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Review

Endometriosis: New Therapeutic Targets and Clinical Management

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ABSTRACT

Endometriosis is a chronic gynecological condition characterized by the presence of functional endometrial tissue outside the uterine cavity, affecting about 10% of women of reproductive age and up to 50% of those with infertility or chronic pelvic pain. Its pathophysiology involves peritoneal inflammation, excessive angiogenesis, local hormonal imbalance and immune dysfunction factors that contribute to adhesion formation, ovarian nodules and intense pain. Traditional management includes combined oral contraceptives, GnRH analogs and laparoscopic surgery, but side effects, osteopenia and high recurrence limit long-term efficacy. In recent years, new therapeutic targets acting on molecular processes of endometriosis have been identified. Selective progesterone receptor modulators (SPRMs), such as ulipristal acetate, have demonstrated up to 60% reduction in lesion volume and relief of pelvic pain without inducing chemical menopause. Aromatase inhibitors (letrozole, anastrozole) have proven effective in suppressing local estradiol production, resulting in an 80% reduction in dysmenorrhea intensity when combined with oral contraceptives. Second-generation oral GnRH antagonists, especially elagolix, allow dose-dependent partial estrogen suppression, minimizing bone and vasomotor side effects seen with injectables. Beyond hormonal therapies, antiangiogenic agents such as bevacizumab inhibit VEGF and reduce lesion vascularization, although they still lack large-scale clinical trials due to concerns about delayed healing. Immune modulation by microRNAs (miR-200, miR-199) and monoclonal antibodies against pro-inflammatory cytokines is a promising strategy to rebalance the peritoneal microenvironment but remains in preclinical stages. Cellular therapies with adipose-derived mesenchymal stem cells show migration capability and secretion of anti-inflammatory factors but require safety and oncogenic risk assessment. Future investigations should prioritize long-term randomized clinical trials, assess predictive biomarkers of therapeutic response and develop protocols to prevent recurrence.

Keywords: Endometriosis; Hormonal therapy; GnRH antagonists; Antiangiogenic agents; Immunomodulation

Introduction

Endometriosis is a chronic and progressive gynecological disorder, defined by the presence of endometrial glands and stroma outside the uterine cavity. It affects approximately 10% of women of reproductive age and up to 50% of those suffering from chronic pelvic pain or infertility. Classical symptoms include severe dysmenorrhea, persistent pelvic pain, deep dyspareunia and frequently, impaired fertility, significantly impacting quality of life and psychological well-being. From an etiological perspective, Sampson's theory of retrograde menstruation remains the most accepted, proposing that endometrial fragments travel through the fallopian tubes to the peritoneum, implanting and forming ectopic foci. However, this hypothesis does not account for all cases, especially those in atypical locations such as the lungs or central nervous system. Alternative theories such as coelomic metaplasia and lymphatic or hematogenous dissemination of endometrial cells help explain the wide anatomical distribution observed. The molecular substrate of endometriosis involves persistent inflammatory cascades: M2 macrophages secrete pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemotactic factors, supporting the survival and proliferation of ectopic tissue. Additionally, increased aromatase expression in implants leads to local estradiol synthesis, establishing a feedback loop that promotes inflammation and angiogenesis through VEGF and FGF.

Despite advances in imaging diagnosis, such as 3D transvaginal ultrasound and high-resolution MRI, laparoscopy remains the gold standard for histological confirmation, resulting in an average diagnostic delay of 7–10 years after symptom onset. This delay hinders early intervention, facilitates lesion progression and raises the risk of complications like extensive adhesions and irreversible infertility. Conventional management is based on hormonal suppression and surgery. Combined oral contraceptives and progestins reduce estrogenic stimulation, but with partial effectiveness and high recurrence rates after discontinuation. GnRH analogs induce chemical menopause and provide symptomatic relief but are limited to short-term use due to adverse effects like bone loss, vasomotor symptoms and mood disturbances. Laparoscopic resection of endometriotic lesions may relieve pain and improve fertility, but recurrence rates reach 50% within five years if not combined with adjuvant treatment.

These limitations have driven the search for novel therapeutic targets acting on the molecular and cellular mechanisms of the disease. SPRMs such as ulipristal acetate exert antiproliferative effects on implants, reducing lesion volume by up to 60% with fewer systemic effects, avoiding chemical menopause. Aromatase inhibitors (letrozole, anastrozole) effectively suppress local estradiol production, leading to an 80% reduction in dysmenorrhea intensity when combined with oral contraceptives, though bone density monitoring is necessary. Second-generation oral GnRH antagonists (elagolix, linzagolix) enable dose-dependent estrogen suppression, balancing pain relief and bone preservation, with 70% symptom reduction within six months and better safety profiles compared to injectables. Since angiogenesis is central to lesion maintenance, antiangiogenic therapies like bevacizumab target VEGF and have shown reduced vascularization and adhesions in animal models.

Beyond hormonal and antiangiogenic strategies, immunomodulators based on microRNAs (miR-200, miR-199) and monoclonal antibodies targeting inflammatory cytokines (IL-6) are in preclinical phases, indicating potential rebalancing of the peritoneal microenvironment[1,2]. Mesenchymal stem cell therapies demonstrate regenerative and anti-inflammatory potential but demand long-term safety assessments[3]. In this multifactorial context, integrating conservative surgery, conventional and innovative hormonal therapies, antiangiogenic agents, immunomodulation and multidisciplinary support (physiotherapy, nutrition, psychotherapy) appears essential for personalized treatment, optimizing outcomes and reducing recurrence[4,5].

Objectives

This article reviews the central pathogenic mechanisms of endometriosis and discusses emerging molecular and cellular targets, focusing on novel therapeutic strategies. The combination of conservative surgical approaches with innovative hormonal and immunomodulatory treatments, along with multidisciplinary interventions (pelvic physiotherapy, nutritional support, psychological care), is crucial for personalizing clinical management, improving outcomes and reducing recurrence.

Materials and Methods

A literature review was conducted using the databases PubMed, SciELO, Google Scholar and ScienceDirect.

Discussion

Recent advances in the understanding of endometriosis pathophysiology have enabled the development of increasingly targeted therapies. SPRMs, particularly ulipristal acetate, stand out as alternatives to traditional hormonal management[6-8]. Their selective antiproliferative effect on ectopic endometrium does not induce chemical menopause nor significantly alter systemic estrogen levels, offering up to 60% lesion volume reduction and significant pelvic pain relief. This specificity improves treatment adherence and minimizes side effects, making them viable for medium- and long-term use. Simultaneously, aromatase inhibitors (letrozole, anastrozole) have been validated in patients resistant to standard treatment. By directly inhibiting estradiol synthesis in ectopic foci, these drugs yield up to 80% reductions in dysmenorrhea severity when combined with oral contraceptives. However, the resulting hypoestrogenism necessitates monitoring of bone mineral density and implementation of prophylactic measures to reduce vasomotor symptoms, limiting their use in populations at higher osteoporotic risk.

The introduction of second-generation oral GnRH antagonists like elagolix and linzagolix offers therapeutic flexibility. Unlike injectable analogs that cause complete estrogen suppression, these oral antagonists allow for dose adjustment to achieve partial suppression, balancing analgesic efficacy and bone preservation. Clinical trials show that intermediate doses of elagolix reduce pelvic pain by 70% within six months, with lower incidence of severe vasomotor symptoms and moderate bone loss[9]. This personalized dosing broadens treatment options, especially for women aiming to preserve bone and metabolic health. Antiangiogenic approaches have also shown promise. VEGF antagonists like bevacizumab significantly reduced vascularization and adhesion formation in experimental models, suggesting potential to modulate nutrient supply to implants and limit growth. However, transitioning to large-scale clinical trials remains limited by safety concerns, including delayed wound

healing, thromboembolic events and renal toxicity, requiring cautiously calibrated protocols[10].

In immunomodulation, redistribution of peritoneal macrophage populations and regulation of specific microRNAs (miR-200, miR-199) offer strategies to restore immune balance. Preclinical studies show that miRNA modulation inhibits proliferation and migration of endometrial cells in vitro, while anti-IL-6 monoclonal antibodies significantly reduce peritoneal inflammation[11,12]. These early-stage approaches represent a paradigm shift, targeting the inflammatory microenvironment rather than merely suppressing sex hormones. Mesenchymal stem cell therapy from adipose tissue adds a regenerative dimension. These cells preferentially migrate to lesion sites, secrete anti-inflammatory and antiangiogenic factors and promote tissue remodelling. However, key gaps remain regarding long-term safety, oncogenic potential and risk of ectopic formation, warranting rigorous clinical trials before routine use.

Combining different therapeutic modalities conservative surgery to remove implants, followed by SPRMs or oral GnRH antagonists, plus ultidisc antiangiogenic or immunomodulatory ultidi-demonstrates ultidi in symptom control and recurrence reduction. Integrative protocols including pelvic physiotherapy, nutritional counselling and psychotherapy show additional benefits in quality of life and coping with chronic disease. Despite progress, challenges remain. Molecular heterogeneity among patients requires development of predictive biomarkers to guide optimal therapy choices. Long-term randomized trials are essential to directly compare new therapies and current standards and to define recurrence prevention protocols tailored to clinical and molecular profiles. In sum, endometriosis therapy is evolving from empirical approaches to strategies targeting specific pathogenic mechanisms[13]. Personalized care based on hormonal, inflammatory and genomic profiles, supported by ultidisciplinar approaches, promises to reduce recurrence, minimize side effects and significantly improve patient quality of life.

Conclusion

Endometriosis remains one of the most challenging conditions in modern gynecology due to its clinical and molecular heterogeneity, delayed diagnosis, psychological impact and high recurrence rates. In-depth understanding of central mechanisms chronic inflammation, exacerbated angiogenesis, local estrogen imbalance and immune dysfunction has paved the way for therapies that go beyond simple hormonal suppression or surgical excision. SPRMs, exemplified by ulipristal acetate, have shown significant efficacy in reducing lesion volume and pain relief without inducing chemical menopause, enhancing adherence. Aromatase inhibitors like letrozole and anastrozole effectively suppress peritoneal estradiol production, achieving up to 80% reduction in dysmenorrhea, although bone density monitoring is required. Second-generation oral GnRH antagonists (elagolix, linzagolix) expanded the therapeutic arsenal by allowing dose-dependent estrogen suppression, balancing analgesic efficacy and bone preservation, with 70% pelvic pain reduction and a more favorable adverse effect profile compared to injectables. Antiangiogenic agents like bevacizumab proved effective in reducing vascularization and adhesions in preclinical models, but still require validation in large-scale clinical studies due to safety concerns. Immune modulation by microRNAs (miR-200, miR-199) and cytokine-targeting antibodies (IL-6) yielded promising experimental results, suggesting restoration of peritoneal balance and inhibition of ectopic proliferation. Mesenchymal stem cell therapy offers regenerative and anti-inflammatory potential, though further research is needed on tumorigenic risk. In this multifactorial context, optimal management combines conservative surgery, innovative hormonal therapies, antiangiogenic and immunomodulatory agents, tailored to each patient's clinical and molecular profile. The inclusion of multidisciplinary support pelvic physiotherapy, nutrition and psychotherapy enhances care, improves coping with chronic illness and amplifies outcomes.

To consolidate this personalized care model, long-term randomized clinical trials comparing new therapies and validating recurrence prevention protocols are essential. Developing predictive biomarkers of treatment response is crucial to guide decisions, ensuring efficacy while minimizing adverse effects. In conclusion, the shift from empirical to molecularly and cellularly targeted strategies signals a new era in endometriosis treatment. Personalized care, based on clinical, genomic and inflammatory profiles and supported by integrative guidelines, promises to reduce recurrence, improve quality of life and expand therapeutic options for women affected by this debilitating condition.

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