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Novel Diagnostic and Therapeutic Approaches in Endometriosis: Integrating Biotechnology with Clinical Practice

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A B S T R A C T :

Endometriosis is a chronic, estrogen-dependent gynecological disorder marked by the presence of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age. Often underdiagnosed due to asymptomatic cases, it commonly involves the ovaries and is associated with significant symptoms, including dysmenorrhea, dyspareunia, and pain during defecation or urination. These symptoms severely impact quality of life and may persist even after lesion excision due to inflammatory or neuropathic pain. Endometriosis is prevalent among infertile women and is linked to poorer outcomes in assisted reproductive technologies. It also correlates with increased risks of cardiovascular disease, irritable bowel syndrome, and ovarian cancer. Current treatments include hormonal therapy, surgery, and assisted reproduction, but these approaches carry limitations such as side effects, surgical risks, and high recurrence rates. As a result, there is growing interest in innovative therapies, including photodynamic therapy, hyperthermia treatment, gene therapy, immunotherapy, stem cell therapy, and advanced drug delivery systems. These emerging treatments offer promising alternatives by minimizing invasiveness and side effects while enhancing therapeutic efficacy. Continued research is crucial to improving outcomes and quality of life for patients with endometriosis.

Keywords: Endometriosis, Inflammatory.

Introduction

Endometriosis, an estrogen-dependent gynaecological condition, is characterized by the presence of endometrial-like tissue outside the uterine cavity. About 10% of women develop endometriosis in their reproductive years. The actual incidence of endometriosis can be underestimated as asymptomatic patients are often not diagnosed. Endometriosis usually involves the ovary. Endometriosis symptoms are not disease stage- or non-specific and are routinely cited as causing painful menstruation, painful sex, and pain on defecation and micturition, amongst other symptoms that significantly affect women's quality of life. The pain could be inflammatory or neuropathic, and in some patients, the pain continues even after excision of the lesion. Endometriosis is more prevalent among infertile women, with 25-50% of cases having difficulty becoming pregnant. Additionally, endometriosis is strongly correlated with adverse results for assisted reproductive technology treatment. Patients with endometriosis have a higher risk of cardiovascular events and IBS. Interestingly, in the present research, individuals with endometriosis were found to have a substantially reduced appreciation for body functionality compared to those without endometriosis. Most critically, the rate of ovarian cancer is very high among women who have been diagnosed with endometriosis.

Currently, usual clinical approaches to endometriosis are medical treatment, surgery, and assisted reproduction. Due to the hormone dependency, endocrine treatments are the first-line drugs. It is worth mentioning, however, that endocrine medications for endometriosis have adverse mental images and feelings, as well as an array of side effects. If medical treatment gives little result, surgical treatment should be undertaken. The operative procedure poses the threat of injury to the ovaries and surrounding structures, and this is very much dependent on the technical skill of the surgeon .And surgery may only alleviate pain in certain individuals rather than universally. The recurrence rate of symptoms after five years remains approximately 50 % regardless of the treatment utilized, approximately 28 % of patients with complete endometriosis excision may need an additional surgical procedure within ten years. Consequently, an emphasis needs to be placed on developing innovative therapies, minimizing side effects, and improving therapy effectiveness. With the advancement of biotechnology and research, new therapeutic approaches are becoming available, such as photodynamic therapy (PDT), hyperthermia treatment (HTT), gene therapy, immunotherapy, stem cell treatment, drug delivery platforms, etc. The minimal invasiveness of PDT makes it an attractive treatment option with negligible adverse effects, desirable scarring outcomes, and no impact on organ structure or function. By exposing intralesional temperatures to external stimulation, HTT is capable of selectively elevating intralesional temperatures and eradicating lesions. Gene therapy and stem cell treatment have high efficiency, high selectivity, low side effects, as well as no drug resistance. It has been suggested that immunotherapy could be used as a new mainstay for eradicating endometriosis based on the patient's immune system, which would likely be an effective clinical treatment for the disease. Nano and micron-scale drug delivery platforms enhance drug efficacy and mitigate systemic adverse effects.

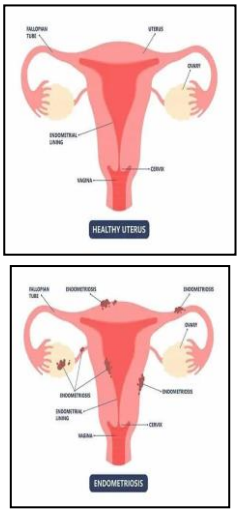

Fig.1 – (a.) Healthy and (b.) Infected Uterus

1. WHAT IS ENDOMETRIOSIS?

- The American Society of Reproductive Medicine's rASRM staging classification system categorizes endometriosis by the extent of lesions and adhesions.
- Various manifestations of endometriosis are superficial, yellow, red, brown, blue, or black lesions in the peritoneal space, ovarian endometrioma, distal intra-epidural endometriosis, and extra-pelvic endometriosis.
- Immune response, inflammatory processes, hormonal regulation, and the formation of blood vessels are involved in the progression of endometriosis.
- Retrograde menstruation, which transports menstrual trash with intact endometrial cells from the uterus to the peritoneum, is an important cause of endometriosis.
- Other possible causes may be involved in endometriosis, such as transformation of peritoneal mesothelium, lymphatic and vascular metastasis, and gene linkage studies.
- Epigenetics plays an ever-growing role in understanding endometriosis, such as DNA methylation, histone modification, and in situ chromatin arrangement regulators.
- TETs and DNMTs are responsible for endometriosis, and methylation and acetylation are the most frequent histone modifications.
- Endometriotic lesion progression after retrograde menstruation is facilitated by an improperly regulated immune system.
- Pro-inflammatory microenvironments will predominate as endometriosis advances, while in later stages they will lean toward immune tolerance.

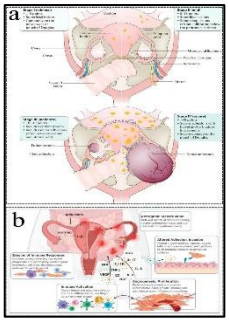

Fig. 2 - Causes and classification of endometriosis in clinical practice. (a) Classification of endometriosis stages (b) The causes and development mechanisms of endometriosis.

2. ENDOMETRIOSIS RISK FACTORS AND LIFESTYLE RECOMMENDATIONS

- Early menarche: The risk of endometriosis is associated with an early first cycle before age 11.
- Shorter than 27-day genital cycles: Genital malformations, such as hymen overgrowth or narrowing of the cervical canal, increase the risk of endometriosis.

- Low BMI: Small number of births, Caucasian race, age 25-29, daily alcohol consumption of at least 10g.
- Obesity: No generally relevant association between BMI and the rate of incidence with endometriosis, however, the increased rate of obesity.
- Diet: Green leafy vegetables, fresh fruits that contain antioxidants, and fiber may help prevent the development of endometriosis.
- Red meat: Highly rich in dioxins, hormones, and fat increases estrogen levels, raising the risk for endometriosis.
- Lifestyle: Adequate lifestyle; rest, activity, and motion are important preventive measures for the primary development of endometriosis.

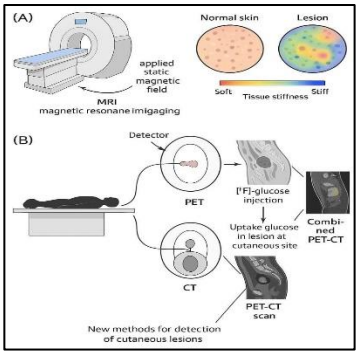

Fig. 3 - New methods for detection of endometriosis lesions. (A) From applied stress tissue fibrosis. It is hypothesised, due to the established relationship between endometriosis lesions and fibrosis, and adhesions, that endometriosis lesions may be detected noninvasively by MRE, though comprehensive clinical trials are required. (B) The tracer 18Ffluorodeoxyglucose (18F-FDG) is injected and will localise to areas of increased metabolic activity, such as that found in cancer or endometriosis lesions detected by the PET scanner. Combining CT with PET improves information about location of lesions.

4. IMPROVEMENTS IN TECHNOLOGY HAVE RESULTED IN QUICKER SCANS AND ALLOW FOR LOWER EXPOSURE OF RADIATION.

- Non-invasive imaging techniques such as Transvaginal ultrasound (TVS) and magnetic resonance imaging (MRI) are utilized to diagnose ovarian and deep disease.
- Other techniques such as ultrasound sheer wave elastography (US-SWE), magnetic resonance elastography (MRE), and positron emission tomography (PET) with computerised tomography (CT) are being investigated to diagnose superficial endometrial disease. • A meta-analysis demonstrated that elastography in combination with TVS had good specificity and sensitivity for the diagnosis of deep endometriosis or adenomyosis.
- MRI can also be utilized in a diagnostic classification (endo-MRI) for radiologic reporting of all various phenotypes.
- MRE provides an additional dimension to imaging outputs through the measurement of tissue mechanical properties (i.e., stiffness and viscosity).
- PET employs intravenously, radiolabeled tracers that are aimed to localize within regions where a disease process of concern is present.
- PET/CT fusion with images gives both biological and anatomic information, and combined PET-CT scanners have the added benefit of more accurate anatomic co-registration of both image sets.
- Total body PET-CT scanner development provides additional advantages since images are of superior quality and are easier to acquire than for traditional hybrid PET-CT scanners.
- Artificial intelligence (AI) diagnostic imaging combined with imaging-based technologies could provide better compared to traditional methods for visualizing reproductive anatomy and finding endometriosis-related pathology that leads to infertility.
- Adenomyosis, frequently identified in concert with a diagnosis of endometriosis, is another diagnostic problem with implications for infertility.

5. CONVENTIONAL METHOD OF TREATMENT

Endometriosis is a chronic, challenging medical problem that can be treated either through pharmacological means, surgery, or combinations of these treatments. Symptoms include complaints of pain and pregnancy problems. Early detection is important, but if reported late, complications arise. Treatment ranges from hormonal to symptomatic with hormonal treatment permissible for three months without histopathological evidence. Proper diet and way of life are also part of its treatment.

- **Pharmacological treatment:** For women in their reproductive years, pharmacological treatment aims to reduce or dismiss pain, prevent further development of endometrial foci, and regain fertility. It may be prescribed following a clinical examination and can be used before and after surgery. The most commonly used drugs are non-steroidal antiinflammatory drugs, complex estrogen progestogen therapy, and progesterone derivatives. The latest drug to be approved by the FDA is elagolix, a non-peptide GnRH antagonist. It results in a significant reduction of common types of endometrial pain, which include pelvic pain and sex-related pain. Although it has a risk of bone loss, the effect on long-term risks of fractures is minimal.

Table 1: The Main Medication Types used in the Treatment of Endometriosis, their examples, and their purposes.

Group	Medication Type	Examples	Purpose/Action
Pain Relievers	NSAIDs	Ibuprofen, Naproxen	Reduce pain and inflammation
Hormonal Treatments	Combined Oral Contraceptives (COCs)	Ethinyl estradiol/norethindrone, Ethinyl estradiol/desogestrel	Regulate menstrual cycles, reduce pain and bleeding
	Progestins	Medroxyprogesterone acetate, Norethindrone acetate	Reduce or stop menstruation, shrink endometrial tissue
	GnRH Agonists	Leuprolide acetate, Goserelin	Suppress ovarian function, reduce estrogen production
	GnRH Antagonists	Elagolix	Reduce estrogen levels quickly, fewer side effects
Aromatase Inhibitors	Aromatase Inhibitors	Letrozole, Anastrozole	Block estrogen production by inhibiting aromatase
Synthetic Steroids	Danazol	Danazol	Suppress estrogen production, induce menopause-like state
Surgical Treatments	Surgery (Laparoscopy)	N/A	Remove or destroy endometrial tissue (postsurgery hormone therapy may follow)
Fertility Medications	Ovulation Inducers	Clomiphene Citrate	Induce ovulation for fertility
	Gonadotropins	FSH, hCG	Stimulate ovaries to produce eggs

- **Surgical Treatment:** The treatments of endometriosis can be done surgically, such as sparing or radical methods. It recommended the use of laparoscopy and combines with surgical and pharmacological treatment. The robot-assisted laparoscopy is a feasible resection method, but then there may arise complications in the gastrointestinal, urinary, and sexual tract. Research suggests that patients having complex pelvic situations can benefit from robot-assisted laparoscopy.

- **Physiotherapy in Endometriosis:** The therapy of physiotherapy in endometriosis is focused on the non-invasive treatment of pelvic floor disorders in women to restore tissue efficiency and quality of life. This involves manual therapy and osteopathic techniques for improved mobility of the internal organs. The application of physical therapy helps reduce pain, improves quality of life, by teaching the person muscle relaxation, and breaks the pain cycle. Regular exercise also has anti-inflammatory properties, induces reduced menstrual flow, ovarian stimulation, and effects of estrogen. However, there is no controlled and randomized trial determining the benefits of exercise for endometriosis patients.

6. LIMITATIONS OF CURRENT ENDOMETRIOSIS TREATMENT MODALITIES

- **Suppressive Rather than Curative Therapy**: Most endometriosis treatments are suppressive, temporarily relieving symptoms. After discontinuation, symptoms recur, with recurrence rates estimated at 21.5% at 2 years and 40% to 50% at 5 years. Recurrence rates are higher in older women with advanced disease stages and lower in infertility women.
- **Contraceptive Rather than Fertility-Promoting Therapy:** Currently, endometriosisassociated pain is treated with contraceptives, and it blocks the hypothalamopituaryovarian axis and suppresses ovulatory function. Hormone therapy hinders embryoimplantation, making it difficult for patients who experience painful symptoms and want to conceive. Several randomized controlled trials exhibit no improvement in natural conception after ovarian suppression, and thus, NSAIDs remain the only medical treatment option for painful endometriosis patients. Pretreatment with a gonadotropin-releasing hormone agonist before in vitro fertilization has shown to improve clinical pregnancy.
- **Endometrioma: Lack of Effective Medical Treatment and Hazardous Surgical Options**- Pain treatment for endometriomas to avoid rupture and malignancy exclude, thereby reducing the occurrence of symptomatic and enlarging cysts. With most present forms of medical management being unsuccesful for the dissolution of endometriomas, an increase in its management laparoscopically is occurring, although removal surgically depresses ovarian reserve: AMH values have shown postoperative falls.
- **Limited Medical Options for Deep Infiltrating Endometriosis and Extrapelvic Disease**: Deep infiltrating endometriosis is the term for endometriosis affecting several organs, which include uterine, bowel, ureters, and bladder. It may be treated by either medical therapy or surgery. For the suppression of hormones, the primary agents are GnRH agonists. Most patients need extensive surgery : Central sensitization significantly contributes to endometriosis-associated pain: it amplifies pain signaling coming from the periphery and can be associated with myofascial trigger points and psychological comorbidities. Its treatments are desperately needed in selected patients, while the area for women with endometriosis is poorly developed. There are clinical applications to tricyclics and antiepileptics without any evidence relating to endometriosis-related co-morbidities. The search for an optimal medical treatment for endometriosis is ongoing since the pathogenesis and natural history of the disease are unclear as well as the pressure for new therapies due to the failure of treatment. Hence, further studies are required in order to evaluate the treatment options.
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7. EMERGING STRATEGIES FOR THE TREATMENT OF ENDOMETRIOSIS

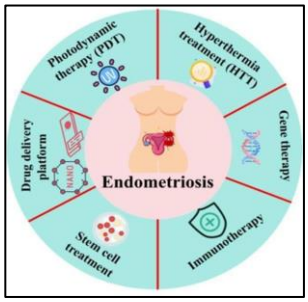

Fig. 4 - Different strategies for treatment of endometriosis

Photodynamic therapy (PDT)

Photochemotherapy (PDT) is a clinical method of eradicating undesirable cells, like cancer cells, by inducing wound healing and providing antimicrobial activity. Photodynamic processes activate photosensitizers that are then exposed to light after the medication has been taken. The availability of photosensitizers in their triplet state causes oxidation of substrates through two pathways and produces reactive oxygen species (ROS) like peroxides and superoxide anions. High concentrations of ROS in PDT can induce inflammation/immune reactions, resulting in cell death of photo-oxidized cells as well as breakdown of the vasculature. PDT has been intensively studied as a means to treat endometrial disorders.

Table 2: PDT in endometriosis.

Photosensitizers	**Method**	**Sample**	**Conclusion**
5-ALA	The utilization of 5-ALA in PDT results in the buildup of protoporphyrin IX.	Primary endometriosis epithelial cells	Upon bulb illumination, cells showed disturbed chromatin concentration and fragmentation after 48 h. When exposed to a laser beam, strong apoptosis was induced 24 h later
5-ALA	Verapamil blocked P-GP for PDT.	Primary endometriosis epithelial cells	PDT was more potent on ectopic epithelium than on eutopic epithelium after preincubation with verapamil, as well as with ALA alone.
Protoporphyrin IX	Examine the correlation between fluctuations in hormones and the accumulation and degradation of photosensitizers.	Primary endometriosis epithelial cells	Optimal results can be achieved by performing photodynamic diagnosis and PDT of endometrial epithelium during the secretory phase of the endometrium.
ALA	The application of ALA-PDT was employed for the treatment of endometriosis in a rat model.	Rats	After systemic administration of ALA, endometriotic explants were ablated by photoactivating light for periods as brief as 10 min. Normal peritoneum was completely resurfaced after exposure to ALA-PDT.

Hematoporphyrin	The management of individuals suffering from pulmonary endometriosis involved the utilization of hematoporphyrin, a photosensitizer, for therapeutic purposes	Patient	After a 2-year follow-up period, the patient's chest CT scans conducted at different stages of her menstrual cycles showed that the exudative lesions in the left upper lobe were completely absorbed.

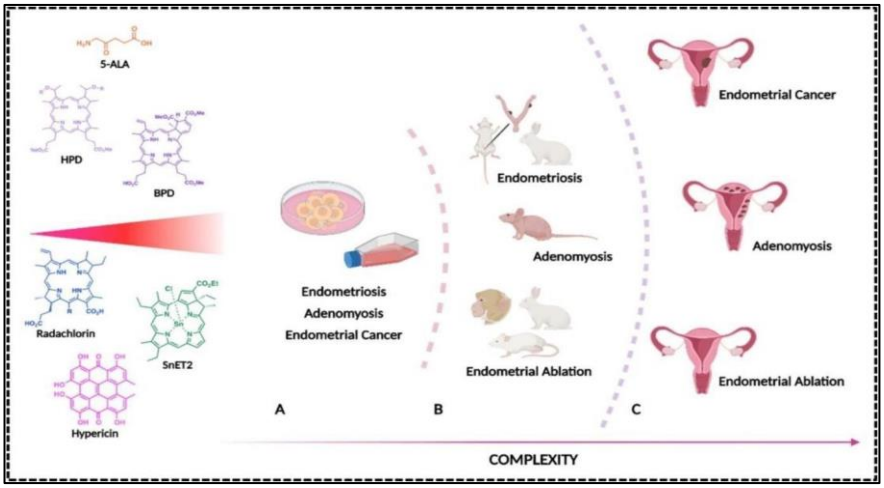

Fig.5.- PDT in endometriosis. The utilization of PDT in endometrial conditions involves conducting studies in laboratory settings, performing experiments on animals, and carrying out trials with human subject.

➢ **Benefit of PDT**
- Photocytotoxicity is localized and selective to irradiated tissues.
- No pain or discomfort involved.
- Can be combined with other treatment modalities.
- Degree of invasiveness varies with the site of treatment.
- Facilitates diagnosis and therapy of certain gynecologic malignant disorders.

➢ **PDT and 5-Aminolevulinic Acid (5-ALA)**
- PDT works effectively to treat endometriosis.
- Exogenous administration of 5-ALA accumulates protoporphyrin IX, an effective and natural photodynamic sensitizer.
- PDT has stronger effects on endometriosis-affected cells than on normal endometrial cells.
- The secretory phase of the endometrium is the best time for photodynamic diagnosis and treatment of endometrial epithelium.

➢ **ALA-PDT Study**
- Systemic ALA and subsequent 10 or 15 min of photoactivation completely ablated all explants following harvest.
- Complete removal of the lesion with minimal adhesion morbidity.

➢ **PDT Case Study**
- Patient underwent PDT for pulmonary endometriosis.
- Experiments showed no reappearance of exudative lesions or abnormal opacities in the left upper lobe.

➢ **Posensitizer Activity and PDT**
- The activity of a photosensitizer differs in different tissues.
- There has been a lot of research on 5-ALA, an exogenous photosensitizer.
- The level of PpIX induced by 5-AlA was considerably greater in the endometrium.

➢ **PDT's Significance**
- High selectivity, localized characteristics, minimally invasive characteristics, and promising potential for the treatment of endometriosis.
- PDT is less likely to have undesirable effects than hormone therapy and surgery.
- The process of choosing a light source and photosensitizer for treatment demands extensive research.

Hyperthermia treatment (HTT)

A hyperthermic treatment is of great potential as an adjuvant cancer treatment since it enhances tumour blood flow and oxygenation and spares adjacent healthy tissues. Hyperthermia damages some biological processes. High temperatures specifically suppress DNA repair enzymes, enhancing the sensitivity of cancer cells to chemotherapy and radiation. Hyperthermia modifies heat shock proteins. These proteins are crucial for cancer treatments, such as enhancing immune function. In addition, hyperthermic treatments can enhance the effectiveness of immune checkpoint inhibitors by enhancing the immune system's capacity to fight tumours. Mild systemic hyperthermia (39-41 °C) simulates fever-like states, stimulating immune cells and enhancing metabolic function. High temperatures above 50 °C can release tumour antigens, boosting immune responses. Hyperthermia has been applied in treating some types of cancer. Hyperthermia has a great potential for the cure of endometriosis because it causes minimal damage to the adjacent tissue. Considerable research work is currently being done on photo and magnetic hyperthermia.

Table.3. HTT in endometriosis.

Material	Stimulate	Sample	Conclusion
SiNc; PEGPCL nanoparticles	NIR	Immunodeficient mice	After the application of NIR light, the SiNc-NPs demonstrated efficient eradication of endometriotic lesions without any observed negative consequences.
TNYL; HAuNS	NIR	Mice	Upon exposure to NIR laser, TNYLHAuNS demonstrated remarkable efficacy in inhibiting tumor growth and promoting the regression and degeneration of ectopic endometrium without causing any harm to healthy tissues.
LTZ; PDA; AG	NIR	Human endometrial stromal cells; Rats	The LTZ-PDA@AG hydrogel demonstrated a notable increase in temperature during both in vitro and in vivo photothermal treatment.
Hydrogel microsphere; curcumin	NIR	Rats	The interventional hydrogel microspheres (Cur-FeHMPs) can raise the temperature of the endometriotic lesions to 43.65 °C, inducing endometriotic lesion elimination
Hexagonal iron-oxide nanoparticles	AMF	Mice	The nanoparticles exhibit exceptional efficacy in accumulating within endometriotic lesions, inducing a specific temperature rise above 50 °C inside the lesions upon exposure to an external AMF, and effectively eradicating them with a single therapeutic intervention.

Photothermal therapy

- The near-infrared (NIR) laser is employed to destroy tumor cells within the tumor itself, a method commonly known in cancer therapy.
- Endometriosis, like malignant tumors, has been associated with greater vulnerability to many forms of cancers.

  Photothermal therapy, given its brief period and fewer side effects, has the potential in treating endometriosis.
- PEG-PCL and SiNc-coated nanoplatform was effective in detecting and removing endometriosis tissues by Fluorescence and photothermal therapy (PTT).
- Hollow gold nanospheres and CdTe quantum dots have the potential to accumulate in lesions of endometriosis and inhibit lesions progression, thereby lowering TNF-alpha and estradiol levels.
- An injectable hydrogel composed of polydopamine (PDA), letrozole (LTZ), and agarose (AG) hydrogels has been designed to treat endometriosis.
- An interventional hydrogel microsphere releases curcumin non-surgically upon exposure to NIR energy, suppressing the inflammation response in endometriosis.
- Scientists now aim to enhance the drug delivery efficacy via photothermal therapy.

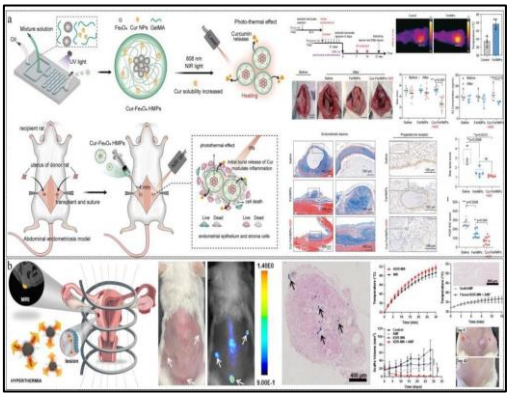

Fig.6. HTT in endometriosis. (a) Synthesis and assessment of therapeutic effectiveness of hydrogel microspheres incorporating Cur-Fe3O4HMPs in a murine model mimicking endometriosis (b) Schematic illustration of the utilization of nanoparticles for magnetothermal treatment in endometriosis and their effectiveness in therapeutic outcomes among mouse.

- **Magnetic hyperthermia**

- Magnetic nanoparticles cause hyperthermia, a non-surgical cure for cancers.
- Efficacy of the therapy relies upon the type of disease and the method of heating utilized.
- Temperature and time of heat treatment have an impact on cellular reactions related to hyperthermia.
- Mild hyperthermia or heat shock, and duration of the treatment, may impact the initiation of autophagy, apoptosis, or necrosis.
- Limited work has been done on its application in the treatment of endometriosis.
- Park et al. showed the efficacy of magnetic nanoparticle hyperthermia for endometriosis, which caused therapeutic temperatures (>50 °C) within lesions.
- In vivo experiments resulted in the complete eradication of grafts by the nanoparticles without any side effects.
- There is a need for more research on safe, effective, and suitable light and media for hyperthermia therapy of endometriosis.
- Specific tumor site targeting and tracking methods are of prime importance in order to obtain therapeutic effects of benefit.

Gene therapy

Epigenetic Disorders and Endometriosis

- Epigenetic disorders are thought to cause endometriosis.
- Gene therapy is intended to change gene expression in order to change living cells' biological characteristics.
- Vectors employed in gene therapy can be classified into viral and non-viral vectors.
- Non-viral vectors have advantages such as chemical controllability and unlimited capacity.

Nanocarrier Delivery in Gene Therapy

Nanocarrier delivery in gene therapy holds promising potential in cancer management.

- A gene delivery system was engineered by Zhao et al. with lipid-modified chitosan (CSOSA) to deliver pigment epithelium-derived factor (PEDF) to endometriotic lesions.
- Chitosan oligosaccharide and polyethylenimine linked with small interfering RNA created a novel type of nanoparticle system that caused a remarkable reduction in CD44 expression in ectopic endometrium.

Target Nanoparticles for Gene Delivery

- Targeted nanoparticles (NPs)-based delivery platform was developed to deliver genes.
- The PEI-SA/DNA HA gene delivery system regulates autophagic activity and hence has potential as an endometriosis treatment.

Potential of R6p-cRGD Peptide-Based Polymers

- A significant reduction in the formation of endometriotic implants and vascular endothelial growth factor A gene expression was observed in previous studies.
- Finding a safe and efficient vector and a suitable target gene is important for clinical use.

Table.4. Gene therapy in endometriosis.

Material	Conclusion
CSO-SA; PEDF	The utilization of CSO-SA/PEDF nanoparticles in gene therapy led to a considerable decrease in the dimensions of endometriotic lesions and prompted noticeable shrinkage and deterioration of the ectopic endometrium.
HA; CSO-PEI; siRNA	The treatment with (CSO-PEI/siRNA) HA resulted in a significant reduction in the size of endometriotic lesions, along with a decrease in CD44 expression within epithelial cells when compared to the control group.
PEI; HA; DNA/siRNAs; SA	This gene delivery system of (PEI–SA/DNA)HA stimulated autophagy in order to help treat endometriosis.
EI-PEG-RGD; miR-200c mimic and inhibitor	The administration of miR-200c using the delivery system composed of PEI-PEG-RGD effectively inhibited the growth of ectopic endometriosis protrusions.
R6p-cRGD peptide; antiVEGF siRNA	VEGFA gene expression was decreased when siRNAs against VEGFA were combined with R6p-RGD complexes, inhibiting endometriotic implant growth.

Immunotherapy

- Endometriosis is associated with peritoneal inflammation, elevated immune cells in peritoneal fluid, and ectopic lesions.
- The disease is thought to result from changes in innate and adaptive immunity.
- Endometriosis patients exhibit reduced macrophagic phagocytosis, resulting in immune imbalances.
- CD47, one of the major cytotoxic killer cells in macrophages, can be decreased using siRNA or neutralizing antibodies, enhancing macrophage phagocytosis.
- Anti-exocrine treatment of endometriosis patients may augment macrophage accumulation to ectopic lesions, reducing the number of MII-type phagocytes and enhancing the phagocytic capture of abnormal endometrial cells.
- Mycobacteria in immune therapies has been employed to treat a number of diseases, with one study indicating that cytotoxic killer cells induced by mycobacteria can eliminate endometrial stromal cells.
- Sunitinib, a receptor tyrosine kinase inhibitor, is also capable of treating endometriosis effectively by shrinking the size and weight of endometriotic lesions.
- Combination of IL-33-Ab and Erastin treatment can alleviate the disease, which shows that immunotherapy and ferroptosis therapy can be used effectively together.
- Immunotherapy based on nanotechnology can increase the efficacy of treatment by targeting the endometriosis lesions while avoiding damage to the adjacent tissues and organs.
- More studies are necessary to define the safety of human use of endometriosis immunotherapy.

Table.5. Immunotherapy in endometriosis.

Material	Sample	Conclusion
Mycobacteria	Human endometrial stromal cells	Mycobacteria can activate killer cells in endometrial stromal cells.
Sunitinib	Mice	The anti-inflammatory properties of sunitinib inhibited the growth of endometriotic lesions by maturing MDSCs in peritoneal fluid and inhibiting their immunosuppressive activity
IL-33-Ab; Erastin	Mice	Endometriosis was alleviated with the combination of IL-33-Ab and Erastin treatment.
PLGA; anti-CTLA-4	Mice	PLGA encapsulation of CTLA-4 antibody (anti-CTLA-4) demonstrates greater efficacy in halting endometriosis progression in a mouse model compared to using anti-CTLA-4 alone.

M1NVs	Mice	The migration and invasion of EM-ESCs are effectively suppressed by the M1NVs, either through direct or indirect mechanisms.

Stem cell treatment

Potential of Stem Cells in Regenerative Medicine

- They possess the ability for self-renewal, which allows them to differentiate into different cellular lineages.
- They possess immunomodulatory effects that suppress inflammation.
- They have been found to effectively treat incurable diseases as well as organ transplantation.

Kinds of Stem Cells in Research

- Stem cell research employs different forms of stem cells: reprogrammed pluripotent stem cells
- (iPSCs), embryonic-derived stem cells (ESCs), mesenchymal stem cells from different tissues (MSCs), and blood-producing stem cells (HSCs).
- EMSCs, which originate from menstrual blood, bear CD140b+CD146+ or SUSD2+ markers. • EMSCs have been shown to migrate to endometriotic lesions and thus may have therapeutic potential for targeted drug delivery systems in the treatment of endometriosis.

Potential Therapeutic Use of Adipose Tissue-Generated Stem Cells (ASCs)

- ASCs infused in endometriotic lesions suppressed lesion development with endometriosislike features.
- MSCs are able to normalize the processes of very small embryonic-like stem cells (VSELs) and EnSCs, correcting conditions of the uterus.

Ethical and Social Implications

- Ethical and social concerns regarding applying human ESCs in experiments or therapeutic treatments have generated intricate arguments.
- The introduction of iPSCs offers a new methodology, which counters ethical issues with respect to the destruction of embryos.
- iPSCs might be derived from different somatic cells available within the human system and are thus easily accessible and useful.

Table.6. Stem cells in endometriosis

Stem cell type	**Sample**	**Conclusion**
EMSCs	Mice	The utilization of EMSCs as a drug delivery system holds promise for effectively targeting endometriosis therapy.
ASCs	Murine	The utilization of ASCs has demonstrated significant efficacy in inhibiting the development of lesions resembling endometriosis, as well as reducing fibrosis and proliferation.
MSCs	Mice	MSC-Adsflt-1 can decrease the number and size of endometrial glands in the mice with endometriosis model.

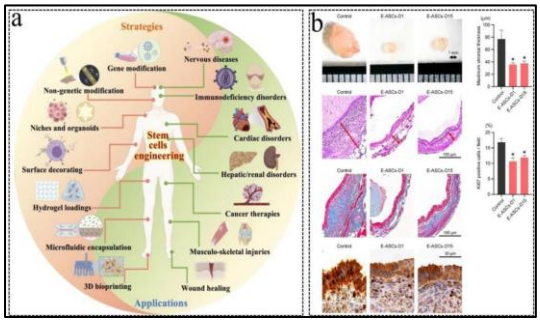

Fig.7. Stem cell therapy in endometriosis. (a) Applications of stem cell engineering and their biomedical implications in the field of engineering (b) The examination of the changes in macroscopic and histopathological characteristics of lesions resembling endometriosis after administering ASCs treatment.

Drug delivery platform

Hormone therapy is the main therapeutic strategy for endometriosis in medical practice but has its long-term application restricted through related side effects, decreasing effectiveness. Localised drug delivery has tremendous potential since it enables maximum medication levels within the complex and dynamic environment of the upper genital tract. Nano- and micronscale drug delivery systems have the ability to deliver drugs with high precision, permitting continuous drug release at a localized site in an effort to sustain optimum concentration as well as desired therapeutic effects. This section discusses drug delivery systems for endometriosis developed using nano- and micron technologies.

Nanotechnology

Nanotechnology examines and applies substances between 1 and 100 nm, presenting benefits in the form of targeting specific locations, compatibility with biological systems, stability, and low toxicity levels. The nanomaterials have been employed in treating different health conditions, such as inflammatory disorders, cardiovascular disease, infectious diseases, and cancer. Nanocarrier drug delivery systems are being employed in cancer research more and more because they are capable of delivering platinum drugs to tumor tissue, thus lowering side effects and enhancing efficacy. The nano platform was found to cause iron sag, enhance the efficacy of PDT, and suppress tumor development in live animals when used with Pt drug chemotherapy. Nanotechnology-based methods are found effective in diagnosis and management of endometriosis with minimal effects on the system, which is a potential for management of endometriosis. This chapter reports a broad overview of nanomaterials as therapeutic drugs and pharmaceutical carriers for treatment of endometriosis control.

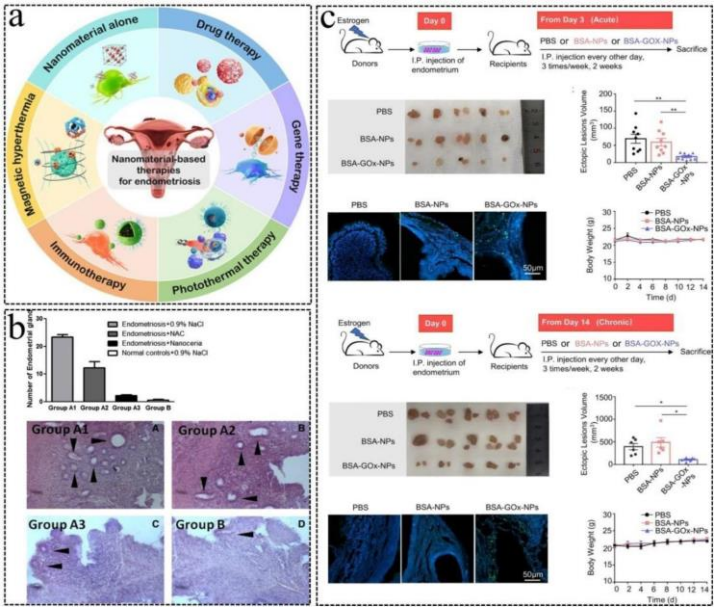

Fig.8.- Nanotechnology in treatment of endometriosis. (a) Therapeutic approaches utilizing nanomaterials for managing endometriosis. (b) The hematoxylin and eosin staining demonstrated the influence of nanoceria on the glands located within the intimal tissue. (c) Process and effectiveness of BSA-GOx-NPs in the treatment of endometriosis.

Table.7. Nanotechnology in treatment of endometriosis.

NPs	**Sample**	**Conclusion**
Nanoceria	Mice	The administration of nanoceria alleviates endometrial lesions in a mouse model and protects against oocyterelated adverse effects associated with endometriosis.
MM-NS	Mice	The MM-NS targeted therapy for ectopic lesions was successfully administered in vivo in a mouse model of endometriosis, resulting in effective inhibition of lesion growth.
COPA-PVP	Primary ESCs	After conducting in vitro pharmacological studies, treatment with COPA nanocomposite significantly decreased the survival rate and proliferation ability of endometriosis cell culture.
CPO-PLGA	Primary ESCs	After incubation with CPO nanoparticles for 48 h, the viability of ectopic endometrial and normal-location endometrial tumor cells derived from patients with endometriosis was significantly diminished.
BSA-Gox-NPs	Mice	The application of BSA-GOx-NPs has shown impressive effectiveness in managing both the severe and persistent inflammatory phases linked to endometriosis.
BML@CaNP	Endometriotic stromal cells; Mice	The BML@CaNP treatment induced apoptosis in endometriosis cells, while the in vivo experiments demonstrated the effective inhibition of lesion growth by BML@CaNP in a mouse model of endometriosis.
EGCG-DoxPLGA	Mice	The treatment with nanoparticles carrying dual drugs significantly attenuated oxidative stress, angiogenesis, and matrix metalloproteinase activity, while concurrently reducing the presence of endometrial glands and microvascular density.
CSOSA/NLC/A317491	Rats	The administration of CSOSA/NLC/A-317491 demonstrated long-term efficacy in reversing mechanical and heat hyperalgesia in rats with endometriosis.

Curcumin-PCLPEG	Mice	The in vivo experiments demonstrated the efficacy of these implanted nanofibers loaded with curcumin in alleviating endometriosis, as evidenced by a significant reduction in both endometrial glands and stroma, along with a notable decrease in inflammatory cell infiltration.

Nanoceria's Therapeutic Potential

- Nanoceria has exhibited vast therapeutic promise in reducing pathogenic processes involved in endometriosis.
- It was applied to treat endometrial lesions of mice models, decreasing levels of oxidative stress, as well as slowing down angiogenesis processes.
- Nanoceria also possesses protective qualities towards oocytes, essential for a successful pregnancy.

Nanoenzymes as Treatment carriers

- A MnO2 nanosheet-modified biomimetic macrophage cell membrane (MM-NS) was prepared to treat endometriosis by effectively clearing estrogen.
- The nano system has good solubility and high activity in clearing estradiol, significantly inhibiting cell growth and inflammation.

Nanomaterials as Carriers for Endometriosis Treatment

- Nanocomposites prepared by the combination of copaiba oil-resin (COPA) with the polymer polyvinylpyrrolidone (PVP) exhibited remarkable inhibition of the viability and growth rate of endometriotic cell cultures.
- Optimized copaiba oleoresin (CPO)-containing nanoparticles proved effective against the viability of endometrial cells.
- A cost-effective and scalable approach to deliver bovine serum albumin nanoparticles encapsulating glucose oxidase (BSA-GOx-NPs) to aberrant lesions was developed.

Nanomaterials as Novel Platforms for Drug Development

- Nanomaterials allow for drug delivery, improve target treatment, and reduce unwanted effects.
- They possess great potential as new drug-development platforms.

Nanomedicine and Endometriosis

- Nanotechnology's advances promise research into endometriosis and reproductive diseases.
- Drug-loaded nanoparticles have demonstrated significant promise in the management of endometriosis by neutralizing constraints related to drug use, drug targeting, and therapeutic activity against the illness and reducing side effects on other organs and tissues.

Microencapsulation technology

➢ **Microencapsulation Process**

- Microencapsulation encompasses the encapsulation of an active molecule with a thin wall material, which forms tiny particles varying from 1 μm to 1000 μm in diameter.
- In drugs, it improves the stability of molecules, hides unwanted taste, odor, or activity, alters release characteristics, reduces side effects, and enhances drug bioavailability.

➢ **Key Techniques**

- Methods are extracting solvents, evaporative removal of liquids, phase separation (coacervation), and spray drying.
- Methods are incorporation of bioactive molecules, droplet formation, removal of solvents, harvesting micro-particles, and drying.

➢ **Electrohydrodynamic and Microfluidic Technology Role**

- Electro spraying, or electrohydrodynamic atomization (EHDA), has advantages like better dissolution rate of poorly soluble drugs in water, scalability for batch processing, reproducibility, low-pressure operation, single-pot production, and high encapsulation efficiency.
- Microfluidic methods provide precise control over the size, morphology, chemical composition, and organization of uniform microparticles.

➢ **Microencapsulation in Endometriosis Treatment**

- Microencapsulation technology has been found to be beneficial in the development of drugs used to treat endometriosis.
- Researchers have prepared microparticles made up of photo-crosslinked hydrogel microparticles from bovine serum albumin for controlled release and cell attachment inside the microparticles.
- The contact between the PLGA depots and the hydrogel resulted in excellent drug encapsulation and less initial release, thereby providing an extended dosing interval.

➢ **Challenges and Future Directions**

- Formulation of long-acting GnRH analogue preparations still faces challenges in achieving high encapsulation efficiency and desired release characteristics.
- Further studies are required to identify the best compound type and concentration for a maximum drug encapsulation rate and the best performance in drug release.

Table.8. Microencapsulation technology in the treatment of endometriosis.

Material	Sample	Conclusion
D@P–B MPs	Mice	The growth of lesions was significantly hindered, inflammation was reduced, and angiogenesis was suppressed in mice suffering from endometriosis upon the administration of D@P–B MPs.
GOS-PLGA	Rats	The GOS-PLGA demonstrated a notably superior level of relative bioavailability in comparison to the Zoladex implants.

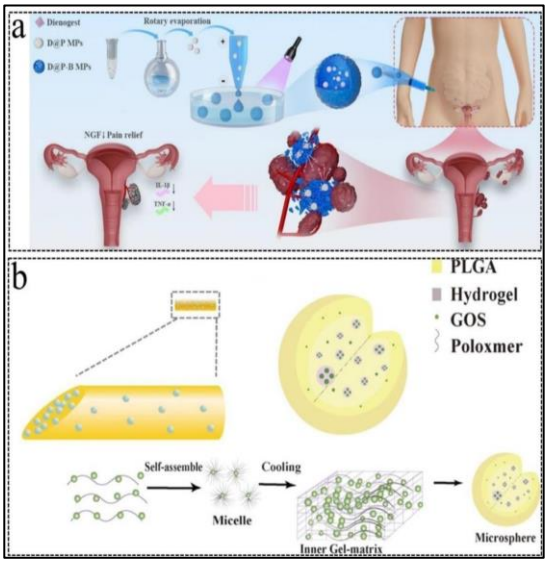

Fig.9. Microencapsulation technology in the treatment of endometriosis. (a) The application of the microfluidic electrospray method was utilized to produce PLGA- BMSA microspheres coated with dienogest, aiming at addressing endometriosis treatment. (b) Preparation and characterization of Poloxam hydrogel-incorporated PLGA microspheres containing Goserelin acetate.

8. CONCLUSION

Endometriosis remains a major clinical dilemma with its intricate pathogenesis, heterogeneous symptomatology, and rampant recurrence post-standard treatment. Although the existing therapeutic regimens like hormonal suppression and surgery provide relief of symptoms, their shortcomings justify the need for better and more sustainable management. This thesis shows the potential of newer technologies to diagnose and manage endometriosis with greater accuracy, less side effects, and improved patient outcomes. Photodynamic and hyperthermia therapies portray successful targeting of lesions and reduced invasiveness, and gene and immunotherapies usher in the era of personalized medicine. Stem cell strategies and nano/micro drug delivery platforms present new mechanisms for tissue healing and therapeutic release under control. Combined, these advances herald a paradigm shift toward multidisciplinary, non-hormonal, and patient-specific management practices. But the translation of preclinical promise to clinical reality needs high-level trials, optimization of delivery systems, and longterm safety assessments. Future studies need to aim to incorporate these modalities within a holistic and accessible treatment platform to benefit the lives of millions of women affected by endometriosis.

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