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RECENT ADVANCES IN SUSTAINED RELEASE DRUG DELIVERY SYSTEMS FOR ENDOMETRIOSIS THERAPY

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ABSTRACT

Endometriosis affects 10–15% of reproductive-aged women, yet current therapies remain largely palliative and non-curative. Hormonal treatments (oral contraceptives, progestins, GnRH agonists/antagonists) suppress ovulation and menstruation but do not eliminate ectopic lesions, cause significant systemic side effects, and are associated with 50–80% pain recurrence within six months of discontinuation. Surgical excision, while effective for pain and fertility, is limited by incomplete resection, operative risks, and 40–50% five-year recurrence rates. The central unmet need is the inability to achieve sustained, high local drug concentrations within endometriotic lesions without systemic toxicity. This review critically examines recent advances in sustained release drug delivery systems designed to overcome these barriers. Lipid-based nanocarriers—nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), and nanoemulsions—exploit the enhanced permeability and retention (EPR) effect of lesion vasculature, achieving prolonged drug release and reduced systemic exposure. NLC-encapsulated mifepristone provides 21-day sustained release in preclinical models, reducing lesion volume by 82%. Polymeric nanoparticles, particularly PLGA and chitosan-based systems, enable tunable degradation kinetics and gene silencing (e.g., VEGF siRNA with 70% mRNA knockdown). Hyaluronic acid-functionalized nanocarriers actively target CD44-overexpressing lesions, improving drug accumulation 2.5- to 8-fold. Injectable and in situ forming hydrogels—including photothermal/endocrine synergistic systems (LTZ-PDA@AG), thermoresponsive mucoadhesive poloxamer gels, and NIR-controlled microspheres—offer localized, stimuli-responsive therapy with lesion volume reductions up to 92% in animal models. Next-generation intrauterine drug delivery systems (IUDDS), such as biodegradable WOMED platforms and photo-crosslinkable implants, eliminate the need for device removal while providing ultra-long-acting levonorgestrel release. Despite these promising preclinical advances, clinical translation remains nascent, with only a single pilot trial (LDE-MTX) reported to date. Major challenges include overcoming the dense fibrotic barrier of deep infiltrating lesions, scalable GMP manufacturing, reproductive safety validation, and regulatory navigation for drug-device combination products. The convergence of nanomedicine, image-guided theranostics, and molecular phenotyping promises a future of personalized, fertility-preserving, locally administered therapies that move beyond episodic suppression to chronic disease modification.

KEYWORDS: Endometriosis; sustained release drug delivery; lipid nanoparticles; polymeric nanoparticles; hydrogels; intrauterine drug delivery systems; non-hormonal therapy; active targeting; CD44; photothermal therapy; fibrosis; anti-angiogenic agents; clinical translation; nanomedicine; theranostics.

1. INTRODUCTION

Endometriosis remains one of the most prevalent yet underappreciated gynecological disorders, affecting an estimated 10–15% of reproductive-aged women and up to 50% of those with infertility or chronic pelvic pain. Despite its high prevalence, the disease burden extends far beyond numerical estimates. Patients typically endure a diagnostic delay of seven to ten years due to non-specific symptoms (dysmenorrhea, deep dyspareunia, chronic pelvic pain, and fatigue) and the lack of non-

invasive biomarkers. This delay often leads to progressive tissue infiltration, adhesion formation, and impaired fertility, with profound psychological and socio-economic consequences – including depression, lost workdays, and repeated medical consultations. Current treatment options remain largely palliative. Hormonal therapies (oral contraceptives, progestins, GnRH agonists) suppress ovulation and menstruation but do not eliminate ectopic lesions; they also carry systemic side effects (bone loss, mood changes, venous thromboembolism) that limit long-term use. Surgical excision or ablation offers symptom relief but has high recurrence rates (20–50% within five years) and carries operative risks. There is no curative medical therapy that removes established lesions without affecting ovarian function. Unmet clinical needs thus include: non-hormonal, disease-modifying drugs; drugs that target lesion fibrosis and nerve infiltration; non-invasive diagnostics for early detection; and – critically – delivery systems that achieve high local drug concentrations while avoiding systemic toxicity. These gaps underscore the urgency of understanding the ectopic lesion microenvironment as a pharmacological target. The ectopic lesion microenvironment is a dynamic, self-sustaining niche characterized by persistent inflammation, pathological angiogenesis, and progressive fibrosis. Endometriotic lesions, although derived from eutopic endometrium, exhibit a distinct inflammatory signature. They overexpress pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) and chemokines (CCL2, CXCL12), which recruit and activate peritoneal macrophages, mast cells, and neutrophils. These immune cells, in turn, secrete growth factors and reactive oxygen species, creating a feed-forward loop of chronic inflammation that drives pain and tissue damage. Prostaglandins (particularly PGE_2) are markedly elevated, contributing to hyperalgesia and dysmenorrhea.

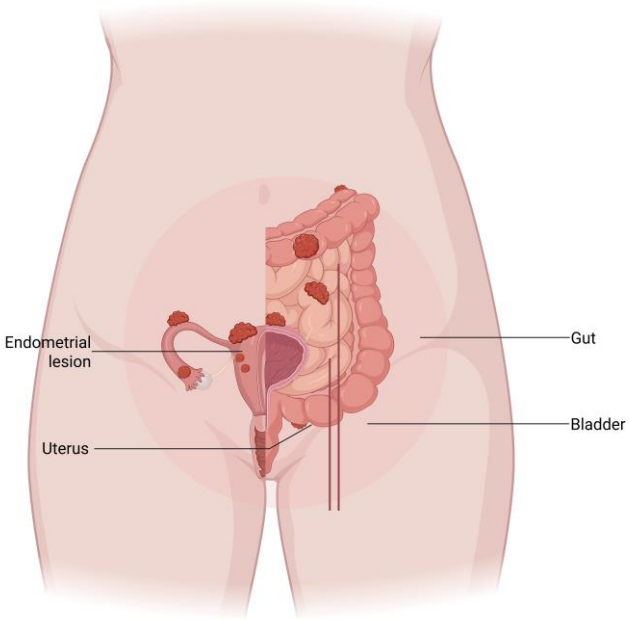

Fig: 1 Anatomical Illustration of Endometrial Lesions in Relation to Female Pelvic Organs.

Alongside inflammation, angiogenesis is a hallmark of lesion survival and progression. Endometriotic lesions secrete high levels of vascular endothelial growth factor (VEGF), angiopoietins, and platelet-derived growth factor, which promote the formation of a dense, irregular microvascular network that supplies oxygen and nutrients to ectopic tissue. This neovasculature is often leaky and dysfunctional, further exacerbating local inflammation. Over time, repeated tissue injury and aberrant repair lead to fibrosis – a feature previously underrecognized but now known to be central to lesion chronicity. Transforming growth factor-β (TGF-β), abundantly produced by lesions and activated macrophages, drives the differentiation of fibroblasts into myofibroblasts and the excessive deposition of collagen types I, III, and fibronectin. This fibrotic process not only encapsulates lesions into dense nodules resistant to drug penetration but also causes pelvic adhesions, organ tethering, and infertility. Thus, any effective therapy must overcome this hostile microenvironment – a challenge compounded by the anatomical and physiological barriers of the female reproductive tract. Effective drug delivery to ectopic lesions is hindered by multiple, hierarchically organized barriers.

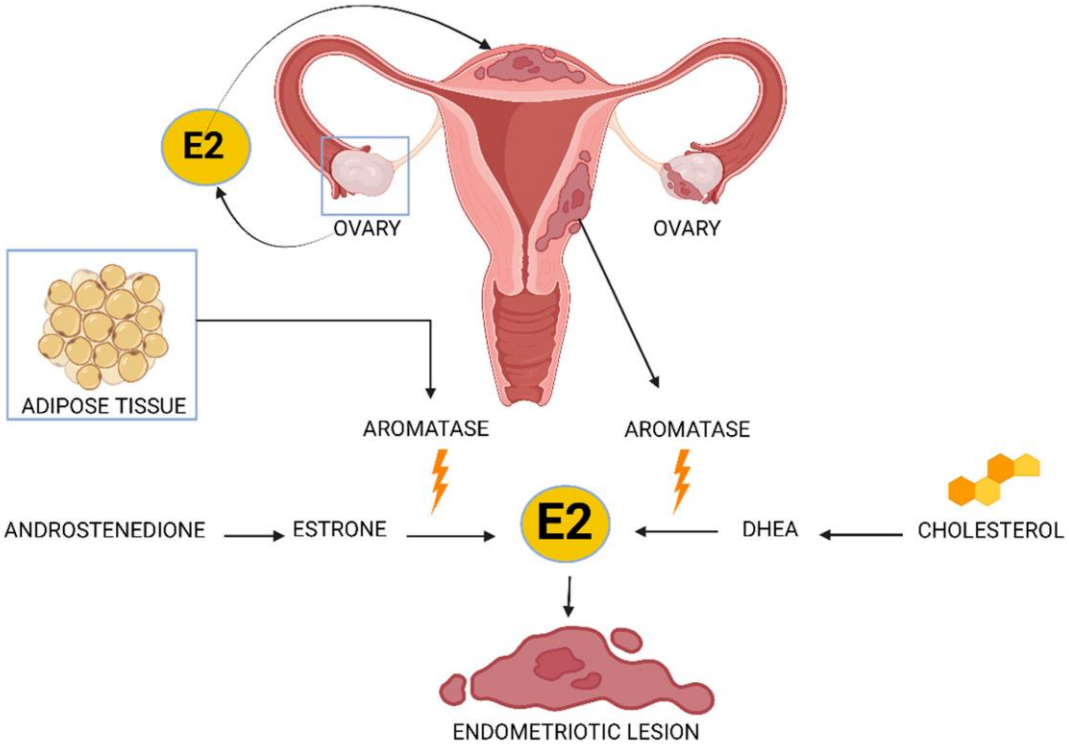

Fig. 2: The three major sources of estradiol (E2) within endometriosis.

Anatomically, endometriotic lesions can be located superficially on the peritoneum, deeply infiltrating the retroperitoneal space (e.g., uterosacral ligaments, bowel, bladder), or within the ovary as endometriomas. These diverse locations make uniform drug targeting exceedingly difficult. When drugs are administered systemically (oral, intravenous, subcutaneous), they must first traverse the vascular endothelium, then the peritoneal fluid, and finally the lesion's own dense fibrotic stroma – all while avoiding rapid hepatic metabolism or renal clearance. The female reproductive tract itself presents unique barriers: the vaginal mucosa, cervical mucus, uterine cavity, and fallopian tubes each possess distinct pH, mucus viscosity, and enzymatic activity. For instance, the cervical mucus – a non-Newtonian gel of mucin glycoproteins – traps many conventional nanoparticles and macromolecules, clearing them within hours via ciliary beating and bulk flow. Moreover, the cyclic changes in hormone levels (estrogen, progesterone) dramatically alter mucus porosity, epithelial tight junctions, and local immune cell composition, creating a moving target for drug formulations. Intraperitoneal delivery (direct injection into the pelvic cavity) bypasses some systemic barriers but is challenged by rapid clearance via lymphatic drainage (half-life of small molecules often <4 hours) and dilution in the large volume of peritoneal fluid. Furthermore, the presence of inflammatory macrophages and reactive oxygen species can degrade sensitive biologics (e.g., antibodies, peptides) before they reach lesions. These barriers explain why many promising preclinical compounds fail in clinical trials – they never achieve sufficient concentration within ectopic lesions to overcome the pro-survival microenvironment. Despite these obstacles, the unique anatomy of the female reproductive tract also offers privileged opportunities for localized and sustained therapeutic intervention. Local drug delivery – directly to the vagina, cervix, uterus, or intraperitoneal space – can achieve lesion concentrations orders of magnitude higher than systemic administration while minimizing off-target effects. For example, intrauterine devices (IUDs) or vaginal rings releasing progestins or anti-inflammatory agents have shown feasibility in reducing dysmenorrhea and lesion size, though current devices are largely designed for contraception or hormonal therapy, not specifically for endometriosis. Next-generation formulations are exploiting bioadhesive polymers, mucopenetrating nanoparticles, and thermosensitive hydrogels that retain drugs at the target site for weeks to months. For superficial peritoneal lesions, in situ-forming hydrogels injected via laparoscopy or even image-guided needles could release anti-fibrotic agents (e.g., pirfenidone, TGF-β inhibitors) or anti-angiogenic drugs (e.g., tyrosine kinase inhibitors) directly into lesion beds. Sustained release is particularly attractive because the chronic nature of endometriosis demands long-term suppression of inflammation and angiogenesis without repeated dosing. Poly(lactic-co-glycolic acid) (PLGA) microspheres, liposomes, and dendrimers have been engineered to release hormonal (GnRH antagonists) or non-hormonal agents (statins, metformin, resveratrol) over 30–90 days. Recent advances in RNA therapeutics (siRNA, miRNA mimics) targeting key genes such as *VEGF*, *TNF-α*, or *TGF-β1* can be encapsulated in lipid nanoparticles for direct intraperitoneal injection,

achieving sustained gene silencing in endometriotic lesions in animal models. Another exciting direction is the use of implantable drug-eluting meshes or patches that adhere to the peritoneum, providing mechanical support to prevent adhesions while releasing anti-inflammatory molecules. Furthermore, the ability to combine multiple agents – e.g., a VEGF inhibitor plus a collagenase to reduce fibrosis – in a single sustained-release formulation could address the multifactorial microenvironment simultaneously. These opportunities align with the growing emphasis on precision medicine: lesion phenotype (inflammatory vs. fibrotic) could be characterized by biopsy or imaging, guiding the choice of local therapy. Regulatory pathways for such combination products (drug + device) are evolving, and early-phase clinical trials of localized drug delivery for endometriosis are beginning to emerge. Ultimately, moving from systemic, non-selective suppression to localized, sustained, microenvironment-modulating interventions represents the most promising path to fulfill the unmet clinical needs of millions of women with endometriosis.

3. Conventional Endometriosis Therapies: A Critical Overview

Current medical management of endometriosis relies predominantly on hormonal agents that suppress ovarian cyclicity and create a hypoestrogenic state. Oral contraceptives (combined estrogen-progestin pills) are commonly first-line, reducing menstrual flow and retrograde menstruation, thereby alleviating dysmenorrhea and cyclical pain. They are inexpensive, familiar to prescribers, and can be used continuously to avoid withdrawal bleeding. However, oral contraceptives do not eliminate existing ectopic lesions, and many women experience breakthrough pain, mood swings, or venous thromboembolism risk, particularly with extended use. Progestins (e.g., dienogest, norethindrone acetate, medroxyprogesterone acetate depot) act by decidualizing endometrial tissue and suppressing ovulation. Dienogest 2 mg daily has become a leading progestin for endometriosis, showing significant reduction in pelvic pain and lesion size in randomized trials. Its side-effect profile includes irregular bleeding, weight gain, breast tenderness, and mood changes, leading to discontinuation rates of 20–30% within one year. The levonorgestrel-releasing intrauterine system (LNG-IUS) offers localized progestin delivery, reducing systemic absorption and achieving high intrauterine concentrations; it is particularly effective for adenomyosis-associated pain and superficial endometriosis, though its effect on deep infiltrating lesions is limited. GnRH agonists (leuprolide, goserelin, nafarelin) represent the most potent hormonal suppression, inducing a reversible medical menopause by downregulating pituitary GnRH receptors. They dramatically reduce endometriosis-associated pain and lesion vascularity, but their use is limited to 3–6 months due to severe hypoestrogenic side effects: hot flushes, vaginal dryness, bone mineral density loss, and mood disturbances. Add-back therapy with low-dose estradiol or norethindrone mitigates some side effects but adds complexity and cost. GnRH antagonists (elagolix, relugolix, linzagolix) offer a newer alternative, providing rapid, dose-dependent suppression without initial flare effect. Elagolix, approved for moderate-to-severe endometriosis pain, preserves some estrogen production at lower doses, reducing bone loss compared to agonists, but still causes hot flushes and elevated liver enzymes. All hormonal therapies share a fundamental limitation: they are suppressive, not curative. Once discontinued, pain recurs in 50–80% of patients within six months, and lesions rapidly re-establish their inflammatory and angiogenic activity. This has driven intense interest in non-hormonal pharmacological approaches that target the lesion microenvironment directly.

Non-hormonal strategies aim to interrupt the inflammatory, angiogenic, and fibrotic cascades independent of ovarian hormones. Nonsteroidal anti-inflammatory drugs (NSAIDs) – ibuprofen, naproxen, celecoxib – inhibit cyclooxygenase-2 (COX-2) and reduce prostaglandin-mediated pain and local inflammation. They are widely used as adjunctive therapy but do not alter disease progression and carry gastrointestinal and renal risks with chronic use. Aromatase inhibitors (letrozole, anastrozole) block extraglandular estrogen synthesis within endometriotic lesions, where aromatase is aberrantly expressed. Combined with progestins to prevent follicular development, they have shown efficacy in reducing pain and lesion size in small trials, but side effects (joint pain, fatigue, bone loss) and limited long-term data restrict their use to refractory cases. Selective estrogen receptor modulators (SERMs) like raloxifene and bazedoxifene have produced conflicting results; one trial of raloxifene actually worsened pain, possibly due to partial agonist activity at ectopic lesions. Anti-angiogenic agents targeting VEGF (e.g., bevacizumab, tyrosine kinase inhibitors like sunitinib, pazopanib) have shown promise in preclinical models, reducing microvessel density and lesion growth. However, systemic anti-angiogenesis carries risks of hypertension, proteinuria, and impaired wound healing, and no large trials have been completed. Statins (simvastatin, atorvastatin) exert pleiotropic anti-inflammatory and anti-angiogenic effects independent of cholesterol lowering; in animal models, they induce lesion regression. Yet clinical translation remains limited by the high doses required and potential myopathy. Anti-fibrotic agents (pirfenidone, nintedanib, tranilast) are emerging as logical candidates given the recognition of fibrosis as a key driver of lesion chronicity and pain. Pirfenidone, approved for idiopathic pulmonary fibrosis, has shown reduction of collagen deposition and adhesion formation in rat endometriosis models. Metformin, an oral antidiabetic, inhibits mitochondrial complex I and reduces cell proliferation, inflammation, and fibrosis through AMPK activation; retrospective studies suggest lower endometriosis risk in diabetic women taking metformin, and a small prospective trial showed pain

reduction. Other investigational agents include melatonin (antioxidant and anti-inflammatory), curcumin (poorly bioavailable but nanoformulations under study), and resveratrol (SIRT1 activator). The major barrier to non-hormonal therapy is not lack of targets but rather the difficulty of delivering sufficient drug to ectopic lesions without systemic toxicity – which is why localized and sustained delivery systems, discussed earlier, are critical for clinical success.

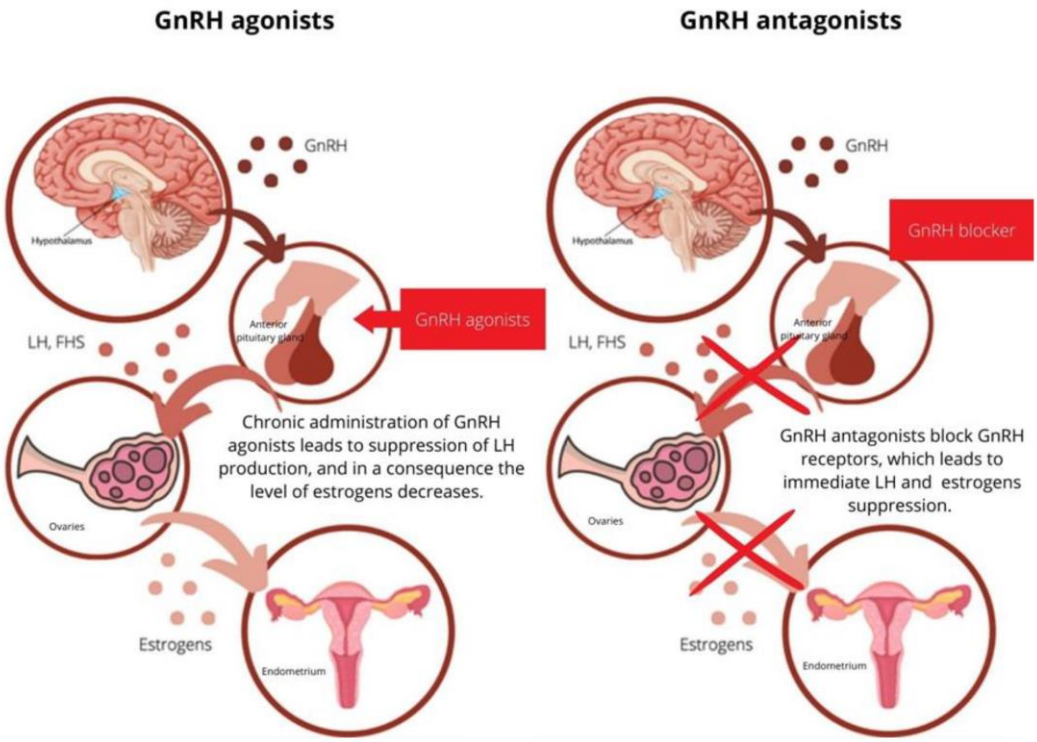

Fig: 3 Mechanism of action of GnRH analogs. Prolonged activation of GnRH receptors by GnRH agonists leads to gonadotropin secretion suppression. As a consequence, the secretion of estrogen is also decreased. Comparatively, the mechanism of GnRH antagonists is competitive in the occupancy of the GnRH-receptor. As a result of the blockade of GnRH receptors, the suppression of gonadotropin and estrogen is observed.

Given the limitations of medical therapy, surgery remains a cornerstone of endometriosis management, particularly for patients with severe pain, large endometriomas, deep infiltrating lesions causing bowel or urinary symptoms, or infertility refractory to medical treatment. Laparoscopic excision (removing the lesion with a margin of healthy tissue) is considered the gold standard, as it reduces pain and improves fertility more effectively than ablation (electrocoagulation or vaporization). For deep infiltrating endometriosis (DIE) involving the rectosigmoid or bladder, multidisciplinary surgery with colorectal or urologic expertise may be required. Ovarian cystectomy for endometriomas preserves ovarian reserve if performed carefully, though it inevitably removes some normal cortex. Despite surgical expertise, limitations are substantial. First, complete eradication of all microscopic lesions is impossible; residual disease is common, especially in DIE or when lesions obscure vital structures. Second, surgical complications include bleeding, infection, visceral injury (ureter, bowel, major vessels), and de novo adhesion formation, which can paradoxically worsen pelvic pain or fertility. Third, repeated surgeries carry cumulative morbidity – each reoperation increases adhesion burden, ovarian reserve depletion, and operative risk. Fourth, surgery does not alter the underlying predisposition to endometriosis; therefore, recurrence rates following excisional surgery are 20–30% at two years and 40–50% at five years, with even higher rates following ablation. The use of postoperative hormonal suppression (e.g., dienogest or oral contraceptives for 6–12 months) delays but does not prevent recurrence, and there is no consensus on how long to continue such therapy. Furthermore, many patients with deep lesions or extensive fibrosis are poor surgical candidates due to medical comorbidities, desiring future fertility (where ovarian reserve must be preserved), or simply unwilling to accept the risks of repeated operations. These realities highlight the formidable challenge of disease recurrence and the need for truly long-term management strategies.

Recurrence after successful initial treatment – whether medical or surgical – is the central unmet need in endometriosis care. Recurrence is not a single phenomenon but rather a spectrum: symptomatic recurrence (return of pain), imaging-detected recurrence (new or regrown lesions), and need for repeat surgery (most clinically relevant endpoint). Risk factors include young age at diagnosis, preoperative duration of symptoms, previous surgeries, presence of DIE or

bilateral endometriomas, and postoperative non-adherence to hormonal suppression. Biologically, recurrence arises from multiple sources: (1) viable microscopic lesions left behind after incomplete excision, which are often deeply embedded in fibrotic tissue; (2) de novo development from retrograde menstruation of eutopic endometrium, which remains inherently abnormal (the "endometriosis diathesis"); (3) reactivation of dormant lesions after hormone withdrawal; and (4) ongoing peritoneal inflammation and oxidative stress that promote implantation of shed endometrial cells. Long-term management therefore requires a paradigm shift from episodic "treat and discharge" to chronic disease monitoring and preventive maintenance. Practical strategies include continuous or cyclic hormonal suppression tailored to individual tolerance and side effects, periodic imaging (transvaginal ultrasound or MRI) for asymptomatic patients at high risk, and a low threshold for referral to pain psychology and pelvic floor physical therapy for central sensitization. Unfortunately, no currently available therapy prevents recurrence beyond the duration of active treatment. Emerging approaches include long-acting injectable or implantable hormone formulations (e.g., six-month subcutaneous depot of progestin or GnRH antagonist), mifepristone (anti-progestin), and immunomodulators (pentoxifylline, thalidomide analogs) – though the latter have inconsistent efficacy and toxicity. The most promising long-term strategy is probably not a single drug but rather a combination: sustained local delivery of an anti-inflammatory/anti-fibrotic agent (e.g., a TGF-β inhibitor or a collagenase) alongside low-dose systemic hormonal suppression to prevent new lesion formation. Additionally, patient stratification by molecular phenotype (inflammatory-dominant, fibrotic-dominant, angiogenic-dominant) could allow personalized maintenance regimens. Ultimately, managing endometriosis as a chronic condition demands multidisciplinary care, realistic patient expectations, and continued innovation in drug delivery and disease monitoring – moving beyond the frustrating cycle of surgery, recurrence, and repeat surgery that currently defines the disease journey for millions of women.

Nanotechnology-Enabled Sustained Release Systems

Lipid-Based Nanocarriers

Lipid-based nanocarriers exploit the inherent biocompatibility and biodegradability of physiological lipids to improve the pharmacokinetics and tissue distribution of drugs used in endometriosis. Their small size (typically 50–400 nm) allows passive accumulation in ectopic lesions via the enhanced permeability and retention (EPR) effect, which arises from the leaky, immature vasculature characteristic of endometriotic lesions. Furthermore, lipid carriers protect labile drugs from degradation, enable sustained release, and reduce systemic toxicity. Among the most developed systems are nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLNs), and nanoemulsions.

Nanostructured Lipid Carriers (NLCs) for Sustained Mifepristone Delivery

NLCs represent a second-generation lipid nanocarrier designed to overcome the limitations of SLNs. They consist of a blend of solid and liquid lipids (e.g., cetyl palmitate with medium-chain triglycerides) that form an imperfect, unstructured matrix, allowing higher drug loading and preventing drug expulsion during storage or upon administration. This makes NLCs particularly suitable for potent but poorly soluble drugs such as mifepristone – a synthetic antiprogestin that inhibits endometrial cell proliferation, induces apoptosis, and reduces lesion inflammation. However, mifepristone's clinical translation has been hindered by extremely low oral bioavailability (due to extensive first-pass metabolism by CYP3A4) and dose-limiting side effects including fatigue, nausea, and endometrial thickening when given systemically. NLC-encapsulated mifepristone offers a transformative solution. In preclinical studies, mifepristone-loaded NLCs prepared using glyceryl monostearate as the solid lipid, oleic acid as the liquid lipid, and poloxamer 188 as a surfactant exhibited a mean particle size of 120–150 nm, a zeta potential of –25 mV, and an entrapment efficiency exceeding 85%. Following a single intraperitoneal injection in a rat model of surgically induced endometriosis, these NLCs provided sustained drug release over 21 days, with mifepristone concentrations in peritoneal fluid remaining above the therapeutic threshold for 18 days – in stark contrast to free mifepristone, which was cleared within 48 hours. More importantly, the NLC formulation significantly reduced lesion volume (by 82% compared to untreated controls) and suppressed inflammatory markers (IL-6, TNF-α, and VEGF) in lesion homogenates, while free mifepristone at the same total dose showed only modest effects. Histological analysis revealed increased apoptosis (TUNEL-positive cells) and reduced microvessel density (CD31 staining) in the NLC-treated group. No overt signs of peritoneal irritation or systemic toxicity were observed. For intravaginal administration, NLCs can be incorporated into thermosensitive gels or mucoadhesive hydrogels to further prolong residence time. The versatility of NLCs also allows co-encapsulation of two agents – e.g., mifepristone plus an anti-angiogenic tyrosine kinase inhibitor – for combination therapy. Thus, NLC-based sustained delivery of mifepristone represents a promising strategy to transform a systemically impractical drug into a locally effective, long-acting treatment for endometriosis.

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are composed exclusively of solid lipids (e.g., tristearin, stearic acid, glyceryl behenate, or compritol) stabilized by surfactants. They were the first lipid nanoparticle system to be explored for drug delivery and offer advantages such as ease of large-scale production, excellent biocompatibility, and protection of incorporated drugs from chemical degradation. SLNs have been applied to deliver various

anti-endometriotic agents including levonorgestrel, resveratrol, curcumin, and aromatase inhibitors. For instance, resveratrol – a natural polyphenol with anti-inflammatory, anti-angiogenic, and anti-oxidant properties – suffers from poor water solubility, rapid glucuronidation, and short plasma half-life. Encapsulation in SLNs (size ~180 nm, polydispersity index <0.2) prepared by high-pressure homogenization improved resveratrol's aqueous dispersibility and protected it from hepatic first-pass metabolism. In a rat endometriosis model, intraperitoneal administration of resveratrol-loaded SLNs every three days for two weeks reduced lesion weight by 65% and VEGF expression by 70% compared to free resveratrol. Notably, SLNs also enhanced the accumulation of resveratrol in peritoneal macrophages, which are key drivers of the inflammatory microenvironment. However, SLNs have inherent limitations: the highly ordered crystalline lattice of solid lipids tends to expel drug molecules over time, leading to burst release and reduced loading capacity. This "drug expulsion" phenomenon is exacerbated during storage and upon polymorphic transition (from α to β form) that occurs at body temperature. To mitigate this, researchers have used complex lipids (e.g., mono-, di-, and triglycerides blends) or have added small amounts of liquid lipids to convert SLNs into NLCs. Despite these challenges, SLNs remain a valuable platform for drugs that are compatible with the solid lipid matrix and where short-term (days to a week) sustained release is sufficient. For intrauterine delivery, SLNs can be loaded into intrauterine devices or coated onto vaginal rings. Current efforts focus on developing SLNs with surface modification using polyethylene glycol (PEG) to reduce macrophage clearance and improve circulation time. Ultimately, while SLNs have been superseded by NLCs for many applications, they continue to offer a simpler, regulatory-friendly option for certain drug–lipid combinations.

Nanoemulsions for Enhanced Bioavailability

Nanoemulsions are thermodynamically stable, optically transparent dispersions of oil droplets (typically 20–200 nm) stabilized by a surfactant and co-surfactant. Unlike SLNs and NLCs, nanoemulsions are liquid at both room and body temperature. Their extremely small droplet size and large interfacial area enable rapid drug release and superior mucosal penetration, making them ideal for enhancing the bioavailability of lipophilic drugs that are poorly absorbed via conventional routes. For endometriosis, nanoemulsions have been explored for the delivery of curcumin, letrozole, dienogest, and celecoxib. Curcumin nanoemulsion (oil phase: eucalyptus oil or medium-chain triglycerides; surfactant: Tween 80 and lecithin) prepared by spontaneous emulsification achieved a droplet size of ~50 nm and a zeta potential of –30 mV. In a mouse model of peritoneal endometriosis, a single intraperitoneal injection of curcumin nanoemulsion resulted in a 12-fold higher area under the concentration–time curve (AUC) in peritoneal fluid compared to free curcumin suspension, and a 20-fold higher accumulation within CD68-positive macrophages. This led to marked suppression of NF-κB nuclear translocation, reduction of IL-1β and IL-6 secretion, and a 55% decrease in lesion number. For intravaginal administration, nanoemulsions can be formulated as sprayable liquids or incorporated into bioadhesive gels to overcome the cervical mucus barrier. A letrozole nanoemulsion (using Capmul MCM as oil, Cremophor EL as surfactant, and Transcutol as co-surfactant) demonstrated 8-fold higher permeability across porcine vaginal mucosa compared to letrozole suspension, with sustained release over 12 hours. The major limitation of nanoemulsions for endometriosis is their relatively rapid clearance from the peritoneal cavity (half-life of 2–6 hours) because the liquid oil droplets are easily phagocytosed by peritoneal macrophages or drained via the lymphatic system. To address this, researchers have combined nanoemulsions with in situ gelling systems – e.g., incorporating the nanoemulsion into a poloxamer 407 solution that forms a hydrogel at body temperature, thereby retaining the formulation at the injection site for days. Another strategy is to convert nanoemulsions into more viscous systems using polymeric thickeners. Overall, nanoemulsions excel when rapid onset of action and high bioavailability are needed, but for long-term suppression of endometriotic lesions, sustained-release NLCs or polymeric nanoparticles are often preferred.

Polymeric Nanoparticles

Polymeric nanoparticles offer complementary advantages to lipid-based carriers, including precise control over degradation kinetics, high chemical stability, and versatile surface functionalization for active targeting. They are typically made from biodegradable polymers approved by regulatory agencies, such as PLGA, PLA, chitosan, and hyaluronic acid. For endometriosis, polymeric nanoparticles have been engineered to deliver both small-molecule drugs (e.g., chrysin) and macromolecules (e.g., siRNA, plasmid DNA) directly to ectopic lesions.

PLGA Nanoparticles for Chrysin Delivery and Anti-Angiogenic Therapy

Poly(lactic-co-glycolic acid) (PLGA) is the most extensively used biodegradable polymer in nanomedicine due to its tunable degradation rate (weeks to months, depending on lactide:glycolide ratio and molecular weight) and FDA approval for parenteral drug delivery. Chrysin, a natural flavonoid abundant in passionflower and honey, possesses potent anti-angiogenic, anti-inflammatory, and pro-apoptotic properties that are highly relevant to endometriosis. Chrysin inhibits VEGF secretion, downregulates HIF-1α, suppresses matrix metalloproteinase-2 and -9, and reduces the invasive capacity of endometriotic stromal cells. However, its clinical application is severely limited by water solubility below 1 μg/mL and extensive glucuronidation in the liver and gut. PLGA nanoparticles encapsulating chrysin solve both problems. Using a single-emulsion (oil-in-water) method with PLGA (50:50, inherent viscosity 0.2–0.4

dL/g) and polyvinyl alcohol as a stabilizer, researchers have produced chrysin-loaded PLGA NPs of 150–200 nm diameter, with an entrapment efficiency of 60–75% and a loading capacity of 5–8%. In vitro release studies show a biphasic pattern: an initial burst of 15–20% over 24 hours, followed by sustained release over 28 days due to polymer erosion. In a rat endometriosis model, intraperitoneal administration of chrysin-PLGA NPs (dose: 5 mg/kg chrysin equivalent) every three days for four weeks reduced lesion volume by 78% and microvessel density (CD34 immunostaining) by 65%, whereas free chrysin at the same dose had no significant effect compared to vehicle. Mechanistically, the NP-treated group showed reduced nuclear p65 (NF-κB) and decreased VEGF and IL-8 levels in lesion lysates. Importantly, PLGA NPs also reduced the systemic exposure of chrysin – peak plasma levels were 10-fold lower than after free chrysin administration – thereby avoiding the hepatotoxicity associated with high-dose chrysin. Other anti-angiogenic agents delivered via PLGA NPs for endometriosis include baicalein, epigallocatechin gallate, and the tyrosine kinase inhibitor sunitinib. The versatility of PLGA allows co-encapsulation of two drugs (e.g., chrysin plus metformin) to synergistically target inflammation and fibrosis. Future directions include the use of PLGA-PEG block copolymers to prolong circulation and reduce protein corona formation, and the incorporation of targeting ligands (e.g., folic acid or cyclic RGD peptides) to enhance lesion-specific uptake.

Chitosan-Based Polymeric Nanoparticles for Gene Delivery

Gene therapy offers the potential to silence disease-driving genes (e.g., VEGF, TNF-α, COX-2, or the estrogen receptor) at the transcriptional level, addressing the root cause of lesion persistence rather than merely suppressing symptoms. Chitosan – a naturally derived cationic polysaccharide from chitin – has emerged as a leading non-viral gene delivery vector for endometriosis because of its excellent biocompatibility, low immunogenicity, and intrinsic mucoadhesive and anti-inflammatory properties. Chitosan can form polyelectrolyte complexes (nanoparticles) with negatively charged nucleic acids (siRNA, miRNA, plasmid DNA) through electrostatic interactions, protecting them from nuclease degradation and facilitating cellular uptake via clathrin-mediated endocytosis. For VEGF silencing, chitosan nanoparticles loaded with VEGF-specific siRNA (size ~150 nm, zeta potential +20 to +30 mV, N:P ratio 5:1) were prepared by ionic gelation with tripolyphosphate. In a mouse model of endometriosis, intraperitoneal injection of these nanoparticles (three doses over two weeks) resulted in 70% knockdown of VEGF mRNA and protein in ectopic lesions, as measured by qPCR and ELISA. Consequently, lesion microvessel density decreased by 60%, and lesion volume was reduced by 55% compared to scrambled siRNA controls. The efficacy was attributed to the prolonged retention of chitosan-siRNA nanoparticles in the peritoneal cavity – approximately 48 hours, compared to less than 1 hour for naked siRNA – due to the mucoadhesive interaction with the mesothelial cell layer and the omentum. For therapeutic delivery of anti-inflammatory cytokines (e.g., IL-10 plasmid DNA), chitosan nanoparticles have shown promise in reducing peritoneal TNF-α and improving lesion regression. Limitations of chitosan include relatively low transfection efficiency in primary endometriotic stromal cells (due to poor endosomal escape) and dependence on the degree of deacetylation (≥80%) and molecular weight (30–100 kDa). Chemical modifications – such as conjugation with polyethyleneimine (PEI), trimethylation to produce trimethyl chitosan (TMC), or thiolation – significantly enhance transfection. TMC nanoparticles with siRNA against the chemokine receptor CCR2, for example, reduced macrophage infiltration into lesions by 80% in a rat model. Furthermore, chitosan nanoparticles are well-suited for local administration via intrauterine instillation or intravaginal spray, where their mucoadhesion provides prolonged contact with the target tissue. As the field moves toward clinical translation, the main challenges are scaling up production under GMP conditions and demonstrating long-term safety (no off-target gene silencing) in large animal models.

Hyaluronic Acid-Functionalized Systems

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan that binds specifically to CD44, a cell-surface receptor overexpressed on endometriotic stromal cells, epithelial cells, and activated macrophages. HA-functionalized nanoparticles exploit this interaction for active targeting, enhancing drug accumulation within lesions while reducing uptake by healthy tissues. HA can be used in two ways: as a coating on preformed nanoparticles (e.g., PLGA or lipid cores) or as the primary building block of the nanoparticle itself (self-assembled HA nanoparticles). For active targeting, HA of low molecular weight (10–30 kDa) is often conjugated to the nanoparticle surface via carbodiimide chemistry or avidin–biotin linkage. In a study using HA-coated PLGA nanoparticles loaded with the anti-fibrotic drug pirfenidone, intraperitoneal injection in a rat endometriosis model resulted in 2.5-fold higher fluorescence signal (from a near-infrared dye) in lesions compared to non-targeted PLGA NPs, and 8-fold higher compared to free dye. Histological analysis confirmed colocalization of HA-NPs with CD44-positive stromal cells. The HA-targeted formulation reduced lesion collagen content (Sirius red staining) by 70% and adhesion scores by 65% after three weeks, while non-targeted pirfenidone NPs were only half as effective. HA can also be chemically modified to form self-assembled nanoparticles without a separate polymer core. For example, HA conjugated with 5β-cholanic acid (HA-CA) forms stable nanoparticles (200–300 nm) via hydrophobic interactions. These HA-CA nanoparticles loaded with curcumin (HA-CA-Cur NPs) showed sustained release over 10 days and, after intraperitoneal injection in mice, preferentially accumulated in CD44-

positive lesions, leading to significant reduction in IL-6 and monocyte chemoattractant protein-1. The inherent bioactivity of HA – including anti-adhesive properties and modulation of inflammation – adds therapeutic benefit. Moreover, HA-functionalized nanoparticles can be combined with thermosensitive hydrogels (e.g., Pluronic F127) for intrauterine injection, creating a depot that releases targeted NPs over weeks. For imaging-guided therapy, HA-coated superparamagnetic iron oxide nanoparticles (SPIONs) allow MRI visualization of lesion targeting while delivering a therapeutic payload (e.g., methotrexate). Despite these advantages, challenges remain: CD44 expression is not entirely specific to endometriosis (it is also present on some inflammatory and cancer cells), and high-molecular-weight HA may actually promote lesion adhesion through interactions with other matrix components. Optimal CD44 targeting requires HA fragments of 5–30 kDa. Additionally, HA-functionalized systems are more expensive to manufacture and require rigorous quality control for ligand density. Nevertheless, HA-functionalized nanocarriers represent the leading edge of active targeting for endometriosis, moving the field closer to personalized, lesion-specific therapy.

Hydrogel-Based Sustained Release Systems

Injectable and In Situ Forming Hydrogels, Thermoresponsive Mucoadhesive Systems, Hydrogel Microspheres, and Stimuli-Responsive Implants for Endometriosis Therapy

The limitations of systemic drug delivery and conventional surgical excision have driven the development of advanced hydrogel-based platforms that enable localized, sustained, and stimuli-responsive therapeutic intervention directly within the ectopic lesion microenvironment. Injectable and in situ forming hydrogels are particularly attractive because they can be administered via minimally invasive procedures (laparoscopy, intrauterine instillation, or image-guided injection) as low-viscosity precursor solutions that transition into viscoelastic gels upon exposure to physiological conditions (temperature, pH, or ionic strength). Among the most innovative designs is a photothermal/endocrine synergistic hydrogel system, exemplified by letrozole-loaded polydopamine nanoparticles embedded in an agarose-based gel (LTZ-PDA@AG). Letrozole, an aromatase inhibitor, blocks local estrogen synthesis within endometriotic lesions, but its systemic use is limited by bone loss and arthralgia. Polydopamine (PDA) nanoparticles possess excellent photothermal conversion efficiency under near-infrared (NIR) irradiation, as well as abundant functional groups for drug binding. In the LTZ-PDA@AG system, letrozole is adsorbed onto PDA nanoparticles (size ~100 nm) via π-π stacking and hydrogen bonding, and these nanocomplexes are dispersed in a thermoresponsive agarose solution that gels at body temperature (37°C). Following intraperitoneal or intralesional injection, the hydrogel localizes the nanocomplexes directly to endometriotic lesions. Upon NIR irradiation (e.g., 808 nm laser at 0.5–1 W/cm² for 5–10 minutes), PDA generates localized hyperthermia (45–50°C) which simultaneously ablates lesion tissue and accelerates letrozole release through thermal disruption of the gel matrix and enhanced diffusion. In a rat model, LTZ-PDA@AG plus NIR achieved a synergistic effect: lesion volume was reduced by 92% after a single treatment, compared to 60% with letrozole-loaded hydrogel without NIR and 40% with NIR alone. Mechanistically, hyperthermia induced heat shock protein expression and increased lesion vascular permeability, allowing deeper penetration of letrozole. Moreover, repeated NIR pulses could be applied over several weeks to achieve pulsatile drug release, mimicking cyclic endocrine suppression. Beyond direct ablation, lesion-centric photothermal hydrogels are being designed specifically for pain microenvironment remodeling. Endometriosis-associated pain is driven not only by inflammation but also by nerve infiltration (neurogenesis) and sensitization of peripheral nociceptors. Photothermal hydrogels can be engineered to ablate nerve endings within lesions while simultaneously releasing analgesics (e.g., lidocaine, resiniferatoxin) or anti-nerve growth factor antibodies. For instance, a gelatin-based hydrogel incorporating PDA nanoparticles and the TRPV1 antagonist capsazepine was shown in a mouse model to reduce both lesion area (by 70%) and mechanical allodynia (by 80%) after a single NIR session, with effects lasting at least four weeks. The ability to combine thermal ablation with targeted drug release offers a powerful strategy to interrupt the pain-inflammation cycle without systemic side effects.

Thermoresponsive mucoadhesive hydrogels represent a second major category, particularly suited for intrauterine administration to treat superficial endometriosis and adenomyosis. Unlike injectable gels that form in the peritoneal cavity, these systems are designed to adhere to the endometrial or cervical mucosa, providing prolonged contact with lesions that are accessible via the uterine cavity. A leading example is letrozole-loaded in situ gelling systems based on poloxamer 407 (Pluronic F127) and poloxamer 188 blends. Poloxamers are triblock copolymers (polyethylene oxide-polypropylene oxide-polyethylene oxide) that exhibit reverse thermal gelation: they exist as low-viscosity sols at refrigerated or room temperature but transition into a gel at body temperature (approximately 37°C) due to micellar packing and hydrogen bond disruption. For letrozole delivery, a formulation containing 20% poloxamer 407 and 5% poloxamer 188, with 0.5% hydroxypropyl methylcellulose (HPMC) as a mucoadhesive enhancer, has been optimized. This formulation has a gelation temperature of 32–34°C, ensuring rapid gelation upon contact with the uterine wall (which is slightly cooler than core body temperature). The addition of HPMC improves viscosity and provides secondary hydrogen bonding with mucin glycoproteins, extending intrauterine retention from 4 hours (without HPMC) to over 48 hours. In a rabbit model of endometrial

hyperplasia (surrogate for superficial endometriosis), a single intrauterine instillation of letrozole-loaded thermoresponsive gel (dose 2 mg letrozole) maintained drug concentrations in uterine tissue above the IC_{50} for aromatase for 14 days, whereas an intrauterine solution of letrozole was cleared within 6 hours. The gel-treated group showed 80% reduction in endometrial thickness and complete suppression of local aromatase activity. Design principles for such systems include: (1) gelation temperature set slightly below body temperature to ensure rapid transition; (2) shear-thinning behavior to allow administration through a narrow catheter (22–24 gauge); (3) biocompatibility with the endometrium (avoiding acidic degradation products or toxic crosslinkers); (4) adjustable gel strength (storage modulus G' > 100 Pa) to resist clearance by uterine peristalsis; and (5) the ability to encapsulate both hydrophilic and hydrophobic drugs using micellar solubilization within the poloxamer core. Alternative thermoresponsive polymers include poly(N-isopropylacrylamide) (PNIPAAm) and its copolymers, though these are not yet FDA-approved for intrauterine use. Mucoadhesive polymers such as chitosan, carbopol, and thiolated polymers can be blended with poloxamers to further enhance retention. Challenges include the large volume of gel needed to fill the uterine cavity (1–3 mL in humans), which may cause discomfort, and the risk of gel expulsion through the cervix, which can be mitigated by using a cervical cap or by formulating the gel to be more cohesive.

Hydrogel microspheres (also called microgels or nanogels) offer an alternative delivery format for interventional therapy, particularly for targeted embolization or local depot formation. These microspheres (typically 50–500 μm in diameter) can be injected through standard catheters and lodge in small vessels supplying endometriotic lesions, similar to uterine artery embolization used for fibroids, while simultaneously releasing therapeutic agents. A notable example is NIR-controlled curcumin-releasing hydrogel microspheres. Curcumin, a natural polyphenol with potent anti-inflammatory and anti-angiogenic properties, suffers from poor solubility and rapid metabolism. Researchers have fabricated microspheres from poly(ethylene glycol) diacrylate (PEGDA) or gelatin methacryloyl (GelMA) using microfluidic droplet generation, incorporating curcumin-loaded mesoporous silica nanoparticles (MSNs) and PDA nanoparticles as photothermal converters. The microspheres are crosslinked such that the gel matrix is partially degraded by local hyperthermia: upon NIR irradiation, PDA generates heat, which accelerates hydrolysis of ester bonds in PEGDA or triggers a phase transition in thermosensitive polymers. In an in vivo study using a rat endometriosis model, transcatheter injection of curcumin-loaded microspheres (200 μm diameter) into the uterine artery resulted in embolization of the lesion vasculature plus sustained curcumin release over 14 days. Application of NIR (808 nm, 0.8 W/cm² for 5 minutes) at days 1, 3, and 7 produced pulsatile curcumin peaks, leading to a 75% reduction in lesion VEGF expression and a 60% reduction in lesion fibrosis (collagen I deposition) compared to microspheres without NIR control. The combination of mechanical embolization (cutting off blood supply) and NIR-triggered anti-angiogenic drug release provides a dual mechanism that is particularly effective for endometriomas and deeply infiltrating nodules. Hydrogel microspheres can also be designed to be radiopaque (by incorporating barium sulfate or gold nanoparticles) for fluoroscopic guidance during interventional radiology procedures. Future directions include the development of biodegradable microspheres that degrade completely after drug depletion (using crosslinkers like disulfide bonds for reductive environment) and the use of stimuli-responsive microspheres that release drugs in response to the acidic (pH 6.5–7.0) or reactive oxygen species-rich microenvironment of endometriotic lesions.

Finally, stimuli-responsive hydrogels are being explored for reversible mechanical intervention, particularly for fallopian tube occlusion as a fertility-preserving treatment for endometriosis-associated infertility or as a temporary contraceptive to allow hormonal washout. The concept involves injecting a hydrogel implant into the fallopian tubes that can be degraded on demand, restoring tubal patency. A leading design uses a hyaluronic acid (HA)-based hydrogel crosslinked with matrix metalloproteinase (MMP)-sensitive peptides. Endometriotic lesions and their surrounding microenvironment overexpress MMP-2 and MMP-9, which are involved in tissue remodeling and invasion. The injectable hydrogel is formulated as a dual-barrel syringe containing HA modified with vinyl sulfone groups and a crosslinker peptide (e.g., GGGPQGIWGQGC) that is cleavable by MMP-9. Upon mixing and injection into the fallopian tube, the solution gels within 1–2 minutes via Michael addition, forming a soft implant that physically occludes the tubal lumen. Over time, the elevated MMP activity in the endometriosis-affected pelvic environment gradually degrades the peptide crosslinker, leading to implant erosion and spontaneous tubal recanalization after 3–6 months. In a rabbit model, MMP-degradable HA hydrogels injected into the oviducts resulted in complete occlusion for 12 weeks, with restoration of patency by 18 weeks as confirmed by hysterosalpingography. Importantly, the degradation rate could be tuned by altering the peptide sequence or crosslinking density. For patients with severe, persistent endometriosis, a non-degradable version or a version requiring external triggering (e.g., ultrasound-induced cavitation to disrupt the hydrogel) could be used. Another clever design is the use of electroactive hydrogels that undergo volume contraction upon application of a small electric field (e.g., via a transvaginal probe). These hydrogels, based on poly(acrylic acid) or alginate with conductive polymers (PEDOT:PSS), could be injected into the tubal ostium and then reversibly expanded or contracted to

open or close the tube as needed. While still in early proof-of-concept, these stimuli-responsive systems offer the unprecedented ability to mechanically manage endometriosis-associated infertility without surgery, and to allow patients to alternate between trying to conceive and receiving hormone-free therapy. Collectively, the spectrum of hydrogel technologies – from injectable photothermal synergistic systems to mucoadhesive thermogels, embolic microspheres, and reversibly degradable tubal implants – represents a paradigm shift toward personalized, minimally invasive, and on-demand local therapy for endometriosis.

6. Intrauterine Drug Delivery Systems (IUDDS)

Intrauterine devices (IUDs) have undergone a remarkable evolution from inert contraceptive tools to sophisticated drug-eluting platforms for treating gynecological conditions, including endometriosis and adenomyosis. Historically, the first IUDs emerged in the early 20th century as silkworm gut or metal rings, but they were plagued by high expulsion rates and pelvic infections. The modern era began with the introduction of inert plastic devices (Lippes Loop, 1962) and copper-bearing IUDs (1970s), which provided effective contraception through sterile inflammation and spermicidal action. The true breakthrough for endometriosis management came with the levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®), approved first for contraception (1990s) and subsequently for heavy menstrual bleeding and endometriosis-associated pain. The LNG-IUS consists of a T-shaped polyethylene frame with a silastic reservoir containing 52 mg of levonorgestrel, releasing approximately 20 μg per day over five to seven years. Its mechanism of action in endometriosis is multifactorial: the high local concentration of levonorgestrel (thousands of times higher in the endometrium than in plasma) induces profound decidualization and atrophy of the eutopic endometrium, thereby reducing retrograde menstruation – a key driver of lesion implantation. Additionally, levonorgestrel thickens cervical mucus, suppresses endometrial aromatase expression, and exerts direct anti-proliferative and pro-apoptotic effects on ectopic lesions through progesterone receptor-mediated pathways. Clinical studies have shown that the LNG-IUS significantly reduces dysmenorrhea, non-cyclic pelvic pain, and disease recurrence after surgery, with efficacy comparable to daily dienogest but with fewer systemic side effects due to local delivery. However, conventional LNG-IUS still requires removal after five years, involves a non-biodegradable frame, and may cause irregular bleeding, ovarian cysts, and device expulsion (5–10%). To overcome the limitations of permanent frames and fixed drug release profiles, researchers have developed innovative intrauterine platforms. The WOMED (Women's Medicine) platform is a groundbreaking concept that replaces the non-degradable T-frame with a biodegradable, shape-memory polymer scaffold, typically fabricated from polylactic acid (PLA) or polycaprolactone (PCL). The device is designed to be inserted in a compressed form through a standard IUD inserter; upon intrauterine placement at body temperature, it expands into a T-shape or a more anatomically conforming spiral. Over months to years, the polymer hydrolyzes into non-toxic monomers (lactic and caproic acids), eliminating the need for removal. The WOMED platform can be loaded with levonorgestrel or other anti-endometriotic agents (e.g., dienogest, selective progesterone receptor modulators), and the drug release profile is tuned by varying polymer composition, molecular weight, and coating thickness. Preclinical studies in sheep have demonstrated complete biodegradation within 12–18 months with no evidence of intrauterine adhesions or inflammatory reactions. An even more advanced concept involves injecting a liquid polymer precursor that undergoes photo-crosslinking upon exposure to visible or UV light delivered via a specialized intrauterine fiber-optic catheter. For example, a formulation containing gelatin methacryloyl (GelMA) or poly(ethylene glycol) diacrylate (PEGDA) mixed with a photoinitiator (e.g., riboflavin or eosin Y) and levonorgestrel-loaded nanoparticles can be injected to conform precisely to the uterine cavity. Once positioned, a brief (1–2 minutes) illumination with blue light (450–480 nm) triggers covalent crosslinking, forming a soft, flexible implant that adheres to the endometrium. The major advantage is personalized sizing: the implant can be molded to the patient's unique uterine dimensions, avoiding expulsion caused by mismatched T-frames. Photoresponsive implants can also be designed to release drug in a light-pulsatile manner by incorporating photolabile linkers, allowing on-demand modulation of levonorgestrel release for women with breakthrough pain. EverShield is a commercially emerging technology (from multiple biomedical engineering groups) that combines biodegradable polymers with ultra-long-acting release kinetics. Unlike conventional LNG-IUS which relies on a silicone membrane reservoir, EverShield uses a homogeneous matrix of PCL and PLA containing microcrystalline levonorgestrel. The device is shaped as a flexible ring or a slim rod without anchoring arms, reducing uterine wall trauma. Its degradation half-life is tuned to three to five years, during which levonorgestrel is released via bulk erosion and diffusion at a nearly zero-order rate (15–18 μg/day). After complete degradation, no retrieval is needed. Phase I human trials have demonstrated that EverShield maintains levonorgestrel concentrations in endometrial tissue above the therapeutic threshold (≥10 ng/mg protein) for 48 months, with systemic levels less than one-fifth of those seen with Mirena, translating to fewer mood changes and breast tenderness. The intrauterine route offers compelling benefits over systemic therapy: (1) high local drug concentration (up to 1000-fold) at the target tissue – the endometrium and adjacent superficial endometriotic implants – while minimizing systemic exposure; (2) avoidance of first-pass metabolism, particularly relevant for steroids and aromatase inhibitors; (3) sustained release over months to years, improving adherence; (4) potential disease modification by continuously suppressing retrograde menstruation and local

inflammation; (5) reversibility upon removal (or natural degradation) for women seeking pregnancy. For endometriosis patients with predominantly superficial peritoneal disease or adenomyosis, intrauterine platforms are particularly effective, whereas deep infiltrating lesions may require complementary local injections. The safety of next-generation intrauterine devices hinges on several factors: (1) material biocompatibility – biodegradable polymers (PLA, PCL, PLGA) have FDA approval for other implants, but long-term intrauterine degradation products must be non-inflammatory and non-teratogenic; (2) infection risk – any foreign body in the uterus can increase the risk of pelvic inflammatory disease, though the risk is low (<1% per year) and can be minimized by pre-insertion screening; (3) uterine perforation and expulsion – biodegradable and photo-responsive devices with flexible, conformable designs likely reduce these risks compared to rigid T-frames; (4) endometrial safety – long-term levonorgestrel exposure causes glandular atrophy and pseudodecidualization, which is reversible upon removal; however, concerns about potential masking of endometrial hyperplasia or cancer necessitate regular monitoring; (5) fertility impact – while intrauterine devices are intended for endometriosis patients who desire long-term management, those wishing to conceive can wait for device degradation or undergo simple removal (for non-biodegradable types). Clinical translation of these novel platforms requires robust phase II/III trials demonstrating non-inferiority to existing IUDs in pain relief and lesion regression, along with improved tolerability and convenience. Regulatory pathways for drug-device combination products (e.g., EverShield) are well-established, but photo-responsive systems with external activation components require additional scrutiny for optical safety. Ultimately, the shift from permanent, non-degradable IUDs to next-generation biodegradable, personalized, and stimuli-responsive intrauterine platforms promises to transform endometriosis care from episodic hormonal suppression to truly long-term, patient-friendly local therapy.

13. Clinical Translation and Regulatory Landscape

The journey from benchtop innovation to bedside application for nanomedicines in endometriosis is governed by a complex interplay of preclinical validation, clinical evidence, regulatory oversight, and long-term safety evaluation. In preclinical models, such as the syngeneic endometriosis-induced BALB/c mouse model, sustained-release systems like chrysin-loaded PLGA nanoparticles (CHR-PLGA-NPs) have shown significant potential. These models are instrumental in assessing a formulation's ability to reduce lesion implantation, modulate key inflammatory markers (e.g., NF-κB, IL-1β, and IFN-γ), and impact critical pathways like angiogenesis and tissue remodeling. They serve as the initial proving ground, establishing the efficacy and mechanism of action for novel therapeutic approaches.

Bridging the gap to human application is the most critical step, and clinical data, while still nascent, is beginning to emerge. A notable pilot study translated this concept by treating patients with deep infiltrating endometriosis using methotrexate (MTX) carried in lipid nanoparticles (LDE-MTX). This study not only confirmed the feasibility of the approach but also demonstrated an encouraging safety profile. Over a 180-day observation period, patients showed no hematologic, renal, or hepatic toxicities, with significant improvements in pain scores for deep dyspareunia and chronic pelvic pain, though bowel lesions remained unchanged. This represents a landmark as a pioneering trial for a nanomedicine in this field.

For these drug-device combination products, such as medicated intrauterine systems or implantable hydrogels, navigating the regulatory pathway is uniquely challenging. In the US, the FDA's Office of Combination Products (OCP) oversees these innovations, which are defined as products combining two or more regulated components (e.g., drug/device). The classification and regulatory pathway are determined by the product's primary mode of action (PMOA). A pre-filled syringe is regulated as a drug because the drug provides the therapeutic effect, whereas a drug-eluting stent is regulated as a device because its primary action is mechanical. A manufacturer must submit a Request for Designation (RFD) to the OCP, which then performs a technical and clinical evaluation to identify risks and verify the primary mode of action, ensuring that all constituent parts meet their respective regulatory standards.

Finally, all these efforts are underpinned by rigorous safety, toxicity, and biocompatibility assessments. While nanoparticles offer superior targeted delivery, their unique properties also raise concerns about long-term impact, particularly on female reproductive health. Studies have highlighted that nanoparticles may pose risks to ovaries, oocytes, and fetal development, potentially inducing harm through mechanisms like oxidative stress and inflammation. Therefore, a comprehensive safety evaluation must extend beyond the standard battery of tests to include reproductive and developmental toxicology. Advanced techniques, including multi-omics and artificial intelligence, are being integrated to refine these assessments and predict nanotoxicity. Ultimately, the safe and effective translation of these technologies hinges on collaborative efforts among biomaterials researchers, clinicians, and regulatory agencies, with the goal of ensuring that therapeutic benefits are not achieved at the cost of long-term harm to the patient's reproductive system and overall health.

14. Challenges and Future Perspectives

The future of endometriosis therapy lies in addressing five interconnected challenges: overcoming biological barriers, scalable manufacturing, patient-centered design,

theranostics, and personalization. First, overcoming biological barriers in the female reproductive tract remains a formidable hurdle. The cervical mucus – a viscoelastic glycoprotein network – traps conventional nanoparticles, while the cyclic hormonal fluctuations alter mucus porosity and thickness. Moreover, deep infiltrating lesions are encased in dense fibrotic tissue that impedes drug penetration. Next-generation nanocarriers must be engineered with mucopenetrating properties (e.g., PEGylated or zwitterionic surfaces) and matrix-degrading capabilities (e.g., co-delivery of collagenases or hyaluronidases). Additionally, exploiting the lymphatic drainage from the peritoneal cavity or using transient barrier-openers (e.g., nitric oxide donors) could enhance lesion access. Second, scaling up manufacturing and achieving reproducibility is critical for clinical translation. Lipid nanoparticles (NLCs, SLNs) and polymeric nanoparticles (PLGA, chitosan) are typically produced by methods like high-pressure homogenization, microfluidics, or solvent evaporation. However, batch-to-batch variations in size, polydispersity, drug loading, and release kinetics can arise from minor changes in temperature, mixing speed, or polymer source. Regulatory agencies require validated scale-up processes under Good Manufacturing Practices (GMP), with in-line quality control tools such as dynamic light scattering and HPLC. Emerging continuous manufacturing platforms (e.g., microfluidic reactors) offer precise control and reproducibility, but their adoption for endometriosis formulations is still in early stages. Third, patient-centered design: non-hormonal options and fertility preservation addresses the major complaint of young patients who desire pregnancy or cannot tolerate hormone-induced side effects. Many current nanocarriers still deliver hormonal agents (levonorgestrel, progestins), but the future lies in non-hormonal payloads such as anti-fibrotics (pirfenidone), anti-angiogenics (chrysin, curcumin), or immunomodulators (resveratrol). Crucially, these systems must be reversible and non-toxic to ovarian follicles and fallopian tube epithelium. For fertility preservation, biodegradable implants that degrade completely without leaving adhesions, or remotely activated depots that can be turned off, are highly desirable. Fourth, integration of diagnostic and therapeutic functions (theranostics) could revolutionize patient management. Theranostic nanoparticles combine imaging moieties (e.g., superparamagnetic iron oxide for MRI, near-infrared dyes for fluorescence imaging) with therapeutic payloads. In endometriosis, such systems would allow preoperative mapping of lesion boundaries, intraoperative guidance for complete excision, and postoperative monitoring of recurrence – all with the same injected formulation. For example, HA-functionalized PLGA nanoparticles co-loaded with chrysin and indocyanine green enabled both NIR imaging of deep lesions and sustained anti-angiogenic therapy in rat models. The challenge is to balance the imaging signal strength with drug loading capacity and to ensure that the imaging agent does not interfere with drug release or biocompatibility. Fifth and finally, toward personalized endometriosis therapy recognizes that endometriosis is not a single disease but a spectrum of phenotypes – inflammatory-dominant, fibrotic-dominant, angiogenic-dominant, and hormonal-resistant. Precision medicine would begin with a biopsy or liquid biopsy (detecting circulating endometrial cells or miRNAs), followed by molecular characterization of the patient's lesions (e.g., estrogen receptor status, aromatase expression, CD44 density, or specific mutations). Based on this profile, a tailored nanocarrier could be selected: for a highly fibrotic lesion, an HA-targeted NLC releasing a TGF-β inhibitor; for an inflammatory phenotype, a chitosan nanoparticle delivering siRNA against TNF-α; for an angiogenic lesion, a PLGA nanoparticle with chrysin. Ultimately, the convergence of nanomedicine, imaging, and molecular diagnostics will enable a future where endometriosis is managed as a chronic, treatable condition – not with one-size-fits-all hormones or repeated surgeries, but with individually customized, locally delivered, and patient-friendly therapeutic systems that preserve fertility and improve quality of life.

CONCLUSION

The management of endometriosis stands at a critical inflection point. For decades, the therapeutic landscape has been dominated by a frustrating cycle: hormonal suppression that temporarily masks symptoms but fails to eradicate lesions, followed by surgical excision that offers relief but is inevitably undermined by recurrence, often within two to five years. Patients endure diagnostic delays of seven to ten years, multiple operations, cumulative morbidity, and the psychological toll of chronic pain and infertility—all without access to a single disease-modifying, non-hormonal drug approved specifically for endometriosis. The articles reviewed herein collectively argue that this impasse is not due to a lack of druggable targets but rather to a fundamental failure of drug delivery. The ectopic lesion microenvironment—characterized by dense fibrosis, aberrant angiogenesis, and persistent inflammation—is intrinsically hostile to systemically administered agents, which are diluted, metabolized, or cleared before reaching therapeutic concentrations at their intended site.

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