other progestines. S2k and CNGOFunderline, that in two RCTs the administration of dienogest showed comparable efficacy to GnRH-analogues with better tolerability

Medroxyprogesterone acetate
Medroxyprogesterone acetate, a 17OH-progesterone derivative.

It is commonly used as a three monthly intramuscularly or subcutaneously administered contraceptive method. It belongs to first line therapies for endometriosis-associated pain according to the two American societies, the Canadian society and ESHRE. Medroxyprogesterone acetate seems to be an effective and very economical therapy in relieving endometriosis-associated pain, with substantially less bone loss than GnRH agonists.

Levonorgestrel-IUS LNG-IUS is a commonly used mechanic and hormonal contraceptive method.

Releasing a 19-nortesterone derivative directly into the uterine cavity over a period of 5 years. The proposed mechanisms of levonorgestrel-IUS on endometriosis therapy are the induction of endometrial glandular atrophy, transformation of the stroma, the downregulation of endometrial cell proliferation and the intensification in apoptotic activities.

ACOG mentions, that levonorgestrel intrauterine system is similar effective as GnRHagonist in reducing endometriosis-associated pelvic. ASRM and CNGOF in concordance to a recent meta-analysis point out, that levonorgestrel intrauterine system reduces the recurrence of dysmenorrhoea after surgical treatment of endometriosis.

Gestrinone

Gestrinone, one of the first drugs for the treatment of endometriosis and myomas, which acts centrally on the hypothalamic pituitary system by supressing the release of lutenizing hormone (LH) and follicle-stimulating hormone (FSH) is actually not widely used.

Only WES and ESHRE discuss the use of gestrinone as a possible medication for the treatment of endometriosis related pain, while ASRM underlines that this therapy is at the moment not available in the United States. WES is the only society which refers that there is limited evidence about the role of gestrinone in the therapy of womenwith infertility.

Aromatase inhibitors:

These are a class of medicines that lower the amount of estrogen in the body. The health care team may recommend an aromatase inhibitor along with a progestin or combination birth control pills to treat endometriosis. Aromatase inhibitors reduce endometriosis-associated pain, intestinal symptoms, urinary symptoms and decrease the volume of laparoscopically visible endometriosis, rectovaginal infiltrating endometriosis and endometriomas. The above treatment improve the quality of life when used with gestagens, oral contraceptives or GnRH-agonists.

These women were given tab letrozole 2.5 mg, tab norethindrone acetate 2.5mg and 1000 mgofcalcium carbonate per day for six months starting from 3rd day of menses. Norethistrone is used as studies have shown it to increase apoptosis locally in endometrial implants and supplement the efficacy of letrozole.

Ferrero et al. conclude that aromatase inhibitors should be offered to women with pain persistence after previous surgical and hormonal treatment.

Endometriosis can affect about 2–5% of postmenopausal patients. In this group, aromatase inhibitors seem to be a possible medical treatment as the largest amount of estrogens is produced from extra-ovarian sources. Long-term use is associated with hypoestrogenic side effects, such as vaginal dryness, hot flushes, headache, arthralgia and with an increased risk for bone fractures, osteoporosis and osteopenia.

Selective estrogen receptor modulators (SERM)

SERMs havetissue-specific estrogen receptor agonist and antagonist effects.

ESHRE, CNGOF and ASR Mrefer that there is not enough evidence for treatment of endometriosis associated pain. NICE guideline does not recommend SERM as endometriosis related infertility treatment.

Selective progesterone receptor modulators (SPRM) Selective progesterone receptor modulators have a variable effect on progesterone receptors which varies from pure agonistic to pure antagonistic. A systematic review showed that mifepristone, is more effective than placebo for dysmenorrhoea and dyspareunia, although the current literature does not provide enough evidence for long-term safety and efficacy of this treatment. WES recommends that SPRM could be a second line therapy, while ESHRE, CNGOF and ASRMunderlines that evidence is not sufficient.

NICE guideline does not recommend SPRM as a treatment for endometriosis associated infertility

Conclusion

This is a review and summary of the eight most widely accepted guidelines concerning the management of endometriosis.

Pain and infertility are the major components of endometriosis that most usually lead patients in seeking an expert opinion. Regarding pharmacological therapies of endometriosis associated pain, the most of the included guidelines suggest progestins, either in the form of dienogest or of medroxyprogestetrone acetate, and combined oral contraceptives as first line therapy with a great evidence grade.

GNRH-agonists and levonorgestrel intrauterine system could be considered as second line treatment. About the remaining medical options such as danazol, gestrinone, aromatase inhibitors, SERMs and SPRMs because of the limited evidence there are discrepancies between the guidelines.

Important is also the role of surgery on treatment endometriosis related pain, where the standard of practice is the excision of the endometrial implants as well as the excision of the endometriomas. In general it is advised to handle the ovarian tissue as atraumatic as possible to reduce the decrease of ovarian reserve.

At last complementary options such as dietary products, acupuncture and

electrotherapy are not yet studied enough in order to have a better perspective of their role. All the above-mentioned guidelines agree that the combined oral contraceptive pill, progestogens are therapies recommended for endometriosis associated pain. Concerning infertility, there is no clear consensus about surgical treatment. Discrepancies are also found on recommendation of the second- and third-line treatments.

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06

Non-Hormonal Pain Management Options

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Hormonal treatment is the first line medical treatment that is given for endometriosis, but it may not hold good for everyone. Based on the pathophysiology of chronic inflammation, angiogenesis, fibrosis, apoptosis etc many drugs are being used to treat the pain associated with endometriosis and many are under trial.

Other than non-hormonal medications there are certain other physical and dietary measures that help in reducing the pain of endometriosis.

This is small compilation of non-hormonal medical treatment and measures available for endometriosis.

1. Pain Medications:

Over the Counter (OTC) Pain Relievers:

- **Acetaminophen**: A mild-to-moderate pain reliever that can provide some relief during mild endometriosis symptoms.

·**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):** Such as **ibuprofen and naproxen**, are effective in reducing pain and inflammation associated with endometriosis.

- **Pentoxifylline**: Demonstrated potential in reducing pain and improving pregnancy rates in several human trials.
- **N-palmitoylethanolamine (N-PEA):** Showed effectiveness in managing pelvic pain related to endometriosis in clinical trials.
- **VEGF Inhibition:**
- **Cabergoline**: Demonstrated potential in reducing endometrioma size in human trials.
- **Prescription Medications:**
  - **Gabapentin and Pregabalin:** These medications, originally developed for epilepsy and neuropathic pain, have shown some effectiveness in managing endometriosis pain.

- **Tricyclic Antidepressants (TCAs):** Such as amitriptyline and nortriptyline, can be helpful in managing chronic pain, including endometriosis-related pain.
- **Antispasmodics:** Medications like dicyclomine can help to relax the smooth muscle in the pelvis, which may reduce pain associated with pelvic adhesions.

2. Complementary and Alternative Therapies:

Acupuncture: This traditional Chinese medicine technique involves inserting thin needles into specific points on the body. Studies have shown that acupuncture may be helpful in reducing pain and improving quality of life in women with endometriosis.

- **Massage Therapy:** Therapeutic massage can help to relax muscles, reduce stress, and improve blood circulation, which may provide some relief from endometriosis pain.
- **Physical Therapy:** Pelvic floor physical therapy can help to improve pelvic floor muscle function, reduce pain, and improve sexual function in women with endometriosis.
- **Mind-Body Techniques:**
- **Yoga**: Can help to improve flexibility, strength, and stress management, which may be beneficial for women with endometriosis.
- **Meditation**: Can help to reduce stress and anxiety, which can worsen pain perception.
- **Deep Breathing Exercises**: Can help to relax the body and mind, and may also help to reduce pain.

- **3. Nerve Blocks:**

Nerve blocks are a valuable tool in managing chronic pelvic pain, including that associated with endometriosis. They involve injecting a local anesthetic or other medications near the nerves that supply the pelvic organs. This can provide temporary pain relief and help to identify the source of pain.

- **Common Nerve Block Techniques:**
  - **Superior Hypogastric Plexus Block (SHPB):** This is one of the most common nerve blocks used for pelvic pain. It targets the hypogastric nerves, which innervate many of the pelvic organs.
  - **Sacral Plexus Block:** This targets the nerves that supply the lower back, buttocks, and legs.
  - **Lumbar Sympathetic Block:** This targets the sympathetic nerves in the lower back, which can contribute to chronic pelvic pain.
  - **Pudendal Nerve Block:** This targets the pudendal nerve, which provides sensation to the genitals and perineum.
- **How Nerve Blocks Work:**
  - The injected medication temporarily interrupts the transmission of pain signals along the targeted nerves.
  - This can provide significant pain relief for several hours or even days.
  - Nerve blocks can also be used for diagnostic purposes to identify the specific nerves contributing to the pain.
- **Potential Benefits of Nerve Blocks:**
  - Reduced pain intensity
  - Improved quality of life
  - Reduced reliance on opioid medications
  - Improved sleep

- **Important Considerations:**

- Nerve blocks are typically performed by pain management specialists.
- There are potential risks associated with any invasive procedure, such as infection or bleeding.
- The effects of nerve blocks are usually temporary, and repeat injections may be necessary.

- **4. Neurostimulation Techniques:**

- **Sacral Neuromodulation:** This technique involves implanting a small device that delivers electrical stimulation to the sacral nerves, which are involved in pain sensation from the pelvic organs.

- **Spinal Cord Stimulation:** This technique involves implanting a device that delivers electrical stimulation to the spinal cord, which can help to block pain signals.

- **Choosing the Right Treatment:**

The best non-hormonal pain management options for endometriosis will vary depending on the individual woman and the severity of her symptoms.

- **Factors to consider:**
- **Severity of pain:** Mild pain may be effectively managed with OTC medications or complementary therapies, while more severe pain may require prescription medications or nerve blocks.

- **Individual preferences:** Some women may prefer to avoid medications altogether and opt for complementary therapies or lifestyle changes.

- **Potential side effects:** It's important to weigh the potential benefits and risks of any medication or treatment.

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- **Overall health:** Women with other medical conditions may have limitations on certain medications or treatments.
- **Important Considerations:**

- **Regular Follow-up:** Regular follow-up with your doctor is essential to monitor your symptoms and adjust your treatment plan as needed.

Lifestyle Modifications:

- **Stress management:** Techniques such as yoga, meditation, and deep breathing can help to reduce stress, which can worsen pain.

Dietary changes:

- **Anti-inflammatory diet:** Consuming a diet rich in fruits, vegetables, and whole grains, while limiting processed foods and saturated fats, may help to reduce inflammation.

- **Limiting caffeine and alcohol:** These substances can worsen some endometriosis symptoms.

    - **Regular exercise:** Moderate exercise can help to improve overall health and well-being, and may also help to reduce pain.

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07

Complementary and Alternative Medicines in Endometriosis

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Endometriosis (EM) is one of the common gynecological conditions causing menstrual and pelvic pain and affects 10%–15% of women of reproductive age. In recent years, the complementary and alternative medical (CAM) treatment for EM has become popular due to the few adverse reactions reported. The CAM therapy for EM includes several different treatments such as herbs (herbal prescription, extract, and patent), acupuncture, microwave physiotherapy, and Chinese herb medicine enema (CHM enema) & psychological interventions. These CAM therapies are effective at relieving dysmenorrhoea, shrinking adnexal masses, and promoting pregnancy, with less unpleasant side effects when compared to hormonal and surgical treatments

CAM commonly designated as “other than” conventional medicine, differs from medical mainstream, is widely accepted as a kind of medical treatment, and encompasses all health systems, practices, and modalities and their accompanying beliefs, theories, and attitude of a particular culture or society in a given historical period, as defined in the 1995 CAM Research Methodology Conference. Most therapies of CAM can be considered as part of five broad classes: biological based approaches, energy therapies, alternative medical systems, muscle and joint manipulation, and mind body therapies.

Herbal Products Treatment on Endometriosis

Herbal products typically involve the use of herbal formulae of between 10 and 20 separate herbal ingredients selected from a Materia Medica of several hundred common herbs that are prepared either as a boiled decoction, as dried herbal extracts, or taken as pills or capsules (patent). Researchers evaluated the potential application and mechanism of herbal products on EM from these aspects: (1) clinical parameters including endometriotic lesion size measured by ultrasound examination;

(2) pelvic pain and dysmenorrhoea measured by determination of clinical pain visual analogue scale (VAS) method; (3) laboratory parameters including some related molecules with immune regulation, antiangiogenesis, anti-inflammatory, and cell proliferation suppression factors; (4) implanted endometrium size measured by weight and volume in EM model

Herbal Decoction Therapies in Endometriosis

There are several common decoctions used to treat EM in China, including Xuefu Zhuyu decoction (XZD), Xiaochaihu decoction (XCHD), Qu Yi Kang (QYK), Yi Wei Ning (YWN), Yi Wei San (YWS), and Huoxue Xiaoyi decoction (HXD). They relieve dysmenorrhoea, shrink ectopic lesions, and promote fertility

Herbal Extracts Therapies in Endometriosis

In recent years, several herbal extracts have been commonly used to EM treatment in China, including tripterygium wilfordii polyglycoside (Twp), puerarin, turmeric, reseratrol, green tea epigallocatechin-3-gallate (EGCG), ginsenoside Rg3, and so on.

3. Acupuncture and Moxibustion Treatment on Endometriosis

Acupuncture and Moxibustion treatment is one of the traditional Chinese acupuncture & has become accepted as a CAM therapy by the U.S.National Institutes of Health, the NHS of the UK and the WHO, and are effective for EM; though a lack of systematic review for these therapies still remains in the scientific literature. \ It was found that the acupoint of Ren Meridian (RN) and Spleen Meridian of Foot-Taiyin (SP) is more predominately involved in the Acupuncture and Moxibustion treatment than that of Bladder Meridian (BL) and Kidney Meridian (KI). The main acupoints and minor acupoints for the treatment of EM in Chinese reports are listed in table.

Main acupoints and minor acupoint for the treatment of endometriosis in reports.

The main acupoint	English name	N	Percentage	The minor acupoint	English name	N	Percen
Guanyuan	RN4	46	30.67%	Zusanli	ST36	21	35%
Sanyinjiao	SP6	34	22.67%	Hegu	LI4	6	10%
Qihai	RN6	26	17.33%	Taichong	LR3	9	15%
Zhongji	RN3	17	11.33%	Shenshu	BL23	9	15%
Zigong	EX-CA1	11	7.33%	Wailing	ST26	4	6.67%
Xuehai	SP10	8	5.33%	Tianshu	ST25	5	8.33%
Diji	SP8	8	5.33%	Taixi	KI3	3	5%
				Guilai	ST29	3	5%

Note: N: total number of reports.

3.1. Acupuncture Treatment on Endometriosis

Acupuncture therapy includes needling, auricular point, and moxa-moxibustion. It has the function of dredging meridian, regulating the balance of Yin and Yang (Chinese medicine believes that the balance of Yin and Yang determines people's health), enhancing “Qi-Blood” circulation, thereby strengthening body's resistance to disease and eliminating pathogenic factors. In clinic, acupuncture therapy for EM is confirmed to improve efficacy with fewer side effects, especially in EM-associated

dysmenorrhoea. Acupuncture analgesia is usually used to treat pelvic pain and dysmenorrhoea related to EM by mediating the central nervous system (CNS) and releasing some specific neurotransmitters. Zeng and Hong used warm acupuncture (needle warming through moxibustion) and ordinary acupuncture to treat 40 EM patients, respectively, with the same acupoint. Both of these two methods were effective and the effective rate was 95.0% and 77.5%, respectively. and the treatment was continued for three consecutive menstrual cycles. Results showed that the total effective rate was 91.4% and 80.0%, respectively.

3.2. Moxibustion Treatment on Endometriosis

Moxibustion originated from the Spring and Autumn Periods and the Warring States Periods in ancient china and has been popular since that time. Moxibustion is a technique which applies heat to acupoints by burning compressed powdered herbal material at the acupoints to stimulate them.

Moxibustion includes moxibustion with moxa cone, moxa stick, and herbal medicine cake, burning rush moxibustion and crude herb moxibustion. Moxibustion with moxa cone or moxa stick is most commonly utilized. Chinese medicine believes that the Moxibustion could warm meridians, relieve pain, and promote blood circulation. Chiu analyzes the factors about function of Moxibustion and demonstrates that with the exception of the temperature-related factors, there are some nontemperature-related factors, including smoke effects, herbal effects, and biophysical effects (far infrared). She and Xiong treated 20 EM patients of dysmenorrhoea using Guanyuan (RN4), Zhongji (RN3), Qihai (RN6), Tianshu (ST25), Sanyinjiao (SP6), Zigong (EX-CA1), and Ashi points with Ginger Moxibustion. The total effective rate was 95.0%, and following six menstrual cycles, the symptoms of dysmenorrhoea did not recur within 18 patients.

Acupuncture Combined with Moxibustion Treatment on Endometriosis

In the clinic, practitioners usually utilize acupuncture and moxibustion together to treat EM. Chen et al. reported that 72 EM patients were treated with

acupuncture and moxibustion therapy, 42 patients were pregnant, and the total effective rate was 93.05%. Combined with acupuncture, moxibustion treatment can effectively arouse the regulating function of meridian, thereby improving the body's immune function to relieve symptoms of EM.

Acupoint Injection Treatment on Endometriosis

Acupoint injection is also known as “water injection” since Chinese herbal and western medicine are injected into acupoints to treat disorders. It is based on the same meridian theory for acupuncture. This therapy collects acupuncture, medicine and meridian effects together.Sun found that the pelvic mass of ovarian chocolate cysts was significantly reduced in 88.6% EM patients after treatment by acupoint injection with Chinese herbal mixture, and the acupoints were Sanyinjiao (SP6), Xuehai (SP10), and Zigong(EX-CA1).

Acupuncture Combined with Chinese Medicine to Treat Endometriosis

In clinic, combining acupuncture and Chinese medicine for EM treatment could achieve better effect through internal recuperate and external stimulation. A clinical observation of EM showed that after treatment with acupuncture and Chinese herbal medicine, the total effective rate was 100% . Fu and Xia found that after treatment with acupuncture and medicine, the levels of serums CA125, PGE2, and PGF2α were lower, while the serum β-EP level was higher than before in EM patients.

Electroacupuncture Treatment on Endometriosis

Electroacupuncture (EA) therapy is a new acupuncture therapy that gives the body a bioelectrical trace current after needling into the acupoint. The advantage of EA is that it can control the stimulation for a long time, adjust the physiological functions of the human body, promote blood circulation, adjust muscle tension, and so forth. EA is commonly used to relieve symptoms of pain, arthralgia, and organ dysfunction in clinic. 80 cases of EM patients were randomly divided into ear EA group and body EA group. The symptoms of dysmenorrhoea were significantly relieved, and the plasma PGE2 level was decreased, while the plasma 6-Keto-PGF1α level was increased in both the ear EA and body EA groups

Acupoint Sticking Treatment on Endometriosis

Acupoint sticking therapy is a noninvasive acupoint therapy via sticking the acupoints with some specially modulated medication, based on the Chinese meridian theory. Acupoint sticking therapy is easy for patients to use themselves, so it is accepted as an adjuvant therapy to the treatment of dysmenorrhoea.The medication typically consists of herbal powder mixed with water, vinegar, wine, egg white, honey, vegetable oil, cool oil, liquid, or saliva. The mechanism of the acupoint sticking therapy is complex and not completely understood yet. Some researchers showed that sticking on acupoint can strengthen drug's absorption and recuperate meridian disorder by directly stimulating acupoint with herbal medicine.

Auricular Acupoint Treatment on Endometriosis

Chinese medicine practitioners believe that acupoint on the ear can reflect the general health of the human body.Auricular acupoint therapy is applied for the situations of pain, inflammatory diseases, functional disorders, and endocrine and metabolic disorders.Auricular acupoint therapy can be used as daily care treatment for EM, which is a convenient method to improve the patient's quality of life. Duan et al. found that auricular acupressure could relieve uterine smooth muscle spasm through meridian induction and neurotransmission, reducing the secretion of serum PGE 2.

The Treatment of Chinese Herbal Enema for Endometriosis

Chinese herbal enema is also known as anorectal drug delivery method which consists of pouring Chinese herbal medicine into the rectum where it remains for four to five hours to make the Chinese herbal medicine fully absorb through the intestinal mucosa to treat some specific diseases. This method can reduce the stimulation of the drug to alimentary canal and avoid the damage of the drug by digestive enzymes. Furthermore, Chinese herbal enema can improve the bioavailability of the drug and reduce the damage to the liver and other organs. There were several observations about treatment of EM with

Chinese herbal enema which found that Chinese herbal enema has significant therapeutic effect, especially on reducing endometriotic lesions. Zhou treated 64 EM patients with Chinese herbal enema (drugs: Common Burreed Tuber 10 g, Red Peony Root 12 g, Aeruginous Turmeric Rhizome 9 g, Turmeric Root Tuber 10 g, Peach Seed 10 g, Degelatined Deer-horn 12 g, Malaytea Scurfpea Fruit 9 g, Cassia Twig l0 g, Ground Beetle 8 g, inner membrane of chicken gizzard 15 g) and found that the total clinical effective rate was 93.8%.

The Treatment of Microwave Physiotherapy on Endometriosis

Microwave is nonionizing radiation and ultrahigh frequency electromagnetic waves with frequency between 300 and 300000 MHz and the wavelength between 1 mm and 1 m. Before treatment with microwave physiotherapy, the patient's medical history is needed to assess the patient's condition. The microwave physiotherapy should be used only in the nonacute phase of EM; it should be used with caution if the patient has metal implants in the body. Ask the patients to take supine position and expose the lower abdomen. Put the microwave physiotherapy instrument facing patient's lower abdomen with the distance of 35–45 cm, depending on patient's skin temperature. 30 min is a course of treatment. Microwave physiotherapy works by absorbing surrounding material and producing a heating effect, without changing the chemical nature of the surrounding substance, and has high security . Kanaoka Y found that microwave physiotherapy could adjust menorrhagia and inhibit uterus enlargement caused by adenomyosis .As an adjuvant treatment for EM, microwave physiotherapy shows a synergistic effect which increases the absorption rate of Chinese herbal medicine.

Chinese Herbal Enema Combined with Microwave Physiotherapy for the Treatment of Endometriosis

Chinese herbal enema and microwave physiotherapy are always combined for the treatment of endometrioses as adjuvant therapy which can produce a heating effect to promote increased absorption of Chinese herbal enema via rectal mucosa. Chinese herbs formula used as enemas can be modified according to the various symptoms patients present with. Microwave

treatment is utilized after Chinese herbal retention enema to strengthen the permeation of medication and promote the absorption and metabolism of inflammation and exudates. Since the rectum and pelvic organs are close to each other, herbal enema can be directly absorbed through the rectum and affect the lesion site directly.

Others CAM Therapies

There are some other therapies effective for EM in addition to these therapies mentioned above, such as hypnosis and thermal biofeedback . But there is lack of detailed data about the mechanisms.

6. Conclusions

CAM therapies utilized in patients with EM in the literature include herbs, acupuncture, CHM enema, microwave physiotherapy, and psychological intervention. None of these therapies are entirely curative for EM and neither can they fully eradicate the endometriotic lesions. These therapies may effectively modulate the progress of EM, however, by shrinking the lesions, suppressing the symptoms, and decreasing the recurrence rate. Although, CAM therapies have been gradually accepted in some countries, some obstacles—such as the lack of more thorough safety and efficacy studies—still hinder more widespread application of CAM therapies throughout the world. The molecular mechanisms of some CAM therapies need to be further investigated and confirmed in the future.

In summary, the active principle of the CAM therapies has a strong scientific foundation and researchers are increasing their interest in this area of medical treatment. Standardizations of the effective CAM therapies are still needed, however, including managing the pharmaceutical form of herbal agents and controlling the quality of acupuncture methods in order to increase the benefits of these alternative medical interventions to patients with EM throughout the world.

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08

Regulatory Updates on Endometriosis Treatments

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Endometriosis is an enigmatic disease which affects 10-20% of women of reproductive age.1 Endometriosis is a chronic condition where tissue similar to the lining of the uterus grows outside it, causing pain and potentially affecting fertility. Pain can be dysmenorrhea, dysuria, dyspareunia, dyschezia and diffuse non-menstrual pain. Infertility can be either primary or secondary. Endometriosis starts from adolescents and progresses through reproductive age up-to menopause

As perASRM guidelines, Endometriosis should be viewed as a chronic inflammatory disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures". 2 Hence, we need to use medical management for pain relief and ART is needed for infertility management. It also depends upon the age, previous treatment, associated pain, need for fertility and ovarian reserve. Let us see what is the management of pain. Pain management is basically surgery or medical.

Safety Guidelines

When considering these treatments, it's essential to consult with a healthcare provider to determine the most appropriate option based on individual medical history and condition severity. Monitoring bone mineral density during treatment is advisable due to potential decreases associated with these medications. Additionally, patients should be aware of possible side effects, including mood changes and liver function alterations, and report any concerning symptoms to their healthcare provider promptly.

These advancements reflect a growing recognition of the need for effective endometriosis treatments, offering new options for those affected by this condition. The treatment of endometriosis involves a range of medications and procedures, each with specific safety considerations.3 Below are detailed safety guidelines for managing endometriosis, including medication use, surgical options, and lifestyle management. Recent advancements in treatment options have been made through regulatory approvals

Safety Guidelines and Regulatory Changes for Endometriosis (2024-2025)

1. European Society of Human Reproduction and Embryology (ESHRE) Guidelines (Updated 2022-2023)

ESHRE is a leading organization focused on reproductive health and fertility.Their updated guidelines provide evidence-based recommendations for diagnosing and managing endometriosis, with a particular focus on minimizing invasive procedures and improving long-term care.4 Key updates include:

Diagnosis

Diagnostic laparoscopy should no longer be the first-line diagnostic tool unless imaging (such as transvaginal ultrasound or MRI) is inconclusive. This is to reduce unnecessary surgical risks. Non-invasive imaging (MRI, ultrasound) is recommended for detecting ovarian and deep infiltrating endometriosis.

Treatment

Being a chronic inflammatory disease with increased COX 2 over expression anti-inflammatory agents like Ibuprofen, Mefenamic acid and Naprosyn can be used. Hormonal suppression (e.g., combined oral contraceptives, progestogens) should be the first-line therapy for pain relief.5 Depot GnRH agonists and oral antagonist are used beyond 16 years. As there is increased aromatase activity, it can be tackled by aromatase inhibitors, like letrozole and Anastrazole which are second line agents.

Postoperative hormone therapy is recommended to prevent recurrence of endometriotic lesions unless the patient needs immediate fertility. Surgery is the only recommended if medical treatments are ineffective or if there are fertility concerns especially when the patient has Endometriosis Associated Pelvic Pain (EAPP).

Adolescent Endometriosis

Early diagnosis is crucial to prevent chronic pain and infertility. Hormonal therapies, including COCs and progestins, are the primary treatment for adolescents to manage symptoms.6 Common progestins used are Norethisterone, Medroxyprogesterone acetate and Dienogest. Beyond 16 years, GnRH agonists like Leuprolide and oral antagonists like Elagolix and Relugolix combination therapy can be used.

2. Federation of Obstetric and Gynecological Societies of India (FOGSI) Recommendations (2024)

FOGSI's new "Good Clinical Practice Recommendations" (GCPR) focus on improving diagnosis and patient-centered treatment in India, where awareness and early diagnosis remain challenges.7 Key recommendations include:

Diagnosis

Symptom-based diagnosis should be prioritized, especially in resource-limited settings. Routine imaging and, if needed, diagnostic laparoscopy for complex cases.

Treatment

Non-surgical management with hormonal therapy is preferred for patients not seeking immediate pregnancy. For severe cases or patients with fertility concerns, laparoscopic management is recommended.

Awareness and Training

Increased training for general practitioners and gynecologists to improve early diagnosis and management.

3. National Institute for Health and Care Excellence (NICE) Guidelines (UK – Updated 2023)

The NICE guidelines focus on timely diagnosis and multidisciplinary care. Their primary objective is to reduce diagnostic delays and ensure patient-centered treatment.8 Key points include:

Diagnosis

Emphasizes early referral for specialist care if symptoms persist despite first-line treatment. Encourages the use of imaging (especially transvaginal ultrasound) before laparoscopy.

Treatment

First-line treatment: Nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives. Surgical intervention is reserved for cases where symptoms do not respond to medical therapy.

Holistic Care

Recommends involving mental health professionals to support patients with chronic pain and emotional distress.

4. U.S. Food and Drug Administration (FDA) Regulatory Changes (2023-2024)

Elagolix : In July 2018, the U.S. FDA approved Elagolix, the first oral gonadotropin-releasing hormone (GnRH) antagonist specifically developed for women with moderate to severe endometriosis pain.9 Clinical trials demonstrated that Elagolix significantly reduced daily menstrual pelvic pain, non-menstrual pelvic pain, and pain during intercourse.

However, it may cause decreases in bone mineral density, and possible serious adverse effects include suicidal thoughts and abnormal liver tests.

Relugolix Combination Therapy - In August 2022, the FDA approved a combination therapy containing Relugolix, Estradiol, and norethindrone acetate (Relugolix Combination Therapy) for treating moderate to severe pain associated with endometriosis.10 Clinical studies showed that Relugolix Combination Therapy reduced menstrual pain and non-menstrual pelvic pain with a loss of mean bone mineral density of less than 1% from baseline through one year of treatment.

Diagnostic Innovation

The FDA granted Fast Track Designation to 99mTc-maraciclatide, a novel imaging agent that can detect superficial peritoneal endometriosis without surgery.

5. NHS England Approval (2025)

As of March 2025, a new daily pill combining Relugolix, Estradiol, and norethisterone has been approved for use in the NHS across England. This "first-of-a-kind" treatment works by blocking specific hormones that contribute to endometriosis while providing necessary hormone replacement.11 The medication eliminates the need for multiple medications and regular trips to clinics for injections.

To conclude, though endometriosis is an enigmatic disease, with changing dilemmas from diagnosis to management. In the past we did not have any definite protocols.12 Recent guidelines from various societies and regulatory bodies give us somewhat uniform view about diagnosis and management of endometriosis.

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09

Impact of Nutrition Supplements in Endometriosis

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Endometriosis is a chronic gynaecological disease , affecting 10 – 15 % of women in reproductive age , characterised by the presence of endometrium like tissue outside the uterine cavity usually associated with inflammation .

Current treatment depends of the symptoms of the patient , their age , the extent and location of endoemtriosis , previous treatment taken , surgeries done , the co morbidities that are present . In view of the need for lifelong therapy , tailoring it to meet the various demands at different points of life in a woman , makes nutrition supplements an interesting option in management .

This article looks at polyphenols , vitamins D and, PUFAs in treatment of endometriosis.

Polyphenols are a large group of bioactive compounds synthesized by plants , widely recognized for their anti-oxidant and anti-inflammatory properties[1]

Quercetin:

Quercetin is a naturally occurring flavonol found in various fruits and vegetables such as onions, cauliflower, apples, berries, and chili peppers .. Quercetin exerts the anticancer effects by reducing cancer cell viability and enhancing apoptosis and autophagythrough the modulation of Akt, mammalian target of rapamycin (mTOR), and HIF-1signaling pathways .

Antiproliferative and anti-inflammatory effects of intraperitoneally injected quercetin were observed in an auto-implanted mouse model of endometriosis

Signorile et al. (2018) investigated 30 patients defined as stage IV of endometriosis treated for three months with a dietary supplement containing, e.g., 200 mg quercetin. , assessing the reduction in the inflammatory response and endometriosis's symptoms and its harmful effects on affected organs in patients with endometriosis. Data proved a significant effect in reducing the pain and other disabling disease symptoms in the patients treated with a dietary supplement. The substantial decrease in serum PGE2 levels observed after treatment indicated supplement anti-inflammatory potential . The authors belive the endometriosis foci' size was reduced due to the decreased serum CA-125 concentration. Further studies of dietary supplement combined with standard therapies are necessary to establish potentially practical new endometriosis treatment strategies.[2]

Curcumin:

Curcumin is a polyphenolic monomer extracted from turmeric of Curcuma longa. Scientific research suggests that curcumin represents some potential therapeutic roles as an anti-inflammatory, anti-cancer, and anti-aging agent . In the murine model, curcumin administration was associated with the reduction in endometriosis progression and apoptosis activation. Curcumin caused the regression of endometriosis predominantly via the cytochrome c-mediated mitochondrial pathway of
apoptosis, and apoptotic responses include both p53-dependent and independent path. Curcumin acted as an inhibitor of NF-_B translocation and downregulated MMP-3, thus mediating endometriosis regression .In experimental rat models, curcumin decreased the weight and volume of endometriotic tissues in a dose-dependent manner via downregulating VEGF expression

Resveratrol:

Resveratrol is a phytoalexin polyphenol, which various plants naturally produce in response to ultraviolet radiation and fungal infections. Resveratrol naturally occurs in many plant species, including peanuts, berries, legumes, and grasses; however, resveratrol's richest sources are grapes and red wine.

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Resveratrol anti-inflammatory potential, including prostaglandin synthesis inhibition, has been suggested to probably contribute to the prevention and treatment of endometriosis. Maia et al. (2012) assessed the advantages of the association of resveratrol with oral contraceptives for the management of endometriosis-related pain. They monitored the resveratrol effect in 12 patients who failed to obtain pain relief after treatment with an oral contraceptive containing drospirenone with ethinylestradiol. After two months of using 30 mg of resveratrol to the standard hormone therapy, 82% of patients reported complete resolution of dysmenorrhea and a significant reduction in pain occurrence. .Combined therapy successfully reduces the aromatase and COX-2 expression compared with hormone therapy alone.

More recently, researchers at the Tehran University of Medical Sciences carried out an exploratory clinical trial, which included 34 patients with endometriosis-associated infertility. Participants of the study, randomly and equally divided into control and treatment groups, took 400 mg resveratrol twice daily for 12–14 weeks along with oral contraceptives in the last three weeks. The clinical trial showed that resveratrol could modify the inflammation process in the endometrium of women with endometriosis. The results obtained revealed downregulation of the mRNA and protein expression of MMP-2 and MMP-9 inendometrium tissue, endometrium fluid, and serum following resveratrol treatment.[3]

Vitamin D is of utmost importance in cellular proliferation, cellular differentiation, and inhibiting angiogenesis. It has been also found to play a role in immune modulation, where it helps in down regulating pro-inflammatory cytokines, such as tumor

necrosis factor alpha (TNF-α), interleukin 1 (IL-1), andIL-6, and up regulating anti-inflammatory ones. Vitamin D responsive elements are present in many tissues.

The primary source of vitamin D is its endogenous synthesis, and dietary sources are responsible for providing less than 20% of circulating levels of vitamin D. Vitamin D can be found in various foods such as fatty fish, mushrooms, fish liver oils, cheese, beef liver, eggs, dark chocolate, and fortified foods like milk, yogurt, and orange juice.

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Vitamin D deficiency is a significant health concern,with a recommended serum level of 20 ng/ml for maintaining calcium balance and 30 ng/ml for optimal cellular health.

Cellular and molecular studies have shown that vitamin D treatment can down regulate key molecules involved in proliferation, invasion, angiogenesis, and inflammation in endometriotic cells. Animal studies further support these findings by demonstrating
regression of endometriotic implants with vitamin D treatment in rat models. Human clinical studies, however, have yielded mixed results regarding the association between vitamin D levels and the risk and severity of endometriosis[4].

Fish oil has been shown to decrease circulating levels of series 2 prostaglandins and decrease dysmenorrhea and inflammatory symptoms. Omega 3 (n-3) and omega 6 (n-6) PUFAs are found in fatty fish and seed/vegetable oils .Akyol et al., in a randomized, single-blind, prospective and controlled experimental trial on female rats, observed that omega 3 caused a considerable recession of endometriotic implants . In a clinical trial by Nodler et al., a reduction in pelvic pain in women withendometriosis who complemented fish oil rich in omega 3 was noted; however, a similar result was noticed in the placebo group.[5]

In conclusion : Knowledge of the precise mechanisms of action of the natural compounds in
the endometriosis's network of several cell signaling pathways is required, and further studies on this topic are needed

Furtherresearch is needed to fully understand the mechanisms and optimal strategies for utilizing vitamin D in the treatment
of endometriosis.

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10

Technological Innovations in Endometriosis Patient Monitoring

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Endometriosis is a chronic condition affecting millions of women worldwide, characterized by the presence of endometrial-like tissue outside the uterus, leading to pain and infertility. Research indicates that 40%–50% of post-surgery patients experience symptom recurrence within five years, often necessitating multiple surgical interventions [1,2] . Recent technological advancements in patient monitoring are revolutionizing the management of endometriosis, providing innovative tools for symptom tracking and treatment optimization. This chapter explores cutting-edge developments in wearable devices, mobile applications, digital imaging, telemedicine, smart implants, and virtual reality (VR) solutions, showcasing their potential to enhance endometriosis care thereby , avoiding unnecessary multiple surgeries. Technological innovations in endometriosis patient monitoring include :

1. Wearable Devices & Biosensors

Advancements in wearable technology are transforming the monitoring and management of endometriosis. Key developments include:

- **Smart Wearables:** Devices such as smartwatches and rings track physiological parameters like heart rate variability, sleep patterns, and temperature fluctuations, which can signal symptom flare-ups. Notable innovations include:
    - Biofourmis and Chugai Pharmaceutical Collaboration: This wearable biosensor system digitally measures endometriosis pain using artificial intelligence to analyze physiological biomarkers, providing continuous pain quantification.[3]

- Femometer Smart Ring: Tracks basal body temperature, menstrual cycles, sleep stages, heart rate, and stress levels, aiding in understanding and managing endometriosis.[4]

- Luna Ring: Focuses on menstrual health, offering period and symptom tracking, smart period predictions, and AI assistance to support individuals managing endometriosis.

- Multifunctional Hybrid Skin Patches: Capable of electrochemical biomarker analysis (e.g., glucose) while simultaneously monitoring physiological signals such as electrocardiograms (ECGs), facilitating chronic disease management.

- Hydrogel Microneedle Sensor Patches: Allow for minimally invasive collection of interstitial fluid while measuring biomarker levels in real time.

Studies suggest that wearable devices provide not only new data modalities but also more accurate and unbiased measurements than self-reported data on sleep and physical activity.

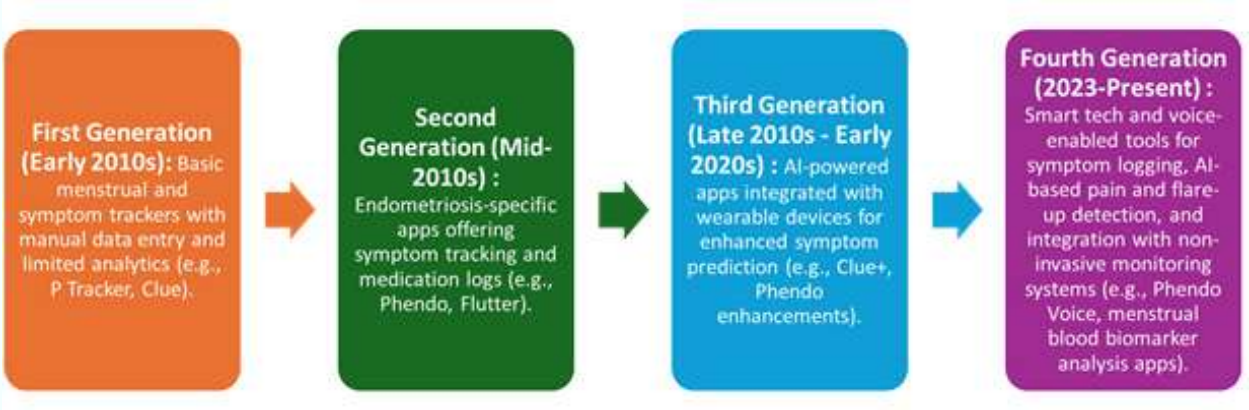
2. Mobile Apps & AI-Powered Symptom Tracking

The evolution of mobile applications has significantly improved symptom tracking and treatment personalization for endometriosis patients:

- **Endometriosis-Specific Apps**: Endometriosis-specific apps like Flutter, Phendo, and Clue enable patients to track symptoms, menstrual cycles, and medication use, providing valuable data for personalized treatment. Additionally, mobile apps such as MindDoc and PainScale support mental health and pain management, while Endometrix, Wana, and Flutter offer comprehensive symptom tracking, community engagement, and menstrual health monitoring.[5]

- **AI Integration:** AI-driven analysis of user data helps predict symptom patterns, enabling healthcare providers to tailor treatment strategies.

Generational Advancements in Endometriosis Apps:



3. Smart Implants & Biodevices

- Innovations in implantable monitoring systems hold promise for real-time symptom detection and early intervention:

- **Implantable Sensors:** Small, biocompatible devices placed in the pelvic region monitor inflammation markers and transmit data for early symptom detection.

- **Verso Biosense's Intrauterine Device (IUD):** A battery-less IUD embedded with sensor technology that continuously measures intrauterine conditions to detect endometriosis-related anomalies early and cost-effectively.

- While these developments are promising, more research and further clinical validation should be done before widespread adoption.

4. Virtual Reality (VR) & AI Chatbots

Emerging technologies in VR and AI-powered support systems are improving symptom management and patient education:

- **VR Pain Management:** Endometriosis Patient with chronic pain can be manage using VR-based cognitive behavioral therapy (CBT) through guided relaxation techniques.

- **AI Chatbots for Support:** AI chatbots like LasaAI, Doctronic's AI Assistant, Phendo are virtual assistants offer round-the-clock guidance on symptoms, lifestyle changes, and treatment adherence. These technological innovations are offering improved quality of life and more effective treatment solutions for patients .These technologies are reshaping how endometriosis is monitored and managed.

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11

Clinical Trials Spotlight: Endometriosis

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1. Introduction

Endometriosis is a chronic, estrogen-dependent, inflammatory disorder that affects 6–10% of reproductive-age women globally. Characterized by ectopic endometrial-like tissue growth, it leads to debilitating symptoms such as chronic pelvic pain, dysmenorrhea, dyspareunia, infertility, and fatigue. Despite its high prevalence and impact, treatment options remain limited and often suboptimal, primarily relying on hormonal suppression, surgery, and analgesics. Traditional treatments, including GnRH agonists and oral contraceptives, are associated with significant side effects, recurrence rates, and fertility concerns. The need for more effective, long-term, and non-hormonal therapies has driven extensive research, leading to multiple ongoing and recently completed clinical trials. These trials aim to explore novel endocrine-based therapies, targeted anti-inflammatory agents, neurogenic pain modulators, and regenerative treatments. This article provides a comprehensive review of recent clinical trials, analyzing their mechanisms, outcomes, and potential impact on clinical practice.

2.Classification of Novel Interventions in Clinical Trials

2.1 Endocrine-Based Therapies: Advancing Beyond Conventional Hormonal Suppression

Hormonal modulation remains a cornerstone of endometriosis treatment. However, recent trials are refining this approach by improving efficacy, reducing side effects, and offering alternative administration methods.

Gonadotropin-Releasing Hormone (GnRH) Antagonists

- Elagolix (Phase III, NCT04333576): A GnRH antagonist showing promise in reducing pain and lesion progression while offering better tolerability than traditional GnRH agonists.

- **Linzagolix (Phase III, NCT03992846, NCT03986944):** A once-daily oral GnRH antagonist with potential for individualized dosing, allowing for partial estrogen suppression to reduce bone mineral density loss.

Selective Progesterone Receptor Modulators (SPRMs) and Androgen-Based Treatments

- **Dienogest (Phase III, NCT04256200):** A progestin-based therapy with improved efficacy for pain relief and lower recurrence rates compared to standard progestins.

Aromatase Inhibitors

- **Letrozole and Anastrozole (Phase II trials):** Designed to reduce local estrogen production in endometriotic lesions, potentially minimizing disease progression and recurrence.

2.2 Non-Hormonal Anti-Inflammatory and Immune-Modulating Agents

Given that chronic inflammation is a key driver of endometriosis-related pain and lesion persistence, clinical trials are investigating targeted anti-inflammatory strategies.

IL-33 Inhibitors (Phase II, NCT03840993 – MT-2990)

- IL-33 is a pro-inflammatory cytokine implicated in lesion formation and pain sensitization.
- MT-2990, a monoclonal antibody targeting IL-33, has demonstrated potential to reduce pelvic pain and lesion activity without hormonal side effects.

TNF-α Modulators (Experimental Phase I/II Trials)

- **Adalimumab,** an anti-TNF-α agent, is under investigation for its potential to halt endometriotic lesion progression and improve pain outcomes.

Gut-Microbiota-Based Interventions

- Microbiome-targeted therapies are being explored for their role in modulating systemic inflammation and immune dysregulation in endometriosis.

2.3 Neuroinflammatory and Pain Modulation Strategies Endometriosis-related pain is often neuropathic, involving central and peripheral sensitization. New trials are focusing on novel neuromodulators to interrupt pain signaling.

● **P2X3 Receptor Antagonists (Phase I, NCT04487431, NCT04471337, NCT04454424)**

- These drugs block pain transmission through purinergic receptors, reducing chronic pain and hypersensitivity.

● **Naltrexone + Norethindrone Acetate (Phase III, NCT03970330)**

- Naltrexone, an opioid receptor antagonist, may alter pain perception and inflammation, offering a non-hormonal pain relief option.

2.4 Regenerative and Fertility-Preserving Therapies

For women with endometriosis-associated infertility, novel approaches aim to enhance endometrial receptivity and ovarian function.

● **Stem Cell Therapies (Preclinical to Early Phase Trials)**

- Endometrial-derived mesenchymal stem cells are being explored for their ability to repair damaged reproductive tissues and improve implantation rates.

● **Quinagolide (Phase II, NCT03749109, NCT03692403)**

- A dopamine D2-receptor agonist, under study for its potential to reduce endometriotic lesion vascularization, potentially aiding fertility preservation.

- **2.5 Ethanol Sclerotherapy: A Minimally Invasive Alternative for Endometrioma Management**

Currently, conventional laparoscopic surgery with divergent cystectomy is still the standard treatment (Nezhat et al., 1989; Vercellini et al., 2006; Hart et al., 2008). However, evidence suggests that the ovarian reserve is compromised during the surgical excision of endometriomas, especially in the case of multiple interventions (Garcia-Velasco and Somigliana, 2009; Roustan et al., 2015). Transvaginal ethanol sclerotherapy treatment (EST) under ultrasound guidance for endometrioma was first described in 1988 in Japan by Akamatsu et al. (1988). Yazbeck et al. (2009, 2012) later standardized the current technique commonly used (Miquel et al., 2021).

EST is easy to perform, allows outpatient treatment, and requires minimal equipment (Miquel et al., 2021). It makes possible the management of isolated endometriomas by avoiding laparoscopic surgery, which is more invasive, requires a longer recovery and poses a higher risk of complications (Garcia-Tejedor et al., 2020). Moreover, using the vaginal method, EST does not present any aesthetic inconvenience.

The meta-analysis of Kim et al. (2021), as well as the article of Ghasemi Tehrani et al. (2022), provide reassuring evidence regarding the benefits and risks of EST for endometrioma. These publications, along with the 2022 guidelines from ESHRE, are starting to acknowledge the potential of EST in the management of endometrioma (The ESHRE Guideline Group on Female Fertility Preservation et al., 2020). The literature suggests that EST effectively reduces the size of endometrioma, alleviates symptoms, and improves fertility outcomes.

3. Challenges in Bringing New Treatments to Market

While these trials are promising, several challenges remain:

- **Patient Recruitment & Heterogeneity:** Endometriosis presents with variable phenotypes, making standardized clinical trials difficult.

- **Long-Term Safety Concerns:** Many new therapies lack long-term data on recurrence and fertility outcomes.

- **Regulatory & Cost Barriers:** New drugs face rigorous approval processes, and affordability remains a key issue for widespread adoption.

4. Future Directions and Clinical Implications

Future research should focus on:

- **Developing Personalized Treatments:** Integrating genetic and biomarker-based profiling into clinical trials.

- **Advancing Non-Invasive Diagnostics:** Utilizing imaging (MRI, PET-CT) and blood-based biomarkers to improve early detection.

- **Exploring Combination Therapies:** Merging anti-inflammatory, neuromodulatory, and endocrine-based approaches for better outcomes.

5. Conclusion

The landscape of endometriosis treatment is evolving, with ongoing and recently completed clinical trials offering exciting prospects. Advances in hormonal, immune-modulating, neuromodulatory, and regenerative therapies provide hope for more effective, patient-friendly interventions. Continued investment in research, global collaboration, and patient-centered approaches will be key in bringing these innovations into routine clinical practice.

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12

Educational Resources for Healthcare Providers

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Resources for endometriosis are crucial for healthcare workers (HCWs) because they help improve diagnosis, treatment, and patient support. The importance of resources includes the following:

1. Early and Accurate Diagnosis – Endometriosis is often misdiagnosed or diagnosed late (average delay of 7-10 years). Resources like clinical guidelines, imaging protocols, and symptom checklists help HCWs recognize signs early and differentiate them from other conditions like IBS or pelvic inflammatory disease.

2. Updated Treatment Approaches – New research and treatment guidelines evolve over time. Access to resources like the European Society of Human Reproduction and Embryology (ESHRE) or American College of Obstetricians and Gynecologists (ACOG) guidelines ensures HCWs provide evidence-based care, including hormonal therapies, surgical interventions, and pain management.

3. Patient Education & Support – Endometriosis is a chronic condition requiring long-term management. Resources help HCWs educate patients on lifestyle modifications, pain management strategies, and available support groups, improving adherence to treatment and quality of life.

4. Multidisciplinary Coordination – Managing endometriosis often involves gynecologists, pain specialists, dietitians, and mental health professionals. Resources facilitate better communication and coordination among HCWs, ensuring holistic care.

5. Fertility Considerations – Endometriosis can impact fertility, and many patients seek advice on reproductive options. HCWs benefit from resources on fertility preservation, assisted reproductive technologies (ART), and counseling.

6. Research and Advocacy – Many endometriosis patients feel unheard or dismissed. Awareness resources help HCWs stay informed about ongoing research, new treatment trials, and advocacy efforts to improve patient outcomes.

Access to well-structured resources ensures HCWs provide compassionate, informed, and effective care for endometriosis patients. Here are some key resources for healthcare workers (HCWs) managing endometriosis:

Clinical Guidelines & Research-Based Resources

1. European Society of Human Reproduction and Embryology (ESHRE) GuidelinesProvides comprehensive, evidence-based guidelines for diagnosis and treatment.

2. American College of Obstetricians and Gynecologists (ACOG) – Endometriosis Practice Bulletin Covers best practices for medical and surgical management.

3. World Endometriosis Society (WES)
Offers global research updates, guidelines, and multidisciplinary approaches.

4. The Lancet and New England Journal of Medicine (NEJM)
Regularly publish the latest research on endometriosis management.
The Lancet | NEJM

Patient Education & Support Resources

5. Endometriosis UK
Provides patient-centered educational materials, symptom trackers, and support group connections.

6. Endometriosis Foundation of America (EndoFound)
Focuses on public awareness, patient education, and clinical resources.

7. The Pelvic Pain Support Network
Helps HCWs guide patients in managing chronic pelvic pain and co-existing conditions.

Multidisciplinary & Surgical Resources

8. International Society for Gynecologic Endoscopy (ISGE)
Provides surgical best practices and training programs.

9. The American Society for Reproductive Medicine (ASRM)
Covers endometriosis-related fertility issues and ART (assisted reproductive technology).

JOURNALS & RESEARCH ARTICLES

1. Journal of Endometriosis and Pelvic Pain Disorders
- Publishes the latest research and case studies.
- JEPPD Journal

2. Human Reproduction (Oxford Academic)
- Features cutting-edge research in reproductive health.
- Human Reproduction

3. Fertility and Sterility (ASRM Journal)
- Covers reproductive endocrinology and surgical advancements.
- Fertility and Sterility

13

Pharmacological Research in Endometriosis

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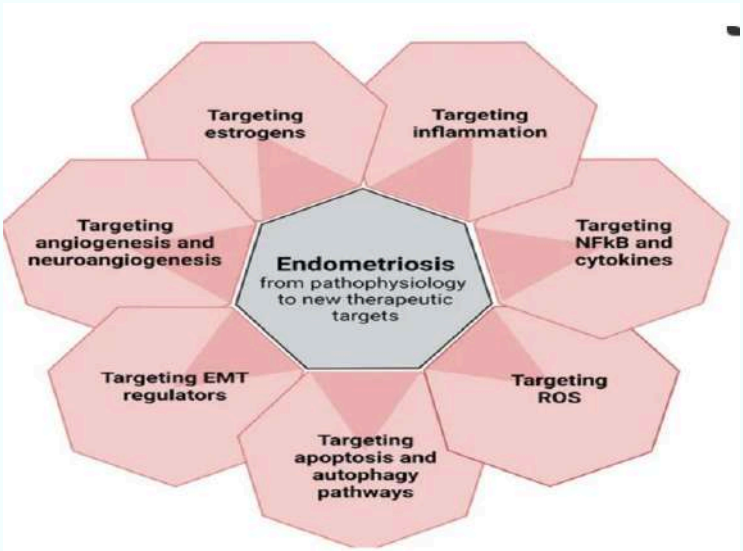
Introduction

Endometriosis is a chronic, estrogen-dependent gynecological condition that affects millions of women worldwide. It is characterized by the growth of endometrial-like tissue outside the uterus, leading to inflammation, pelvic pain, and infertility. While surgical interventions are available, pharmacological treatments remain essential for symptom management and disease suppression. Ongoing research aims to develop novel drugs that are more effective, have fewer side effects, and preserve fertility. This article examines the latest advancements in endometriosis drug development and the future of treatment.

Treatment for endometriosis involves a multi-targeted approach addressing key biological pathways. Hormonal therapies, like oral contraceptives or GnRH agonists, help regulate estrogen levels, while anti-inflammatory treatments such as NSAIDs and corticosteroids reduce pain and inflammation. Inhibiting NF-κB and cytokines can modulate immune responses, and antioxidants like N-acetylcysteine reduce oxidative stress. Drugs targeting apoptosis and autophagy affect cell survival and lesion growth, while preventing epithelial-mesenchymal transition (EMT) limits tissue invasion. Anti-angiogenic therapies control blood vessel formation, helping manage lesion growth. This combined approach aims to target the underlying mechanisms of the disease



Current Pharmacological Approaches

1. Progestogens and Selective Progesterone Receptor Modulators (SPRMs)

Progestogens, such as Dienogest (DNG), work by reducing estrogen levels, inhibiting endometrial proliferation, and suppressing inflammation. While effective for managing mild cases, they are unsuitable for women seeking pregnancy due to ovulation inhibition. Selective Progesterone Receptor Modulators (SPRMs), such as Vilaprisan, show promise in modulating progesterone receptors but were discontinued due to toxicity concerns. Future efforts focus on refining SPRMs to improve their efficacy while minimizing adverse effects.

2. Gonadotropin-Releasing Hormone (GnRH) Agonists & Antagonists
GnRH agonists like Elagolix and SKI2496 suppress gonadotropins, creating a hypoestrogenic state that alleviates symptoms of endometriosis. However, prolonged use of GnRH agonists can lead to bone mineral density loss, necessitating add-back hormone therapy. GnRH antagonists, offering better symptom control with fewer side effects, represent a safer long-term management option.

3. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
NSAIDs are commonly used for pain management in endometriosis. While effective in alleviating symptoms, they do not modify disease progression. Long-term NSAID use can lead to gastrointestinal complications, highlighting the need for alternative anti inflammatory therapies.

4. EP4 Receptor Antagonists

A new class of anti-inflammatory drugs, EP4 receptor antagonists like BAY1316957, target prostaglandin pathways involved in pain and inflammation. Early studies show promising results in reducing pain associated with endometriosis without the hormonal side effects seen in traditional therapies.

5. Selective Estrogen Receptor Modulators (SERMs)
SERMs, such as Bazedoxifene, exhibit a dual action of blocking estrogen in endometrial tissue while preserving its positive effects on bone health. This selective action makes SERMs an appealing alternative for patients at risk of osteoporosis due to long-term estrogen suppression.

6. Aromatase Inhibitors (AIs)
Endometriosis lesions exhibit high aromatase activity, leading to local estrogen production. AIs, like Letrozole, reduce estrogen synthesis, thereby suppressing lesion growth. They may also improve fertility in women with endometriosis, making them a valuable option for those desiring pregnancy.

Emerging and Future Therapies

1.Natural Compounds &Nutraceuticals
Several plant-derived compounds are under investigation for their potential therapeutic benefits. Resveratrol, a polyphenol found in red grapes, has demonstrated anti-inflammatory and anti-proliferative effects in endometriosis models. Other compounds such as curcumin

and epigallocatechingallate (EGCG) from green tea are being studied for their ability to modulate estrogensignaling and inflammation. Harbour and Plant Waste Compounds: Many traditional herbal remedies, such as GuiZhi Fu Ling Wan, have been shown to reduce inflammation and improve pain management. These compounds contain a variety of bioactive molecules with anti-inflammatory properties that may help regulate immune responses and reduce lesion growth. Sulforaphane, derived from cruciferous vegetables, has demonstrated anti-inflammatory and anti-angiogenic properties, reducing lesion size in animal models. Fisetin, a flavonoid, suppresses NLRP3 inflammasome activation, reducing inflammation and fibrosis in models of endometriosis.

Drug Name	Target	Dose	Effects
GuiZhi Fu Ling Wan (GZFLW)	PI3K/Akt pathway	0.54–1.08 g/Kg oral	↓Uterine contractions, ↓NO, ↓PGF2α, ↓Ca2+
		1.89 g/mL	Inhibits inflammation, ↓volume of lesions, ↓sensitivity to pain
		2 caps Gynoclear©/3 td	↓Dyspareunia, ↓fatigue, ↑QoL
Sulphoraphane	PI3K/Akt pathway, Nrf2/ARE	5–30 mg/Kg intragastrical	↓Endometriotic foci, ↓adhesion score, ↓ IL-6, IL-10, TNF-α, IFN-γ, and VEGF
		5,15,30,60 mg/Kg/day intraperitoneal	Inhibit ectopic endometrial tissue growth, ↓pain
Danefukang extract (DEFK)	Not described	15 g/2td/15 days	↑QoL, ↓depression, ↓anxiety, ↓TNF-α, ↓IL-6, ↓Ca125
Fisetin	NLRP3	40 mg/kg/day oral	↓Endometriotic implantation, ↓mast cell infiltration, ↓fibrosis, ↓histological alterations, ↓neutrophil infiltration, ↓cytokine release, ↓oxidative stress, ↓nitrotyrosine, ↓poly ADP ribose expressions, ↑apoptosis in endometrial lesions

Fisetin	NLRP3	40 mg/kg/day oral	↓ Endometriotic implantation, ↓ mast cell infiltration, ↓ fibrosis, ↓ histological alterations, ↓ neutrophil infiltration, ↓ cytokine release, ↓ oxidative stress, ↓ nitrotyrosine, ↓ poly ADP ribose expressions, ↑ apoptosis in endometrial lesions
Quince seed Mucilage	MAPK pathway, Caspase-3	2 cc/day vaginal	↓ Inflammation, ↓ apoptotic process, ↓ mitochondrial damage, restoring the uterine mucosa
		+50 mg/kg/day Hesperidin	
Ferulic acid	Not described	500 µM (in vitro)	↓ Inflammatory cytokines, ↓ angiogenic factor (VEGF)
		4 g/Kg once oral (rats)	↓ Inflammatory cytokines, ↓ angiogenic factor (VEGF)

Resveratrol	MAPK pathway	100 µmol/L (in vitro)	↓ MCP-1, ↓ IL-6, ↓ IL-8, ↓ RANTES
Baicalein	MAPK pathway, Nrf2/ARE	20 µM (in vitro)	Ferroptosis inhibition, Restoration of phagocytosis

1,25 (OH)2 D3	VDR	In vitro	↓TNF-α, ↓inflammatory cytokines
Ascorbic acid	Not described	1000 mg + 800 IU vitamin E/day oral	↓malondialdehyde, ↓ROS, ↓dysmenorrhea, ↓dyspareunia, ↓CPP
Omega fatty acids	Not described	1000 mg/2 td	↓PP, ↑QoL

2. Immunotherapy and Cytokine-Based Treatments

Endometriosis is increasingly viewed as an immune-related disorder, prompting research into immunomodulatory therapies: Interleukin (IL) inhibitors, such as IL-33 antibodies, target cytokines involved in the inflammation associated with endometriosis. Tumor necrosis factor-alpha (TNF-α) inhibitors, commonly used in autoimmune diseases, are also being tested for their ability to reduce lesion progression.These therapies hold significant promise for more targeted and effective treatment by addressing immune dysfunction.

Drug Name	Target	Effects
IL-33 Ab	IL-33	↓Development EM, ↓Ferropoptosis tolerance eESC, ↑M1 macrophage polarization
IL-8 Ab	IL-8	↓Nodular lesions, ↓volume adhesions, neutrophils migration inhibition
IL-6R Ab	IL-6R	Suppress volume endometriotic lesions
CTLA-4 Ab	CTLA-4	Proliferation and invasion of ectopic endometrial cells suppression
CD47 Ab	CD47	Inhibition of growth and cellular migration, ↑apoptosis

CD20 Ab	Rituximab	↓Endometriotic implant size		
EP4 antagonist	PGE2R	↓cAMP levels, ↓expression growth factor		
Lipoic acid	cAMP, protein kinase A signaling/ NF-kB	↓NALP-3, ↓IL-1β, IL-18, ↓ICAM-1, ↓activity MMP2, 9, ↓invasion		
TGR5 agonist INT-777	TGR5	↓proinflammatory cytokines, ↓adhesion molecules, Inhibits NF-κB		
Sunitinib	p-VEGFR-PI3K-AKT-YBX1-Snail signaling pathway	↓tumor migration, ↓tumor invasion		
Gal3C	Galectin3	BSA-GOx-NP	Neutrophils	↓Implantation

BSA-GOx-NP	Neutrophils	↓Implantation

3.Dopamine Receptor Antagonists

Drugs like Quinagolide, which inhibit angiogenesis and lesion growth, have been tested but showed no significant improvement over placebo. Refining the dosage and combining these drugs with other therapies may improve their efficacy in future trials.

4. Epigenetic and Gene-Based Therapies

The role of epigenetics in endometriosis is gaining attention, as research suggests that epigenetic modifications, such as DNA methylation and histone modification, may influence disease progression and immune system dysfunction. Epigenetic therapies aim to modify these alterations and restore normal cellular behavior: MicroRNA (miRNA)-based therapies could be used to regulate the expression of genes involved in inflammation, lesion survival, and immune dysfunction.

Gene-editing technologies, such as CRISPR, hold the potential to directly alter the genetic material of endometrial cells, offering a personalized approach to treat endometriosis by correcting the molecular defects that contribute to the disease.These gene-based therapies could provide more precise and effective treatment options with fewer side effects compared to traditional approaches.

5. Stem Cell and Regenerative Medicine Approaches

Stem cell therapies are being explored for their potential to regenerate damaged tissue and modulate the immune response in endometriosis: Mesenchymal stem cell-derived exosomes are of particular interest, as they may help reduce inflammation, promote tissue repair, and restore immune function in the endometriotic lesions. These exosomes are small particles secreted by stem cells and have been shown to carry bioactive molecules that modulate the immune response. Regenerative medicine aims to promote healing and reduce fibrosis in endometriosis-affected tissues, potentially leading to long-term management and better fertility outcomes. These approaches offer potential for long-term solutions and a non-invasive way to manage endometriosis.

6. Vitamins and Antioxidants

The chronic inflammation and oxidative stress present in endometriosis contribute to disease progression. Vitamins and antioxidants can help mitigate these effects: Vitamin C and E supplementation has been shown to reduce oxidative stress markers and alleviate pain in patients with endometriosis. Resveratrol, a compound found in grapes, has demonstrated anti inflammatory and antioxidant properties, showing promise for managing pain associated with endometriosis. Baicalein, a flavonoid, promotes

ferroptosis, helping eliminate endometriotic cells and reduce inflammation.These natural antioxidants can support the body's defense against oxidative stress and inflammation, offering an adjunct to conventional therapies.

7. Essential Fatty Acids (EFAs)

Essential fatty acids, particularly omega-3 and omega-9 fatty acids, have demonstrated beneficial effects in reducing inflammation and pain in endometriosis models. These fatty acids help modulate the immune response and reduce the production of pro-inflammatory mediators:
Omega-3 fatty acids, found in fish oil and flaxseeds, are particularly effective at reducing pro-inflammatory cytokines and alleviating pain in endometriosis patients.
Omega-9 fatty acids, found in olive oil, have anti-inflammatory properties and may support overall immune health. Incorporating these fatty acids into treatment regimens could reduce the need for long-term pharmacological interventions and offer an additional, natural way to manage symptoms.

Repurposed Drugs

Repurposed drugs offer an exciting opportunity in the treatment of endometriosis, providing faster and more cost-effective alternatives to developing new medications from scratch. While some repurposed drugs show significant promise, it is essential to conduct further clinical trials to confirm their safety and efficacy for this specific condition. By building on the established mechanisms of action of these drugs, future research may unlock a variety of treatment options that better manage endometriosis symptoms while reducing side effects and enhancing quality of life.

Drug Name	Target	Model/Dose	Effects
Levofloxacin	Bacterial topoisomerase IV and DNA gyrase	Women (n = 53) In vivo	Inhibition bacterial topoisomerase IV & DNA gyrase, ↓ tissue inflammation, ↓cell proliferation, ↓angiogenesis endometriotic, ↓ lesions pain.
Clotrimazole	CYP53 enzyme	Rats In vivo 200 mg/kg oral 15 days	CYP53 enzyme inhibition, ↓ inflammation, ↓ endometriotic lesions, ↓ distribution of iNOS, ↑ antioxidant system
Loratadine	TRPV2	Women In vitro Cell culture ESC	Antagonist, ↓ cell proliferation/migration, ↓ inflammation
Quinagolide	Dopamine D2 receptor	Rats In vivo 200 µg/Kg/day oral 4 weeks	↓ Endometriotic implants, ↓ IL-6, ↓ VEGF
		Women (n = 10) In vitro ESC 24 h	Agonist, ↓ lesion size, ↓ invasion and differentiation, ↓ AKT signaling pathway

Cabergoline	Dopamine D2 receptor	Women (n = 227) In vivo 0.25–0.5 mg/twice/week oral cabergoline + hormone therapy 6 months	↓ Pain syndrome
N-acetyl-L-cysteine	COX2 pathway	Women (n = 120) In vivo 600 mg/day/3 consecutive days/week oral 3 months	↓ Dysmenorrhea, ↓ dyspareunia, ↓ CPP, ↓ endometrioma size, ↓ serum Ca125 levels, improve fertility
Niclosamide	Wnt/β-catenin signaling pathway, Macrophage activity	Mice In vivo 200 mg/Kg/day/3 weeks oral 6 weeks	Inhibition of Wnt/β-catenin signaling, ↓ macrophage activity

Conclusion

Pharmacological research in endometriosis is rapidly advancing, with new therapies focused on improving efficacy and minimizing side effects. The integration of epigenetic and gene-based therapies, stem cell and regenerative medicine, natural anti-inflammatory compounds, vitamins, antioxidants, and essential fatty acids offers a multifaceted approach to managing this debilitating condition. As research continues to progress, these novel treatments may offer more personalized, targeted, and effective options for managing endometriosis, providing hope to millions of women worldwide.

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Guidelines for the Use of Medical Imaging in Endometriosis

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Introduction

Endometriosis, a prevalent condition affecting approximately 10% of individuals assigned female at birth, is characterized by the presence of endometrial-like tissue outside the uterine cavity .

This ectopic tissue can lead to a variety of debilitating symptoms, including chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria, and menorrhagia, significantly impacting the quality of life for affected individuals.

The diagnostic and management landscape of endometriosis has been evolving. Initially considered a condition primarily diagnosed through surgical intervention, there is a growing recognition of the crucial role that medical imaging plays, particularly in preoperative planningand the identification of specificmanifestations of the disease.

The ability to visualize and characterize endometriotic lesions non-invasively offers significant advantages in guiding clinical decision-making. Indeed, studies have indicated that the use of preoperative imaging is associated with improved patient outcomes, including decreased morbidity and mortality, as well as a reduction in the need for repeat surgeries by facilitating more complete initial surgical interventions. This report aims to provide a comprehensive and up-to-date synthesis of the guidelines from major medical societies concerning the use of various imaging modalities in different clinical scenarios related to endometriosis. The utility of ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) will be discussed in the context of diagnosis, preoperative planning, and follow-up of endometriosis across different patient populations, including adolescents.

Furthermore, the evolving relationship between imaging and the traditional gold standard of laparoscopy will be explored.

Guidelines from Major MedicalSocieties

American Collegeof Obstetricians and Gynecologists (ACOG)

The American College of Obstetricians and Gynecologists (ACOG) emphasizes that a definitive diagnosis of endometriosis can only be established through histological examination of lesions removed surgically, asserting that imaging studies alone cannot be used to diagnose the condition. Despite this stance, ACOG acknowledges the value of imaging in specific clinical contexts, particularly for patients presenting with pelvic or adnexal masses. In such cases, ultrasonography is recognized as a useful tool for distinguishing ovarian endometriomas from other types of adnexal masses. The characteristic appearance of ovarian endometriomas on ultrasound as cysts containing low-level homogeneous internal echoes, consistent with old blood, makes imaging highly predictive in this specific differentiation. For the broader detection ofendometriosis and deeplyinfiltrating endometriosis (DIE)affecting the rectumor recto-vaginal septum, transvaginal ultrasonography is identified as the preferred initial imaging modality. This preference suggests that TVUS is considered an accessible and cost-effective first-line approach for assessing these particular locations of the disease. ACOG recommends that magnetic resonance imaging (MRI) should be reserved for situations where ultrasound results are inconclusive, and when there is a suspicion of rectovaginal or bladder endometriosis. This recommendation indicates a role for MRI as a secondaryor problem-solving tool, likely reflecting its higher cost and potentially lower availability compared to ultrasound. Furthermore, ACOG provides guidance on the evaluation and management of dysmenorrhea in adolescents, noting that secondary dysmenorrhea is most commonly caused by endometriosis.

Ultrasound is recommended as the initial imaging modality for investigating secondary dysmenorrhea. While MRI may offer benefitsin follow-up assessments, it is not considered the primary imaging approach for adolescents with dysmenorrhea. This highlights the importance of ultrasound as a safe and readily available tool for the initial assessment in this age group, thereby minimizing potential radiation exposure from modalities like CT.

European Societyof Human Reproduction and Embryology (ESHRE)

The European Society of Human Reproduction and Embryology (ESHRE) issued a significant revision to their endometriosis guideline in 2022, marking a notable shift in the diagnostic paradigm. A key change in the updatedguideline is the recommendation that laparoscopy is no longer considered the diagnostic gold standard for endometriosis. This change reflects an increasing confidence in the accuracy of imaging technologies for diagnosing certain forms of endometriosis. The guideline now suggests that imaging techniques, including ultrasound (US) or MRI, should be considered as part of the diagnostic process for women with suspected endometriosis, even if the clinical examination findings are normal. However, ESHRE also cautions that a negative imaging result does not necessarily rule out endometriosis, particularly in the case of superficial peritoneal disease, which may still require surgical visualization for definitive diagnosis . For adolescent patients, the ESHRE guideline recommends transvaginal US as the preferred imaging modality when clinically appropriate for diagnosing ovarian endometriosis. In situations where TVUS is not suitable for adolescents, alternatives such as MRI, transabdominal, transperineal, or transrectal ultrasound scans may be considered . The ESHRE guideline offers comprehensive recommendations encompassing various aspects of endometriosis management, including diagnosis, treatments for pain and infertility, management of disease recurrence, and specific considerations for adolescents and postmenopausal women. Additionally, Annex 8 of the ESHRE guideline providesdetailed evidence tablessummarizing the research supporting different diagnostic and management approaches, including the reliability of medical technologies like ultrasound and MRI in diagnosing endometriosis. The breadth and depth of the ESHRE guideline, along with its emphasis on evidence-based recommendations, underscore the significant role that imaging now plays in the contemporary management of endometriosis.

Society of Radiologists in Ultrasound (SRU)

The Society of Radiologists in Ultrasound (SRU) expert panel has issued recommendations advocating for the use of augmented pelvic ultrasound in premenopausal or early postmenopausal individuals (less than 5 years since the cessationof menses) who present with symptoms suggestive of endometriosis or have a history of the condition or infertility. This recommendation indicates a move towards more specialized ultrasound protocols designed to enhance the detection of endometriosis, particularly deep infiltrating endometriosis (DIE).

Augmented pelvic ultrasound involves specific techniques beyond standard transvaginal sonography, including a focused evaluation of the posterior compartment of the pelvis, careful observation of the relative positioning of the uterus and ovaries (such as the "kissing ovaries" sign, which can suggestDIE), and the application of the uterinesliding sign maneuverto assess for obliteration of the pouch of Douglas, a common finding in DIE . The SRU recommends that both direct and indirect observations of deep endometriosis should be systematically assessed during the augmented ultrasound examination. Furthermore, the findings should be reported using a standardized four-category system: Incomplete (APU-0), normal (APU-1), equivocal (APU-2), and positive (APU-3), with corresponding management recommendations based on the category assigned . The SRU consensus highlights a critical point: routine pelvic ultrasound often fails to detect endometriosis beyond the presence of endometriomas. This underscores the necessity for sonologists to be well-trained in augmented protocols and to have a

heightened awarenessof the subtle sonographic signs of DIE to improvediagnostic accuracy and reduce delays in diagnosis .

American College of Radiology (ACR)

The American College of Radiology (ACR) has developed Appropriateness Criteria to provide evidence-based guidance on the selection of the most appropriate imaging procedures for various clinical scenarios involving suspected or established endometriosis . These criteria categorize different imaging modalities

based on their suitability for specific clinical presentations. For the initial imaging of clinically suspected pelvic endometriosis, the ACR considers ultrasound (both transabdominal and transvaginal, or transvaginal alone) and MRI (with or without intravenous contrast, or without contrast alone) as usually appropriate options . In contrast, CT is generally deemed not appropriate for this initial evaluation . In cases where the initial ultrasound findings are indeterminate or negative, but clinical suspicion for endometriosis remains high, the ACR recommends MRI as usually appropriate for further characterization of the findings or for treatment planning . This reinforces the role of MRI as a valuable second-line imaging tool when ultrasound results are inconclusive. For patients with suspected rectosigmoid endometriosis, the ACR considersultrasound (including transabdominal and transvaginal, transrectal, or transvaginal alone) and MRI as usually appropriate initial imaging modalities . The inclusionof transrectal ultrasound in this recommendation highlights its potential utility in evaluating the involvement of the bowel in endometriosis. In the context of follow-up imaging for patients with a confirmed postoperative diagnosis of endometriosis who are experiencing new or ongoing symptoms, the ACR suggests that MRI with intravenous contrast is usually the most appropriate imaging modality . This recommendation indicates the value of MRI in assessing for disease recurrence or potential complications following surgical treatment. The ACR emphasizes the importance of preoperative imaging in the comprehensive management of endometriosis, noting its crucial role in diagnosis, surgical planning, and overall patient management . Furthermore, the ACR recommends the use of dedicated endometriosis MRI protocols that include intravenous contrast agents to aid in the critical differentiation between benign ovarian endometriomas and potentially malignant ovarian masses, a distinction that is particularly important in patients with endometriosis .

Role of Different ImagingModalities

Ultrasound

Standard transvaginal ultrasound (TVUS) is a widely used initial imaging modality in the evaluation of women with suspected endometriosis. TVUS is particularly effective in identifying ovarian endometriomas, which typically present as cysts with characteristic low-level homogeneous internal echoes, often described as having a "ground glass" appearance. This distinct sonographic appearance makes TVUS a reliable tool for the initial detection of this specific type of endometriosis. TVUS can also detect some instances of deep infiltrating endometriosis (DIE), especially when it involves the rectum or the recto-vaginal septum.

However, standardTVUS has limitations in its abilityto visualize superficial peritoneal implants or smaller endometriotic lesions. Moreover, routine TVUS examinations may not adequately identify DIE beyond the presence of endometriomas. A significant factor influencing the accuracy of TVUS in diagnosing endometriosis is its operator dependency, meaning the skill and experience of the sonographer performing and interpreting the examination play a crucial role in the quality of the findings.

To overcome some of the limitations of standard TVUS, augmented pelvic ultrasound (APU) techniques have been developed to improve the detection of DIE. These techniques involvea more focused assessment of the posterior compartment of the pelvis, a common site for DIE. APU also includes the evaluation of the relative positioning of the uterus and ovaries, such as

the observation of "kissing ovaries," where the ovaries are located close together posterior to the uterus, which can be an indirect sign of DIE . Another key component of APU is the uterine sliding sign maneuver, a dynamic assessment where the sonographer applies gentle pressure on the abdomen while observing the movement between the uterus and the rectum or sigmoid colon; a lack of sliding suggestsobliteration of the pouch of Douglas due to DIE . The Society of Radiologists in Ultrasound (SRU) expert panel recommends the use of these augmented techniques in individuals who are symptomatic for endometriosis or have a relevant history .

During an APU examination, both direct visualization of DIE nodulesand indirect signs should be systematically evaluated and documented using a standardized grading and reporting system, ranging from APU-0 (incomplete) to APU-3 (positive), which helps guide subsequent management decisions .

Three-dimensional (3D) ultrasound represents an advancement in ultrasound technology that offers potential benefits in the diagnosis of endometriosis by providing volumetric imaging and the ability to reconstruct images in multiple planes . This capability can enhance the visualization of complexpelvic structures and improve the detection and characterization of DIE. Furthermore, 3D ultrasound can be valuable in diagnosing uterine malformations that may be associated with endometriosis. While 3D ultrasound holds promise, currentmajor guidelines do not explicitly recommend it over augmented 2D ultrasound, and more research may be needed to define its specific role in the routine diagnostic workup of endometriosis.

Contrast-enhanced ultrasound (CEUS) is an emerging technique that utilizes ultrasound contrast agents to improve the visualization of blood flow and vascular patterns within tissues and lesions. This can be particularly helpful in characterizing poorly vascularized gynecologic tumors or tissues with slow blood flow. CEUS has shown potential in the diagnosis of various gynecological conditions, including ovarianendometrial cysts, adenomyosis, and abdominal wall endometriosis. In cases of intestinal endometriosis, CEUS has demonstrated rapid and heterogeneous enhancement of the lesions. While these findings suggest that CEUS may be a promising adjunctive tool for characterizing endometriotic lesions and potentially differentiating them from other conditions, including malignancies, its widespread adoption and specific recommendations within major endometriosis guidelines are still evolving.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is recognized as an excellent imaging modality for the preoperative diagnosis of endometriosis, particularly for deep infiltrating endometriosis (DIE) . The findings on MRI often correlate well with surgical staging systems and histopathological results, making it a valuable tool for planning complex surgical interventions . Dedicated MRI protocols for endometriosis typically

include specific techniques to optimize the visualization of lesions. Moderatebladder distention and the use of vaginalcontrast are often recommended to improve the conspicuity of lesions involving these structures . Additionally, the administration of intravenous contrast is generally recommended in these dedicated protocols to aid in the differentiation of benign ovarian endometriomas from potentially malignant ovarian masses .

Overall, MRI is considered a highly accurate imaging technique for evaluating endometriosis . Characteristic MRI findingscan help in the diagnosisof different types of endometriosis. Ovarian endometriomas typically exhibit high signal intensity on T1-weighted images, which may or may not show suppression with fat saturation depending on the presence of fatty components (useful for distinguishing from dermoids), and a characteristically low signal intensity on T2-weighted images, often referred to as "T2 shading" or the "T2 dark spot sign" due to the high concentration of iron within the endometrioma . DIE lesions on MRI typically appear as hypointense nodular areas on both T1 and T2-weighted images, often associated with soft tissue thickening and irregular or spiculated margins .

Research has also explored the utility of abbreviated MRI (aMRI) protocols in the diagnosis of pelvic endometriosis . Studies suggestthat non-contrast aMRI protocols can achieve diagnostic accuracy comparable to that of more comprehensive full MRI protocols for detecting pelvic endometriosis . These abbreviated protocols typically include a reduced number of sequences, such as T2-weighted sequences without fat suppression and T1-weighted sequences with and without fat suppression . If further research validates these findings, aMRI could offer a more cost-effective and time-efficient imaging option without compromising diagnostic accuracy.

The role of contrastagents in MRI for endometriosis is nuanced. While intravenous contrastis recommended for differentiating endometriomas from ovarian malignancies , its utility in detecting small peritoneal implants is debated, as small blood vessels can enhance and potentially be misinterpreted as small endometriotic deposits . Furthermore, the enhancement pattern of endometrial deposits after contrast administration can be variable and may not reliably distinguish them

from other benign or malignant processes . Consequently, dynamic contrast-enhanced MRI is not routinely recommended for the evaluation of endometriosis .

Therefore, the use of contrast in MRI for endometriosis shouldbe tailored to the specificclinical question, with a clear benefit in differentiating endometriomas from other ovarian lesions.

Computed Tomography (CT)

Computed tomography (CT) has a limited role in the primary diagnosis of endometriosis . This is primarily due to its suboptimal visualization of pelvic organs and superficial peritoneal implants, which are characteristic features of endometriosis . However, CT can be valuable in detecting complications that may arise from endometriosis, such as bowel obstruction or ureteral involvement leading to hydronephrosis . The appearance of endometriomas on CT scans is generally nonspecific, although the presence of multiple complex cystic lesions with

high-attenuation components might suggest the diagnosis . In the context of preoperative planning, particularly when intestinal involvement is suspected, water enema CT may be utilized to map the extent of bowel lesions, especially in cases with multiple sites of involvement .

Contrast-enhanced CT can also play a role in identifying ureteralinvolvement and assessingfor potential renal insufficiency in patients with endometriosis affecting the urinary tract .

Furthermore, CT may be useful in evaluating certain forms of extra-pelvic endometriosis, such as abdominal wall endometriosis, whereit might demonstrate a homogeneous densitymass or a characteristic "gorgon" sign, which is a linear infiltration radiating peripherally from a central soft tissue nodule. Overall, whileCT is not a primarydiagnostic tool for pelvic endometriosis, it can provide valuable information in specific clinical scenarios, particularly for assessing complications or certain extra-pelvic manifestations of the disease.

Imaging in Specific ClinicalScenarios

Initial Evaluation of Suspected Endometriosis

In the initial evaluation of a patientwith suspected endometriosis, ACOG guidelines recommend starting with a thorough medical history and physical examination to rule out other potential causes of pelvic pain . Transvaginal ultrasound (TVUS) is generally considered the preferred initial imaging modality for further assessment . The European Society of Human Reproduction and Embryology (ESHRE)suggests that clinicians should consider imaging,such as ultrasound or MRI, as part of the diagnostic workup even if the clinical examination is normal . The American College of Radiology (ACR) Appropriateness Criteria indicate that for clinically suspected pelvic endometriosis, ultrasound (either transabdominal and transvaginal, or transvaginal alone) and MRI (withor without intravenous contrast, or withoutcontrast alone) are usually appropriate as initial imaging procedures . This consensus among major medical societies highlights the importance of ultrasound, particularly TVUS, as a key first-line imaging tool in the evaluation of women with symptoms suggestive of endometriosis. MRI is also

recognized as an appropriate initial imaging modality, especially in situations where ultrasound findings are limitedor when there is a strong suspicionfor deep infiltrating endometriosis (DIE).

Preoperative Planning

Preoperative imaging plays a critical role in the management of endometriosis, as it has been shown to be associated with decreased morbidity and mortality during surgery and can reduce the likelihood of needing repeat surgeries . For effective preoperative planning, especially in cases of DIE involving organssuch as the bowel, bladder,or ureters, expandedprotocol TVUS or MRI protocols specifically tailored for the detection of DIE are essential for accurately mapping the extent of the disease . Bowel preparation may be necessary prior to imaging with both ultrasound and MRI to optimize the visualization of any bowel lesions . MRI is particularly valuable for identifying DIE and its findings often correlate strongly with surgical outcomes .

However, some evidence suggests that ultrasound may be more accurate than MRI in determining the depth of invasion in cases of bowel-wall endometriosis . Therefore, a collaborative approach involving

experienced radiologists and gynecologic surgeonsis crucial to effectively utilize imaging in the preoperative planning for complex endometriosis surgeries, ensuring that all relevant anatomical information is obtained and considered.

Follow-up Imaging

For patients who have undergone surgical treatment for endometriosis and subsequently experience new or ongoing symptoms, follow-up imaging is often necessary to assess for potential recurrence or complications. The American Collegeof Radiology (ACR)recommends that MRI with intravenous contrast is usually the most appropriate imaging modality for this purpose . Ultrasound may also be utilized for follow-up, particularly for monitoring known endometriomas or DIE lesions to assess for changes in size or characteristics . The choice of imaging modality for follow-up should be guided by the specific clinical scenario, the type and location of the previously treated endometriosis, and the nature of the patient's current symptoms. MRI is often preferred in the follow-up setting due to its ability to provide detailed anatomical information and its sensitivity in detecting recurrent disease.

Endometriosis in Adolescents

The evaluation of suspected endometriosis in adolescents presents unique considerations. ACOG guidelines recommend that ultrasound should be the initial imaging modality used when secondary dysmenorrhea is suspected, as endometriosis is the most common underlying cause in this age group . While MRI may have a role in follow-up assessments or in more complex cases, it is not typically the primary imaging approach for adolescents with dysmenorrhea .

Similarly, the ESHRE guidelinesuggests that transvaginal ultrasound is the recommended

first-line imagingtechnique for diagnosing ovarian endometriosis in adolescents when clinically appropriate . If TVUS is not feasible or provides insufficient information, alternative imaging modalities such as MRI, transabdominal, transperineal, or transrectal ultrasound scans can be considered. The emphasis on ultrasound as the initialimaging modality in adolescents reflects its safety, accessibility, and ability to

provide valuableinformation while minimizing exposure to ionizing radiation. MRI is reserved for situations where ultrasound findings are inconclusive or when a more detailed evaluation of the extent of disease is required.

Interpretation and Reporting of Imaging Findings

The accurateinterpretation and reportingof imaging findingsare crucial for guiding the clinical management of endometriosis. Key findings that should be documented for different imaging modalities include the size, precise anatomical location, and specific characteristics of endometriomas and DIE lesions . For augmented pelvic ultrasound (APU), it is essential to include the APU classification (ranging from 0 to 3) based on the direct and indirect observations of DIE, as this classification helps in standardizing the reporting and guiding

management decisions . MRI reports should ideally follow a structured format that systematically documents findings in various pelvic locations commonly affected by endometriosis, such as the ovaries, uterosacral ligaments, rectum, and bladder . Radiologists interpreting pelvic MRIs for endometriosis should also be aware of the potential for nerve involvement and evaluate pelvic nerves when clinically indicated . A critical aspect of interpretation is the ability to distinguish benign endometriomas from potentially malignant ovarian cysts, and MRI with intravenous contrast plays a vital role in aiding this differentiation . The implementation of standardized reporting systems and meticulous attention to detail in documenting imaging findings are essential for ensuring clear communication between radiologists and clinicians, ultimately leading to more informed and effective clinical management of endometriosis.

Limitations of Imaging and the Role of Laparoscopy

While medical imaging has become increasingly important in the diagnosis and management of endometriosis, it is essential to acknowledge its limitations. Both ultrasound and MRI can have difficulty in detecting superficial peritoneal lesions, which are a common manifestation of the disease and can still cause significant pain and other symptoms . Historically, diagnostic laparoscopy with histological

confirmation of the lesions was considered the gold standard for diagnosing endometriosis, allowing for direct visualization of the pelvic cavity and the collection of tissue samples for definitive diagnosis . However, the 2022 guideline from the European Society of Human Reproduction and Embryology (ESHRE)represents a significant shift, as it no longer recommends laparoscopy as the criterion standard for the diagnosis of endometriosis .

Instead, ESHRE now suggestsreserving diagnostic laparoscopy for patients who have negative imaging results despite a high clinical suspicion, or in cases where empiric medical treatment has failed or is deemed inappropriate . Despite the advancements in imaging technologies and their increasing role in diagnosis, laparoscopy remains the only definitive way to visuallyconfirm the presence of endometriosis and obtain histological proof . It is also important to note that a negative imaging result, particularly with ultrasound, does not completely rule out the presence of endometriosis, especially superficial disease . The evolving role of laparoscopy in the diagnostic pathway for endometriosis suggests a move towards a more tailored approach, where imaging is often prioritized for the initial assessment, particularly for identifying endometriomas and DIE, and laparoscopy is reserved for specific indications, such as when imaging is inconclusive or when surgical intervention is planned for treatment.

Conclusion

Current best practices in the use of medical imaging for endometriosis emphasize the central roles of ultrasound and MRI. Ultrasound, particularly augmented transvaginal ultrasound, is often the preferred first-line imaging modality, especially for initial evaluation and in adolescent patients. MRI is a valuable tool for problem-solving in cases with inconclusive ultrasound findings, for detailed preoperative planning in patients with deep infiltrating endometriosis, and for follow-up assessments after surgical treatment. Computed tomography has a more limited role, primarily in the detection of complications or the evaluation of certain extra-pelvic manifestations of endometriosis. The importance of multidisciplinary collaboration between clinicians and radiologists who possess expertise in

endometriosis imaging cannot be overstated. Such collaboration ensures the optimalselection, performance, and interpretation of imaging studies, leading to improved patient care. Future directions in endometriosis imaging include ongoingrefinement of augmentedultrasound protocols, furthervalidation of abbreviated MRI protocols to enhance efficiency and accessibility, and continued exploration of emerging techniques like contrast-enhanced ultrasound, which may offer additional diagnostic value.

Continued researchis essential to improve the accuracy of non-invasive diagnostic methods for

all types of endometriosis, including the challenging detection of superficial lesions, ultimately aiming for earlier diagnosis and more effective management strategies for this common and often debilitating condition.

Table 1: Summary of Imaging Modalities and Their Roles in Endometriosis

Modality	Key Strengths	Key Limitations	Primary Applications in Endometriosis
Ultrasound (TVUS)	Cost-effective, readily available, good for ovarian endometriomas and some DIE.	Limited for superficial lesions and DIE beyond specific locations, operator dependent.	Initial evaluation, especially for ovarian cysts and suspected recto-vaginal involvement.
Ultrasound (APU)	Improved detection of DIE through specific techniques (posterior compartment focus, ovarian positioning, sliding sign).	Requires specialized training and expertise.	Screening for DIE in symptomatic patients or those with a history of endometriosis/infertility.
Ultrasound (3D US)	Volumetric imaging, multiplanar reconstruction, may improve DIE detection and assess uterine malformations.	Not yet a standard recommendation over augmented 2D US.	Further characterization of complex cases, assessment of uterine anomalies.
Ultrasound (CEUS)	Improved visualization of blood flow, may help characterize lesions and differentiate from other conditions.	Role in routine endometriosis diagnosis still evolving.	Characterizing lesions, potentially differentiating endometriosis from malignancies.

MRI (Standard)	**Excellent for preoperative planning of DIE, good correlation with surgical findings, detailed anatomical information.**		**Preoperative mapping of DIE, problem-solving in complex cases, follow-up imaging.**
MRI (aMRI)	**Potentially comparable diagnostic accuracy to standard MRI with shorter acquisition time and lower cost.**	**Requires further validation.**	**Potential alternative to standard MRI for initial diagnosis.**
CT	**Useful for detecting complications (obstruction, hydronephrosis) and some extra-pelvic endometriosis (e.g., abdominal wall).**	**Poor visualization of pelvic organs and superficial implants.**	**Detecting complications, evaluating specific extra-pelvic sites.**

Table 2: Summary of Recommendations from Major Medical Societies on Imaging in Endometriosis

Organization	Key Recommendations for Initial Diagnosis	Key Recommendations for Preoperative Planning	Key Recommendations for Follow-up	Specific Recommendations for Adolescents
ACOG	TVUS preferred for detecting endometriosis and DIE of rectum/recto-vagin al septum. MRI for equivocal US or suspected rectovaginal/blader endometriosis.	Imaging useful for pelvic/ adnexal masses. TVUS preferred for rectum/recto-vagin al DIE. MRI reserved for equivocal US or specific DIE suspicion.		Ultrasound as initial imaging for secondary dysmenorrhea. MRI for follow-up, not primary.
ESHRE	Consider US or MRI even with normal clinical exam. Negative imaging doesn't rule out, especially superficial disease.			TVUS recommended for ovarian endometriosis when appropriate. Consider MRI, transabdominal, transperineal, or transrectal if TVUS unsuitable.

SRU	Augmented pelvic US recommended for symptomatic individuals or those with history of endometriosis/infertility.	Augmented pelvic US for mapping DIE.		Augmented pelvic US applicable if symptomatic or history present.
ACR	US (transabdominal and/or transvaginal) and MRI (with or without contrast) usually appropriate for suspected pelvic endometriosis.	MRI pelvis usually appropriate for characterization or treatment planning after indeterminate/neg ative US. US andMRI usually appropriate for suspected rectosigmoid endometriosis.	MRI pelvis with IV contrast usually appropriate for established postoperative endometriosis with new/ongoing symptoms.	US pelvis transvaginal may be appropriate for infertility evaluation.

Table 3: APU Classification for Deep Endometriosis (Based on SRU Consensus)

Category	Description of Findings	Associated Management Recommendations
APU-0 (Incomplete)	Technically limited study with inability to fully assess for DE.	Repeat study with attention to limitations or consider alternative imaging (MRI).
APU-1 (Normal)	No direct or indirect sonographic signs of DE.	Clinical correlation; consider other causes of symptoms.

APU-2 (Equivocal)	One or more indirect signs of DE are present, but no definitive direct signs.	Clinical correlation; consider further imaging (MRI) or referral to specialist.
APU-3 (Positive)	One or more direct sonographic signs of DE are present.	Clinical correlation; referral to endometriosis specialist for management planning.

Table 4: MRI Findings of Ovarian Endometriotic Cyst and DIE

Type of Endometriosis	MRI Sign	MRI Findings	Relevant MRI Sequences
Ovarian Endometrioma	T1-High Signal	Multiple high signal cysts	T1-weighted
Ovarian Endometrioma	T2-Shading	Marked T2 shortening or gradations	T2-weighted
Ovarian Endometrioma	T2 Dark Spot Sign	Discrete markedly hypointense foci within cyst	T2-weighted
DIE	Hypointense Nodules	Hypointense nodular lesions	T1/T2-weighted
DIE	Soft Tissue Thickening	Irregular, indistinct, or stellate margins	T1/T2-weighted

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Advances In Minimally Invasive Surgery In Endometriosis

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INDICATIONS FOR SURGERY IN ENDOMETRIOSIS

1. Failure/noncompliance/intolerance of medical management
2. Incapacitating pain Severe and advanced disease with a significant anatomic distortion of pelvic organs and/or endometriomas
3.Emergencies such as rupture of endometrioma, tubo-ovarian abscess, obstructive uropathy, and bowel obstruction
4.Endometriosis-associated infertility

Preoperative Planning and Counseling

The key to a successful surgery is meticulous pre-operative planning and proper counseling of the patient. Transparency and clear communication during the preoperative counseling process are essential and patients should be thoroughly educated about potential risks, such as reduced ovarian reserve, recurrence, the possibility of injury to adjacent organs, infection, the potential need for conversion to laparotomy, and the requirement for postoperative medical treatment. A written informed consent should be obtained detailing the same. Each patient should be properly assessed prior to surgery by a thorough physical examination and the requisite investigations done. For e.g., apart from ultrasound, a pelvic MRI may be needed in selected cases. Ovarian reserve (AFC, AMH) should be checked in cases of infertility. As far as possible, the surgeon should be clear as regards to the extent of surgery required. It is recommended that endometriosis be operated by an expert in an appropriately equipped center. A multidisciplinary approach is preferred, especially in cases where one suspects severe adhesions or involvement of ureter, bladder, bowel, etc.

Surgical Treatment Options for Endometriosis

The surgery can be conservative aimed at preserving fertility, ablation, or the excision of peritoneal implants, resection of deep infiltrating implants, and removal of endometriomas or hysterectomy, with or without oophorectomy, based on the specific needs of the patient. At each surgery, attempt should be made to treat all the visible lesions . Laparoscopy is the gold standard and is preferable to laparotomy for diagnosing and treating endometriosis-associated pelvic pain and infertility. Laparotomy should be taken into consideration, when multiple complex procedures involving other organ structures are involved or if expertise for laparoscopy is not available

Conservative Surgery

Conservative surgery should be considered for young patients with infertility and/or pain. It is the first-line surgical option for most patients as it conserves fertility and hormone production and is less invasive. The aim of conservative surgery is the treatment of the endometrioma and ablation/excision of all visible endometriotic lesions, excision of adhesions to restore normal pelvic anatomy while preserving the uterus and ovarian tissue. The advantage of excision is that it also provides a sample for histopathology. In an endometrioma, cystectomy is preferred over drainage and coagulation .Unilateral oophorectomy can be considered in a woman who has completed the family.

Laparoscopy in Infertility due to endometriosis

Avoid the excessive resection of ovarian tissue as it decreases the ovarian reserve. Avoid repeat surgery as it results in decreased ovarian reserve and should be recommended only when the patient is not responding to medical management or where malignancy is suspected. Repeat surgery results in a 50% reduction in pregnancy rates compared to the primary surgery. Egg freezing/embryo freezing prior to surgery can be discussed with the patient. Postoperative pregnancy rates in the rASRM stage III/IV cases range from 30% to 67%. The main benefit is observed within 6–12 months after surgery, but severe periovarian adhesions may recur and limit ovum pick-up. Hence, there should be a clear post operative plan for fertility in such cases . Decision for surgery prior to in vitro fertilization (IVF) to be taken in cases where there is difficulty to access follicles at oocyte retrieval for

endometriomas, fear of malignancy, rupture of cyst, and severe pain . The decision between repeat surgery and IVF should be based on age, ovarian reserve, symptoms, male factor infertility, and the presence of complex cysts needing histological diagnosis and the availability of skilled surgeons, and well-equipped setup. ART is more effective than repeat surgery in patients who failed to conceive spontaneously after surgery.

Conservative Surgery for Pain in Endometriosis

Excision is preferred over ablation for reducing endometriosis-associated pain . All visible lesions should be treated and proper adhesioylsis done. Organ damage, fibrosis, and adhesions in advanced stages warrant surgical intervention for pain relief. Postoperative LNG-IUS/hormonal therapy for at least 18–24 months should be considered to prevent recurrence .

NEWER ADVANCES

Robot-assisted surgery, such as the use of the Da Vinci Surgical System, has revolutionized the precision in treatment, especially in cases of deep infiltrating endometriosis (DIE). It features jointed instruments, tremor control, and three-dimensional (3D) stereoscopic vision, enabling precise tissue visualization and manipulation. This allows for complex dissections in difficult-to-reach areas, such as the pelvic sidewalls or rectovaginal septum, with smaller incisions and fewer complications . To minimize damage to critical nerves, nerve-sparing techniques have emerged, helping to prevent complications such as bladder dysfunction, bowel issues, and sexual dysfunction

. Recent advancements in laparoscopic surgery for endometriosis have introduced new techniques to improve precision and outcomes. Transvaginal Hydro Laparoscopy (THL) is a minimally invasive procedure that enables endoscopic examination of the female pelvis. THL allows for precise diagnosis of early stage peritoneal and ovarian endometriosis, with the added benefit of enabling treatment that causes minimal tissue damage .

Total laparoscopic retrograde hysterectomy(TLreH) is a feasible and safe approach for treating severe endometriosis with an obliterated cul-de sac and can be safely performed even on large uteri (≥600 g) affected by this condition .

Regarding symptomatic rectovaginal endometriosis (RVE), two suturing directions—horizontal and vertical—for closing the posterior vaginal defect can be used in women with endometriosis involving vaginal mucosal infiltration. They concluded that horizontal suturing of the posterior vaginal fornix defect may be associated with a higher frequency of severe postoperative complications and less effective pain control.

Endogel® applicationwas compared with ovarian suspension and observed that Endogel® showed superior adhesion reduction within three months, al though pre- and postoperative comparisons were not statistically significant [20].

A novel technique to preserve ovarian reserve by covering the endometrioma wound with modified polysaccharide powder for hemostasis and adhesion prevention, showing an 85% reduction in significant adhesions at follow-up .Using HybridAPC in laparoscopic surgery,offers a promising safe method with easy handling and low adhesion rates . Surgicel® has shown effectiveness in reducing recurrence rates and serves as a viable alternative to traditional cystectomy during laparoscopic drainage, minimizing its impact on ovarian reserve. Initially used for bleeding control, Surgicel® was also found to lower endometrioma recurrence during follow-up .

Plasma energy could serve as a promising alternative to cystectomy, achieving comparable outcomes in terms of pregnancy and recurrence rates, although further research is needed to confirm these findings . Hemostatic sealants may offer an alternative approach to bipolar coagulation for preserving ovarian reserve following laparoscopic ovarian cystectomy for endometriosis . The use of the novel adhesion barrier 4DryField® PH reduced adhesion formation by 85%. This barrier is a powder derived from purified potato starch that transforms into a gel when combined with a saline solution. The gel serves as a temporary physical barrier between surgically traumatized peritoneal surfaces, facilitating mesothelial healing before it is absorbed. When used as a powder, it also functions as a hemostat, which may contribute to its effectiveness in preventing adhesions, as the formation of polyfibrin mesh between surgical trauma sites and adjacent tissues is key to adhesion development .

Pulsed high-intensity laser therapy effectively alleviates pain, reduces adhesions, and enhances quality of life in women with endometriosis . Laparoscopic sclerotherapy for endometriomas larger than 40 mm,performed during surgery for deep infiltrating endometriosis, demonstrated minimal impact on Anti-Mullerian Hormone (AMH) levels and was found to preserve fertility and help prevent recurrence .

Regarding deep infiltrative endometriosis, in particular, colorectal endometriosis, when comparing laparoscopic Natural Orifice Specimen Extraction (NOSE) to conventional laparoscopic colorectal resection ,NOSE Colectomy is a viable surgical option for the treatment of patients with rectal deep endometriosis, although no statistically significant differences in mid-term digestive or pain outcomes were found. We can employ Firefly F imaging with indocyanine green to verify anastomosis both before and after its completion

Although surgery is the gold standard treat ment for pain refractory to medical management or partial occlusion owing to rectosigmoid endometriosis, surgical resection can be associated with major perioperative complications. Compared to general surgery practices, intraoperative proctosigmoidoscopy has proven to be a safer and more effective technique. It allows direct inspection of anastomosis from within, reducing the risk of complications associated with intestinal anastomosis after segmental resection .

Transumbilical single-port laparoscopy (LESS) is commonly used in gynecological surgery; however, its use in treating deep infiltrating endometriosis (DIE) is limited due to its complexity and specific challenges. The study by Zhang et al. suggests that LESS for DIE, based on retroperitoneal pelvic spaces anatomy, may be safe and feasible approach that simplifies the surgery, shortens the procedure time, and minimizes blood loss and complications .Full dissection of the inferior hypogastric and afferent pelvic splanchnic nerves, during deep infiltrating endometriosis (DIE) proceduresshowed an immediate improvement of postoperative urinary outcomes in posterior DIE surgeries .

Laparoscopic nerve-sparing modified radical hysterectomy, with or without robotic assistance, also appears to be a safe and feasible option that offers long-term symptom relief for patients undergoing hysterectomy for various indications, including endometriosis . 3D white-light imaging significantly increased sensitivity compared to conventional 2D white-light imaging while maintaining similar specificity. The highest sensitivity for detecting endometriotic lesions was achieved by combining NBI (narrow bandimaging)with3Dwhite-lightimaging. However,usingNBIorNIR-ICG(near-infrared indocyanine green) alone was less effective, with reduced specificity and sensitivity rates, respectively .Using NBI during laparoscopy to investigate pelvic pain improves the detection of suspected additional areas of endometriosis following a white-light examination

Regarding recent technological advances, the AutoLapTM system aims to overcome challenges in laparoscope control by introducing a transformative approach to camera manipulation technology.

Robotic Surgical Techniques Robot-assisted surgery (RAS) has become an increasingly popular option for the treatment of endometriosis, offering enhanced precision compared to traditional laparo scopic techniques. Several studies have been published regarding RAS techniques in endometriosis. Robot-assisted transvaginal NOTES (RvNOTES) uses the full potential of robotic surgery to improve patient outcomes esp a reduction in chronic pelvic pain associated with endometriosis. Notably, robotic assistance offered three-dimensional visu alization and stabilized instruments, enabling meticulous resection of endometriosis and precise movements during critical anatomical dissection .We can extend the use of RvNOTES for managing stage IV endometriosis during total hysterectomy, with or without complete cul-de-sac obliteration.

Robotic single-site surgery (RSSS) is regarded as a safe, viable, and acceptable platform for surgically treating endometriosis across all stages (I–V) [Two surgical techniques were employed: focal resection for mild disease and butterfly resection for severe or atypical disease. Both methods has proved feasible and effective in reducing pain and recurrence rates. An innovative robotic glove port technique (RGPT) is by adapting the previously established glove port method to robot-assisted single-site surgery (RSSS). This technique

utilizes a parallel arrangement of endowristed rigid instruments, incorporating both coaxial and chopstick methods. It is easily performed via transvaginal and transabdominal approaches .

Fluorescence-guided surgery is used to improve the detection of endometriotic lesions during surgery using fluorescent dyes, such as indocyanine green (ICG).

DEEPLY INFILTRATING ENDOMETRISIOSIS

DIE should be considered in women with severe dysmenor rhea, deep dyspareunia, and dyscheziaBefore surgery, clinical examination, ultrasonography, and magnetic resonance imaging (MRI) can diagnose DE. The sensitivity and specificity of transvaginal ultrasound for detecting DIE in the rectosigmoid were 91.0% (95% confidence interval [CI], 85.0-94.0%) and 97.0% (95% CI, 95.0-98.0%), respectively.

Pain and infertility are indications for DIE surgery. Surgical excision /ablation should be avoided for incidental findings of asymptomatic endometriosis at the time of surgery(ESHRE 2022)D1E detected using ultrasonography alone without clinical symptoms should not be surgically treated .Resection, leaving free margins on all sides, is the treatment of choice for symptomatic DIE .

Steps in DIE surgery include

1)Ovariolysis and temporary ovariopexy

2) Identification and dissection of the ureter Ureterolysis should be performed starting from the level of the upper infundibulopelvic ligament and progressing down ward to the level of the uterine vessels to prevent ureteral injury .

. 3) Mobilization of the sigmoid colon and rectum- It is essential to identify the cleavage plane between the bowel and pelvic sidewall, starting from the pelvic brim to expose the left pararectal space and ovarian fossa . The opening of the pararectal space should be initiated in healthy tissue . Dissection is continued until the healthy rectovaginal space was opened, and both lateral sides of the rectum were freed .Hypogastric nerve identification is necessary during the procedure to preserve bowel, bladder, and sexual functions.

4) Separation of the anterior rectum from the vagina- This procedure can be performed using cold scissors, blunt dissection, or thermal instruments with minimal collateral thermal spread .An end-to-end anastomotic dilator is inserted in the rectum when necessary.

5) Peritonectomy -After dissection of the rectovaginal space, the endometriotic nodules in the uterosacral ligaments and pelvic peritoneum are removed.

Surgery for bowel endometriosis

1) Shaving

2) Discoid excision- if deep endometriotic implants remain after shaving, the rectal wall appears hollow, rigid, and thickened when palpated using a laparoscopic probe .Under such circumstances, full-thickness discoid excision can be performed to complete the
excision .Instead of suturing the defect, discoid excision c.an be performed using transanal staplers, preventing bowel opening into the pelvis

3) Segmental resection This is necessary for advanced stages of rectovaginal DE, where extensive infiltration causes irreducible distortion and stenosis of the bowel. . Segmental resection requires mobilizing the rectum at least 20 mm below the rectal nodule to achieve a healthy margin . Colorectal anastomosis was performed using transanal staplers after ex tracting the rectum through an abdominal wall or a vaginal incision.

4) Nerve-sparing surgery - reduces the incidence of bowel, bladder, and sexual dysfunction without compromising surgical efficacy . The nerve-sparing technique reduced the risk of persistent urinary retention due to iatrogenic injury to the pelvic autonomic nerves compared to the conventional technique . The presacral space can be opened to identify and skeletonize the inferior mesenteric plexus, superior hypogastric plexus, and hypogastric nerves. During this process, it is important to ensure that the fibers are positioned laterally and dorsally, close to the sacrum, and away from the mesorectal plane to be resected . Dissection of the parametrial planes is performed laterally and caudally along the lower hypogastric nerves and proximal part of the inferior hypogastric plexus or pelvic plexus.

When endometriosis affects the posterolateral parametrium, a posterior parametrectomy may be performed while preserving the parasympathetic pelvic splanchnic nerves and the cranial and middle parts of the mixed inferior hypogastric plexus. Dissection in the laterocaudal direction beneath the base of each uterosacral ligament Is performed by pushing and maintaining the isolated and dissected fibers laterally and caudally to preserve the caudal part of the infe rior hypogastric plexus

Adjunct Surgical Intervention

Laparoscopic uterosacral nerve ablation (LUNA) for the management of dysmenorrhea is not recommended as an additional procedure to conservative surgery to reduce endometriosis-associated pelvic pain expertise . Presacral neurectomy (PSN) is an effective additional procedure to conservative surgery to reduce mid-line pain, but requires high degree of skill and is potentially hazardous procedure with side effects such as bladder and bowel disturbances

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CONCLUSION

When performing surgery in women with ovarian endometrioma, clinicians can consider both cystectomy and CO2 laser vaporisation, as both techniques appear to have similar recurrence rates beyond the first year after surgery. Early post-surgical recurrence rates may be lower after cystectomy. ESHRE recommends that patients undergoing surgery particularly for deep endometriosis are informed on potential risks, benefits, and long-term effect on quality of life. Clinicians can consider total hysterectomy (with or without removal of the ovaries) with removal all visible endometriosis lesions, in those women who no longer wish to conceive and failed to respond to more conservative treatments. Women should be informed that hysterectomy will not necessarily cure the symptoms or the disease.When a decision is made whether to remove the ovaries, the long-term consequences of early menopause and possible need for hormone replacement therapy should be considered. There are currently no prognostic markers that can be used to select patients that would benefit from surgery. Such markers would need to be

assessed prior to surgery and predict a clinically meaningful improvement of pain symptoms.

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Ethical Considerations In The Management Of Endometriosis

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An ethical dilemma is faced by the treating physician while communicating the diagnosis of endometriosis as a cause ,in a patient with infertility.The dilemma lies in the conflict between the patient's right to confidentiality and the partner's right to have access to the information.

Ethical considerations in endometriosis management resolve around respecting patient autonomy,ensuring informed consent, balancing potential benefits and risks of treatment and addressing the complex challenges of diagnosis and management, including infertility and chronic pain.

1.Patients autonomy and informed consent.

A.Respecting the patient choices.

Management of endometriosisinvolves complex decisions and patients should be empowered to make informed choices about their treatment based on their individual circumstances, values and goals. Respecting patient autonomy is essential especially when dealing with a condition that can significantly impact quality of life.

B. Thorough information

Patients need clear ,understandable, comprehensive information about the disease, potential treatment options, their benefits, risks and limitations.

This is crucial due to the varying severity of endometriosis and range of treatments frompain management to surgical interventions

2.Balancing benefits and risks.

A.Medical v/s Surgical options.

Endometriosis can be managed medically or surgically. Healthcare provider must carefully weigh the potential benefits and risks of each approach considering the patient's specific situation.

B.Adverse effects of treatment.

Endometriosis treatments, be it surgical or medical management, carry some side effects and complications with them.

This becomes particularly complex when considering treatments that may compromise future fertility. These risks are to be thoroughly discussed with the patients.

C Recurrence

Endometriosis has a disturbing recurrence rate after treatment. Hence patients should be informed about the potential for recurrence and the need for ongoing monitoring.

3. Addressinginfertility concerns

When endometriosis is identified, the treating physician must balance the patient's right to confidentiality with the patients right to information.

4. Assisted reproductive technology (ART)

For women with endometriosis who desire fertility,ART options may be considered.The challenges,ethical considerations,and emotional issues,should be carefully considered.

5.Addressing chronic pelvic pain

The chronic pelvic pain associated with endometriosis must not be considered a trifling symptom,because it is invalidating and it significantly affects the quality of life.

Ethical considerations arise in balancing the use of pain medications, particularly opiods ,with the risk of dependence.

6.Diagnostic challenges

The diagnosis of endometriosis is often delayed ,leading to prolonged suffering.The balance between performing invasive diagnostic procedures while observing the "do no harm"principle is a very important ethical considerations..

The quality of life in endometriosis refers to vitality, general health and mental state,all of which are affected by this chronic disease.

Therefore the physician should try to improve the patient ‘s well being by all available therapeutics means, including psychological counseling by referral to a specialist or support group and explaining the disease to her family,so that they can further sustain her thrivings.

Due to the scientific controversies surrounding treatment options and the impossibility to for see the real benefits of any of the available therapies,it is difficult and frustrating for the physician to correctly advise the patient.

The key for providing themaximum benefit is first identifying the patient’s needs and then finding which therapy best fulfils the patient’s preference.Overalk increasing the quality of life should be the motto of every therapeutic intervention.

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