

Advanced Drug Delivery Systems for Women Reproductive Health: Emerging Therapeutic Strategies and Clinical Applications

Dr. Ruchika Girdher^{1*}, Ritesh Raj², Dr. Nikita Pitty³, Dr. Priyanka Puri⁴,
Ms. Sukhpreet Kaur⁵, Himadri Sharma⁶

^{1*} Assistant Professor (Law).

Email: r.kochar1989@gmail.com.

² Project Research Scientist-I, All India Institute of Medical Sciences (AIIMS), New Delhi.

Email: ritesh.lab@gmail.com

³ Assistant professor, Dept of OBG, Jr Medical College and Hospital.

Email: nikitapitty@gmail.com

⁴ Associate Professor and HOD, University School of Law, Rayat Bahra Professional University.

Email: priyapuri2509@gmail.com

⁵ Research Scholar, School of Law, Lovely Professional University, Punjab.

Email: sukhpreetuppal80@gmail.com

⁶ Assistant Professor Jagannath University.

Email: shimadri726@gmail.com

ABSTRACT

Women's reproductive health presents distinctive drug-delivery challenges arising from cyclical hormonal changes, cervicovaginal mucus, variable pH, epithelial barriers, uterine and ovarian anatomy, pregnancy-associated physiological changes, and the need to minimize systemic and fetal exposure. Conventional oral, parenteral and topical therapies remain indispensable, but may be limited by first-pass metabolism, fluctuating plasma concentrations, poor tissue selectivity, short local residence time, dose-limiting toxicity, adherence problems and disruption of the vaginal microbiome. This comprehensive review examines advanced drug delivery systems for contraception, vaginal infections, sexually transmitted infections, endometriosis, infertility, polycystic ovary syndrome, uterine disorders, gynecological cancers and pregnancy-related applications. Platforms discussed include intravaginal rings, mucoadhesive gels and films, hydrogels, polymeric and lipid nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, micelles, nanoemulsions, electrospun fibers, implants, intrauterine systems, stimuli-responsive biomaterials, nucleic-acid delivery systems and emerging 3D-printed/bioprinted constructs. Particular emphasis is placed on mucus penetration versus mucoadhesion, controlled and stimuli-responsive release, ligand-mediated targeting, microbiome compatibility, translational safety, reproductive toxicology, patient acceptability and clinical feasibility. The review proposes a translational framework integrating disease biology, route selection, carrier engineering, quality-by-design, preclinical models, reproductive safety and patient-centered endpoints. Advanced delivery technologies can improve local exposure, reduce systemic toxicity and enable long-acting or precision therapy, but clinical translation requires rigorous characterization of reproductive and developmental safety, scalable manufacturing, microbiome effects and performance across physiologically diverse patient populations.

Keywords: Women's Reproductive Health, Vaginal Drug Delivery, Nanoparticles, Mucoadhesion, Intravaginal Rings, Endometriosis, Gynecological Cancer, Reproductive Nanomedicine.

How to cite this article: Ruchika Girdher^{1*} Ritesh Raj² Dr. Nikita Pitty³ Dr. Priyanka Puri⁴. Advanced Drug Delivery Systems for Women Reproductive Health: Emerging Therapeutic Strategies and Clinical Applications. Int J Drug Deliv Technol. 2026;16(83s):1793-1801. DOI: 10.25258/ijddt.16.83s.195.

1. INTRODUCTION

Women's reproductive disorders are therapeutically challenging because the target organs are anatomically compartmentalized and exposed to dynamic endocrine, immunological and mucosal conditions. The vagina and cervix provide direct access for local therapy, yet mucus turnover, fluid secretion, pH, microbiota, coital activity and menstrual cycling can alter retention and drug transport. The upper genital tract—the uterus, fallopian tubes and ovaries—adds additional

anatomical and biological barriers. Drug delivery during pregnancy creates a further requirement: maternal benefit must be balanced against placental transfer and fetal developmental risk.¹ Advanced drug delivery systems (ADDS) attempt to control where, when and how a therapeutic agent is released. The principal objectives are to increase residence at the desired site, protect unstable cargo, improve solubility, cross or interact productively with mucus, reduce systemic exposure, achieve sustained or pulsatile

¹Drug delivery to the female reproductive tract must account for dynamic vaginal, cervical, uterine and

ovarian physiology; pregnancy adds placental and developmental-safety considerations.

release, and enable cell- or tissue-selective uptake. These functions are especially relevant to reproductive health, where long treatment courses, recurrent infections, hormone-dependent disease and fertility considerations can make conventional dosing burdensome. The field has progressed from conventional creams, tablets and pessaries toward long-acting rings, polymeric matrices, nanoscale carriers, responsive hydrogels, electrospun fibers and nucleic-acid delivery. Recent reviews also emphasize the vaginal microbiome as both a therapeutic target and a design constraint, because excipients, pH modifiers and antimicrobials may alter *Lactobacillus*-dominant communities and thereby influence mucosal health.² This review synthesizes delivery technologies across major reproductive-health indications and evaluates their pharmaceutical rationale, clinical applications, safety limitations and translational barriers. It is structured as a comprehensive review for a drug-delivery audience and emphasizes formulation science rather than general gynecology.

2. REVIEW METHODOLOGY

A structured narrative review approach was used. Evidence domains were defined a priori: reproductive-tract physiology, vaginal and upper-genital-tract delivery, long-acting contraception, infectious disease, endometriosis and uterine disease, infertility, gynecological oncology, pregnancy-related delivery, biomaterials, nanotoxicology, and clinical translation. Priority was given to peer-reviewed reviews and primary studies indexed in biomedical databases, authoritative regulatory information, and recent literature describing translational platforms. Search concepts included combinations of women's reproductive health, vaginal drug delivery, intravaginal ring, nanoparticle, liposome, polymeric nanoparticle, hydrogel, mucoadhesion, mucus penetration, endometriosis, infertility, cervical cancer, ovarian cancer, contraception and reproductive toxicology. The review is qualitative and does not present a pooled meta-analysis. The synthesis focuses on technologies with a plausible delivery advantage over conventional administration and distinguishes preclinical promise from established clinical utility. Because this article does not report new experiments involving humans or animals, institutional ethics approval is not applicable.

3. BIOLOGICAL BARRIERS AND DESIGN REQUIREMENTS

The vaginal route is attractive because it permits direct access to the reproductive tract, avoids gastrointestinal degradation, can reduce hepatic first-pass metabolism and can support both local and systemic delivery. However, conventional soluble formulations may be diluted or expelled, while epithelial permeability and mucus turnover can shorten residence. Effective systems must therefore negotiate a fundamental design trade-off: retention at the mucosal surface versus penetration through cervicovaginal mucus.³ Mucoadhesive polymers such as chitosan, carbomers, cellulose derivatives and selected polyacrylates can prolong contact by interacting with mucins. In contrast, mucus-penetrating particles are often engineered with small size and low-fouling surface chemistry to minimize adhesive interactions and diffuse through mucus. The preferred strategy depends on the target. Extracellular luminal therapy may benefit from retention, whereas epithelial or intracellular targets may require rapid and uniform mucus penetration. Vaginal pH and microbiota are additional formulation variables. In reproductive-age women, *Lactobacillus*-dominant communities commonly contribute to an acidic environment. Infection, semen, menstruation, menopause and antibiotics can shift pH and microbial composition. pH-responsive carriers can exploit these differences, but formulation-induced pH changes may themselves affect microbiota and mucosal integrity. The upper genital tract is more difficult to target non-invasively. Uterine and ovarian delivery may require transcervical administration, intrauterine devices, systemic carriers with tissue targeting, or locally placed depots. Transport is influenced by uterine contractions, mucus, endometrial cycling, vascular permeability and receptor expression. Disease states such as endometriosis and malignancy alter these features and may create opportunities for ligand- or microenvironment-responsive delivery. Pregnancy changes plasma volume, renal clearance, hepatic enzyme activity, gastrointestinal motility and tissue perfusion. For nanomedicines, placental interactions and fetal exposure add major safety questions. Carrier composition, size, surface charge, degradation products and dose can influence biodistribution. Long-term developmental outcomes are often insufficiently characterized, making reproductive toxicology central to translation.⁴

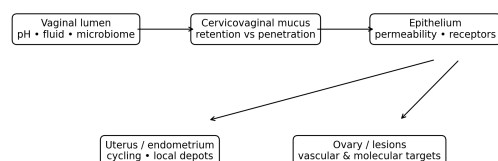
²Recent literature identifies the vaginal microbiome as both a therapeutic target and an important formulation constraint in women's reproductive drug delivery.

³Vaginal nanoparticles may be engineered either for mucoadhesion and retention or for mucus penetration,

depending on the therapeutic target and desired tissue distribution.

⁴Reproductive nanotoxicology requires assessment beyond conventional systemic toxicity, including placental transfer, fetal development, fertility and longer-term offspring outcomes.

Figure 1. Biological barriers shaping reproductive-tract drug delivery



4. MAJOR ADVANCED DRUG DELIVERY PLATFORMS

4.1 Intravaginal rings

Intravaginal rings are among the most clinically mature long-acting reproductive delivery platforms. Drug is incorporated into or contained within a polymeric ring and released over weeks or months. Rings can reduce daily adherence burden, maintain relatively stable exposure and support local or systemic delivery. Their successful use in hormonal contraception demonstrates the translational value of sustained vaginal delivery. Ring design can be extended to antiretrovirals, antimicrobials and multipurpose prevention technologies, although polymer-drug compatibility, release kinetics, user comfort and expulsion must be optimized.

4.2 Mucoadhesive gels, in situ gels and hydrogels

Gels are adaptable vehicles for local anti-infective, hormonal and anti-inflammatory therapy. Thermoresponsive or pH-responsive in situ gels can be administered as low-viscosity liquids and gel after exposure to body temperature or local conditions. Hydrogels can provide high water content, tissue compatibility and controlled diffusion. Their limitations include leakage, dose variability and relatively short residence unless mucoadhesive or depot-forming properties are engineered.

4.3 Vaginal films, tablets and inserts

Thin polymeric films can deliver drugs rapidly or in a controlled manner while offering portability and potentially improved acceptability compared with bulky semisolids. Critical attributes include disintegration time, mechanical strength, moisture sensitivity, drug content uniformity and irritation. Fast-dissolving films are suitable for on-demand therapy, whereas multilayer or slowly eroding films can extend release.

4.4 Polymeric nanoparticles

Polymeric nanoparticles made from biodegradable materials can encapsulate hydrophobic or hydrophilic agents, protect labile drugs and modulate release. Surface chemistry can be tuned toward mucoadhesion or mucus penetration. Ligands may be added for receptor-mediated targeting. The most important translational questions include reproducible particle size, drug loading, residual solvent, sterilization, stability, scale-up and the biological effects of repeated mucosal exposure.

4.5 Liposomes and lipid nanoparticles

Liposomes and related lipid systems can encapsulate both hydrophilic and lipophilic drugs and have a long

Figure 1. Biological barriers and target compartments relevant to advanced drug delivery in women's reproductive health. Source: Authors' conceptual synthesis.

history in nanomedicine. Lipid nanoparticles are also powerful nucleic-acid carriers. For reproductive applications, they offer opportunities in cancer therapy, anti-inflammatory delivery, gene regulation and localized infection treatment. Their composition must be optimized to avoid mucosal irritation and unwanted systemic or placental distribution.

4.6 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles and nanostructured lipid carriers combine lipid biocompatibility with controlled release and improved loading of poorly soluble compounds. NLCs incorporate a mixture of solid and liquid lipids, creating structural imperfections that can increase drug accommodation. They are attractive for vaginal and transdermal delivery but require careful assessment of polymorphic transitions and storage stability.

4.7 Dendrimers, micelles and nanoemulsions

Dendrimers offer multivalent surfaces and defined architecture, micelles improve apparent solubility of hydrophobic drugs, and nanoemulsions can enhance dispersion and mucosal contact. Each platform has distinct toxicity and stability constraints. Cationic surface charge may improve cellular uptake but can also increase membrane interaction and irritation, illustrating the need to balance potency with tolerability.

4.8 Electrospun fibers

Electrospinning produces micro- to nanoscale fibers with high surface area and tunable porosity. Fibers can deliver small molecules, proteins, probiotics or multiple agents and can be engineered for rapid dissolution, sustained release or sequential release. They are promising for vaginal infection prevention, wound healing and multipurpose reproductive products, but manufacturing consistency, dose uniformity and patient acceptability require further clinical validation.

4.9 Implants and intrauterine drug-delivery systems

Subdermal implants and intrauterine systems demonstrate the value of multi-year controlled release. Intrauterine delivery can generate high uterine exposure with lower systemic levels for selected hormones. Future systems may combine sensing, responsive release or biodegradable components, although device placement, bleeding patterns, perforation risk, infection concerns and removability remain clinically relevant.

4.10 Stimuli-responsive and precision systems

Smart materials can respond to pH, enzymes, reactive

oxygen species, temperature or disease-associated receptors. Such systems aim to release cargo preferentially in an infected, inflamed or neoplastic microenvironment. The concept is attractive for

Table 1. Comparative profile of advanced reproductive drug-delivery platforms

Platform	Key advantage	Main limitation	Typical duration	Representative applications	Translation status
Intravaginal ring	Sustained, user-controlled delivery	Expulsion, comfort, polymer compatibility	Weeks – months	Contraception, prevention, hormones	Established/clinical
Hydrogel/in situ gel	Local retention, adaptable formulation	Leakage, residence variability	Hours – days	Infection, inflammation, hormones	Clinical/preclinical
Polymeric nanoparticles	Targeting, protection, controlled release	Scale-up and mucosal safety	Hours – days	Infections, endometriosis, cancer	Mostly preclinical
Liposomes/LNPs	Versatile cargo including	Stability, systemic distribution	Hours – days	Cancer, gene/RNA delivery	Preclinical/clinical by indication

endometriosis and cancer, but complex materials face greater characterization, manufacturing and regulatory burdens.

	nucleic acids				
SLN/NLC	Solubilization and sustained lipid delivery	Polymorphism, storage stability	Hours – days	Local therapy, poorly soluble drugs	Preclinical
Electrospun fibers	High loading, tunable multi-drug release	Manufacturing and user acceptability	Minutes – days	Antimicrobials, probiotics, prevention	Preclinical/early translational
Implants/IUS	Very long acting and adherence-independent	Insertion/removal, device adverse effects	Months – years	Contraception, uterine hormone delivery	Established
Stimuli-responsive carriers	Disease-triggered precision release	Complexity and regulatory burden	Variable	Cancer, inflammation, infection	Emerging

5. APPLICATIONS IN CONTRACEPTION AND MULTIPURPOSE PREVENTION

Contraceptive drug delivery is a benchmark for successful long-acting reproductive technology. Subdermal implants, intrauterine systems and vaginal rings reduce reliance on daily adherence and can maintain therapeutic hormone concentrations for extended periods. Advanced formulation research seeks lower doses, improved bleeding profiles, biodegradable depots and user-controlled systems. Multipurpose prevention technologies attempt to combine contraception with prevention of sexually transmitted infections. From a formulation perspective, this requires co-delivery of molecules with different

physicochemical properties and different target concentrations. Rings, films and fibers are particularly attractive because spatially separated reservoirs or layers can generate distinct release profiles. Patient autonomy and reversibility are important design parameters. A technically sophisticated system may fail clinically if it causes discomfort, unacceptable discharge, bleeding changes or difficulty with insertion. Human-factors research should therefore be integrated early into pharmaceutical development rather than postponed until late-stage trials.

6. VAGINAL INFECTIONS, MICROBIOME AND SEXUALLY TRANSMITTED INFECTIONS

Vaginal infections are a natural target for localized

delivery because high mucosal concentrations can be achieved while systemic exposure is reduced. Conventional creams and tablets are effective for many conditions but can suffer from leakage, short retention and adherence limitations. Nanoparticles, gels, films and fibers may prolong exposure or improve penetration into mucus and biofilms. The vaginal microbiome is increasingly recognized as a design variable. A healthy *Lactobacillus*-dominant ecosystem can support acidic pH and colonization resistance, whereas dysbiosis is associated with bacterial vaginosis and adverse reproductive outcomes. Drug carriers should therefore be evaluated not only for epithelial cytotoxicity but also for effects on commensal organisms, pH and metabolite profiles. Recent literature has specifically proposed microbiome-targeted delivery and probiotic-compatible systems as a frontier in women's reproductive therapeutics.⁵ For sexually transmitted infections, mucosal prevention requires rapid distribution over susceptible epithelium, sufficient residence during exposure and compatibility with sexual activity. Mucus-penetrating nanoparticles and sustained rings can address different use patterns: the former may improve distribution, while the latter can provide adherence-independent prophylaxis.

7. ENDOMETRIOSIS, UTERINE DISORDERS AND PELVIC PAIN

Endometriosis is characterized by ectopic endometrial-like tissue, inflammation, angiogenesis and hormone responsiveness. Systemic hormonal therapies can be effective but may produce adverse effects and are unsuitable for some fertility goals. Targeted nanocarriers offer a theoretical means to concentrate anti-inflammatory, hormonal, anti-angiogenic or gene-regulatory cargo in lesions while reducing systemic exposure. Potential targeting strategies include ligands directed toward receptors or vascular features enriched in lesions, as well as stimuli-responsive release in oxidative or inflammatory microenvironments. These approaches remain predominantly preclinical. Translation requires evidence that targeting meaningfully improves therapeutic index rather than merely increasing formulation complexity. For abnormal uterine bleeding, adenomyosis and selected endometrial disorders, intrauterine delivery can achieve high local hormone exposure. The levonorgestrel-releasing intrauterine system illustrates how anatomical localization can transform pharmacotherapy: a small total drug amount can generate sustained local effects. Future uterine systems may incorporate biodegradable matrices, anti-inflammatory agents or combination therapy.

8. INFERTILITY, ASSISTED REPRODUCTION AND OVARIAN TARGETING

Infertility treatment often relies on injectable

gonadotropins, repeated monitoring and precisely timed dosing. Long-acting or controlled-release formulations could reduce injection burden, but reproductive endocrinology is unusually sensitive to dose and timing. Any depot system must therefore provide predictable pharmacokinetics and allow clinical control if ovarian response becomes excessive. Nanotechnology may contribute to ovarian targeting, delivery of antioxidants or gene-regulatory agents, preservation of gametes and improved local treatment of inflammatory conditions. However, exposure of oocytes and early embryos raises stringent safety requirements. Materials considered acceptable in non-reproductive tissues cannot automatically be assumed safe for fertility applications. Drug delivery may also support assisted reproduction through localized uterine therapies intended to improve endometrial receptivity. Evidence for such approaches must be evaluated carefully because implantation is multifactorial and surrogate biomarkers do not necessarily translate into live-birth benefit.

9. GYNECOLOGICAL CANCERS

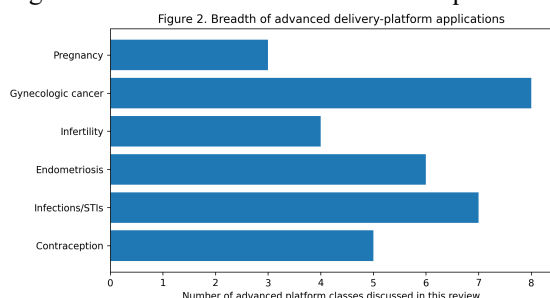
Ovarian, cervical and endometrial cancers are major targets for advanced delivery because conventional chemotherapy is constrained by systemic toxicity, resistance and heterogeneous tumor exposure. Nanocarriers can improve solubility, alter pharmacokinetics, exploit tumor-associated permeability or active targeting, and co-deliver drugs that act on complementary pathways. Reviews of gynecological oncology describe lipid, polymeric and inorganic platforms intended to improve therapeutic index.⁶

Ovarian cancer is particularly attractive for regional delivery because disease often remains within the peritoneal cavity for substantial periods. Intraperitoneal depots or nanoparticles can increase local exposure, although distribution throughout the peritoneum and penetration into tumor nodules remain challenges. Ligands against folate receptor, integrins or other tumor-associated targets have been explored, but receptor heterogeneity limits universal targeting. Cervical cancer creates opportunities for local vaginal or cervical delivery in addition to systemic therapy. Local nanoparticles, hydrogels or films may deliver cytotoxic, radiosensitizing or nucleic-acid cargo while reducing systemic exposure. For premalignant lesions, minimally invasive localized therapy could be particularly valuable if tissue penetration and dose uniformity are demonstrated. Nucleic-acid therapeutics—including siRNA, mRNA and gene-editing components—require carriers that protect cargo from degradation and promote intracellular delivery. Lipid nanoparticles and polymeric systems are leading candidates, but reproductive-organ targeting and off-

⁵Microbiome-compatible delivery aims to preserve or restore beneficial vaginal microbial communities while achieving adequate local therapeutic exposure.

⁶Nanotechnological platforms under investigation for gynecological cancers include lipid, polymeric and inorganic carriers designed to improve targeting, controlled release and therapeutic index.

target effects remain critical translational questions.



10. PREGNANCY-RELATED DELIVERY AND REPRODUCTIVE SAFETY

Pregnancy is the most safety-sensitive context for advanced reproductive delivery. A formulation intended for the mother may cross the placenta directly or alter placental biology indirectly. Nanoparticle size, composition, charge, protein corona and degradation can affect maternal distribution and placental interaction. Contemporary reviews emphasize that long-term developmental safety remains a major knowledge gap for nanodrugs used during pregnancy.⁷ Potential applications include targeted treatment of placental disorders, prevention of preterm birth, localized infection therapy and maternal treatment with reduced fetal exposure. The ideal system would retain drug in the maternal or placental compartment while minimizing transplacental transfer. This goal is biologically complex because the placenta changes throughout gestation and disease can alter barrier function.

Reproductive safety assessment should extend beyond acute maternal toxicity. Relevant endpoints include fertility, implantation, embryo-fetal development, placental function, teratogenicity, postnatal development and, when scientifically justified, multigenerational outcomes. Carrier excipients and degradation products must be assessed alongside the active drug.

11. QUALITY BY DESIGN, CHARACTERIZATION AND PRECLINICAL MODELS

Quality by Design (QbD) provides a useful framework

Table 2. Critical quality attributes and translational tests

Attribute	Why it matters	Typical assessment	Failure risk
Particle size/PDI	Mucus transport, uptake, stability	DLS, microscopy	Aggregation or poor penetration

⁷ Pregnancy-specific nanomedicine development requires careful characterization of maternal biodistribution, placental interactions and developmental toxicity.

Figure 2. Illustrative mapping of platform breadth across major reproductive-health application areas. Values reflect the platform classes synthesized in this review and are not clinical efficacy scores.

for advanced reproductive formulations. The target product profile should specify route, dose, duration, release pattern, storage conditions, user requirements and safety constraints. Critical quality attributes may include particle size and distribution, zeta potential, drug loading, encapsulation efficiency, rheology, mechanical strength, mucoadhesion, release kinetics, sterility or microbial limits, residual solvents and stability. In vitro testing should reproduce relevant physiological conditions rather than rely solely on simple buffer release. Vaginal formulations may require simulated vaginal fluid, mucus models, pH variation, dilution, shear and microbiome-compatible testing. Cell models can assess epithelial toxicity, permeability and inflammatory responses. Ex vivo tissues provide more realistic architecture but have limited viability and variability.

Organ-on-chip and microphysiological systems may improve prediction by recreating flow, epithelial barriers, hormonal environments and multicellular interactions. Animal models remain important for selected questions but differ from humans in estrous cycling, vaginal physiology, microbiota and reproductive anatomy. Translation therefore requires explicit recognition of model limitations rather than assuming direct equivalence. Mathematical and mechanistic modeling can complement experimentation by linking particle properties, mucus diffusion, drug release and tissue uptake. This can reduce iterative formulation burden and support rational optimization.⁸

	y		
Surface charge/chemistry	Mucoadhesion, toxicity, targeting	Zeta potential, surface analysis	Irritation or rapid clearance
Drug loading/release	Dose accuracy and duration	Assay, dissolution/release models	Burst release or subtherapeutic exposure

⁸ Mechanistic and mathematical models can complement in vitro and in vivo experiments by relating carrier properties to mucus transport, release and tissue uptake.

	n		
Rheology/ mucoadhesion	Retention and usability	Rheometry, texture analysis	Leakage or poor spreading
Mechanical properties	Ring/film/fiber integrity	Tensile/compression testing	Breakage or dose inconsistency
Microbiome	Local ecology	Culture/omics-	Dysbiosis

compatibility	ical safety	based assays	
Biocompatibility	Mucosal and systemic safety	Cell/tissue assays, histology	Inflammation/cytotoxicity
Stability	Shelf life and performance	ICH-aligned stability studies	Loss of potency or altered release

12. CLINICAL TRANSLATION AND PATIENT-CENTERED DESIGN

Clinical translation requires more than proof of controlled release. A reproductive product must fit daily life, sexual activity, menstruation, fertility intentions and cultural context. Acceptability influences adherence, and adherence influences real-world effectiveness. Attributes such as insertion method, leakage, texture, odor, visibility to partners, removability and privacy can be as important as laboratory release kinetics. Manufacturing scale-up can change particle size, polymer morphology, residual solvent and release behavior. Sterilization may alter polymers or lipids. Complex combination products can trigger additional regulatory requirements when drug, device and biologic functions overlap. Early consultation with regulatory authorities and development of scalable analytical methods can prevent late-stage redesign. Clinical endpoints should match the intended benefit. For infection therapy, microbiological cure should be accompanied by symptom and recurrence outcomes. For endometriosis, pain, quality of life and fertility goals are relevant. For contraception, effectiveness, bleeding patterns, continuation and reversibility matter. For oncology, pharmacokinetics, response and toxicity must demonstrate an advantage over simpler alternatives. Equity is also a translational issue. Long-acting and advanced systems may reduce treatment burden but become inaccessible if manufacturing costs, cold-chain requirements or specialized insertion procedures are high. Product design should therefore consider resource-constrained settings, self-administration where appropriate and stable formulations.

13. SAFETY, NANOTOXICOLOGY AND REGULATORY CONSIDERATIONS

Advanced carriers introduce material-specific risks in addition to drug-specific toxicity. Cationic polymers and surfactants can disrupt membranes, inorganic particles may persist, degradation products may accumulate, and immune activation can occur. Repeated vaginal administration requires careful

assessment of epithelial integrity and inflammation because subclinical mucosal injury could increase susceptibility to infection. Reproductive toxicology deserves particular emphasis. Nanomaterials may interact with ovarian follicles, sperm after sexual exposure, embryos, placenta or fetal tissues. Recent literature highlights the need for long-term studies and multi-omics approaches to identify pathways of reproductive and developmental nanotoxicity.⁹ Regulatory evaluation should establish a clear relationship between critical material attributes and clinical performance. For nanomedicines, small manufacturing changes can alter biological behavior. Robust control strategies, validated assays and comparability plans are therefore essential. Combination products such as drug-eluting rings or intrauterine systems additionally require integration of device performance with pharmaceutical quality.

14. EMERGING FRONTIERS

Stimuli-responsive biomaterials are moving toward systems that sense local pH, enzymes, oxidative stress or disease-associated molecules and alter drug release accordingly. Recent work in women's health emphasizes mucoadhesive and stimuli-responsive nanomaterials as a route to overcome physiological barriers.¹⁰ 3D printing and bioprinting can personalize geometry, dose and release behavior. Vaginal rings, implants, scaffolds and tissue models may be tailored to anatomy or therapeutic need. The major challenges are reproducibility, validated printing materials, sterilization and regulatory control of decentralized manufacturing. Microbiome-directed delivery may include selective antimicrobials, prebiotics, probiotics, postbiotics or phage-based strategies. The objective is to restore function rather than broadly eradicate organisms. Delivery systems must preserve biological activity and avoid excipients that undermine the intended microbial ecology. Artificial intelligence and computational optimization can accelerate formulation design by relating material descriptors to loading, release, stability and toxicity. Mechanistic models can be combined with machine learning, but datasets in

⁹ Long-term reproductive and developmental safety remain a major translational gap for advanced nanodrug systems, especially when exposure occurs before or during pregnancy.

¹⁰ Stimuli-responsive biomaterials exploit local physicochemical or biological cues such as pH, enzymes, temperature and oxidative stress to modulate release.

reproductive nanomedicine remain relatively small and heterogeneous. Predictive systems should therefore support—not replace—experimental validation. Precision reproductive medicine may eventually combine molecular diagnostics with targeted delivery, for example selecting a carrier based on receptor

Figure 3. Translational framework for reproductive drug-delivery development

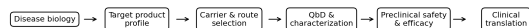


Figure 3. Proposed translational framework

15. RESEARCH GAPS AND FUTURE PRIORITIES

First, reproductive drug-delivery studies need greater physiological realism. Hormonal state, age, menopause, pregnancy, menstrual products, sexual activity and microbiome composition can alter local performance but are not consistently represented in preclinical testing.

Second, studies should compare advanced systems against clinically meaningful conventional controls. Demonstrating that a nanoparticle can encapsulate a drug is insufficient, the platform should improve exposure, efficacy, safety, adherence or another patient-relevant outcome.

Third, long-term reproductive and developmental safety data are needed, particularly for persistent materials and repeated exposure. Standard toxicology panels may miss effects on fertility, implantation or offspring development.

Fourth, clinical research should include diverse populations and patient-reported outcomes. Reproductive products are unusually sensitive to acceptability, privacy and cultural preferences.

Fifth, manufacturing and regulatory strategy should be considered at the beginning of development. Simple, robust systems with a clear therapeutic advantage may translate more successfully than highly complex multifunctional carriers whose incremental benefit is uncertain.

16. CONCLUSION

Advanced drug delivery is reshaping women's reproductive therapeutics by moving treatment from nonspecific systemic exposure toward local, sustained, responsive and potentially personalized delivery. Clinically established rings, implants and intrauterine systems demonstrate that controlled delivery can transform adherence and pharmacology. Nanoparticles, lipid carriers, hydrogels, electrospun fibers, nucleic-acid systems and smart biomaterials extend this concept to infections, endometriosis, infertility, gynecological cancer and pregnancy-related disorders. The most important scientific challenge is no longer simply to create novel carriers, but to demonstrate that they solve a clinically important delivery problem without creating new reproductive, microbiome or developmental risks. Future progress will depend on integrating formulation science with reproductive biology, realistic preclinical models, patient-centered

expression in endometriosis or tumor tissue, or tailoring release to microbiome state. The clinical value of such personalization will depend on whether biomarker testing materially improves outcomes enough to justify added complexity.

integrating biology, formulation engineering, quality-by-design, reproductive safety and clinical implementation.

design, scalable manufacturing and rigorous long-term safety assessment.

REFERENCES

1. International Journal of Drug Delivery Technology. Manuscript Guidelines (Checklist). Accessed September 2026.
2. Bassey PO, Ilomuanya MO, Oseni BA, et al. Advancements in drug delivery systems for women's reproductive health: Vaginal microbiome as a target for innovative drug delivery systems. *Eur J Pharm Biopharm.* 2025;215:114831. doi:10.1016/j.ejpb.2025.114831.
3. Vaginal drug delivery system: A promising route of drug administration for local and systemic diseases. *Drug Discov Today.* 2024;29:104012. doi:10.1016/j.drudis.2024.104012.
4. Ensign LM, Cone R, Hanes J. Nanoparticle-based drug delivery to the vagina: a review. *J Control Release.* 2014;190:500-514.
5. das Neves J, Bahia MF. Gels as vaginal drug delivery systems. *Int J Pharm.* 2006;318:1-14.
6. das Neves J, Amiji M, Sarmiento B. Mucoadhesive nanosystems for vaginal microbicide development. *J Pharm Sci.* 2011;100:3887-3899.
7. Date AA, Shibata A, Goede M, et al. Development and evaluation of a thermosensitive vaginal gel containing raltegravir + efavirenz loaded nanoparticles for HIV prophylaxis. *Antiviral Res.* 2012;96:430-436.
8. Ensign LM, Tang BC, Wang YY, et al. Mucus-penetrating nanoparticles for vaginal drug delivery protect against herpes simplex virus. *Sci Transl Med.* 2012;4:138ra79.
9. Valenta C. The use of mucoadhesive polymers in vaginal delivery. *Adv Drug Deliv Rev.* 2005;57:1692-1712.
10. Alexander NJ, Baker E, Kaptein M, Karck U, Miller L, Zampaglione E. Why consider vaginal drug administration? *Fertil Steril.* 2004;82:1-12.
11. Friend DR. Drug delivery in multiple indication (multipurpose) prevention technologies: systems to prevent HIV-1 transmission and unintended pregnancies or

- HSV-2 transmission. *Expert Opin Drug Deliv*. 2012;9:417-427.
12. Malcolm RK, Edwards KL, Kiser P, Romano J, Smith TJ. Advances in microbicide vaginal rings. *Antiviral Res*. 2010;88 Suppl 1:S30-S39.
13. Boyd P, Variano B, Spence P, et al. In vitro release testing methods for drug-releasing vaginal rings. *J Control Release*. 2019;313:54-69.
14. Caramella CM, Rossi S, Ferrari F, Bonferoni MC, Sandri G. Mucoadhesive and thermogelling systems for vaginal drug delivery. *Adv Drug Deliv Rev*. 2015;92:39-52.
15. das Neves J, Martins JP, Sarmento B. Will nanotechnology contribute to the development of vaginal microbicides? *Adv Drug Deliv Rev*. 2016;103:57-75.
16. Woodrow KA, Cu Y, Booth CJ, Saucier-Sawyer JK, Wood MJ, Saltzman WM. Intravaginal gene silencing using biodegradable polymer nanoparticles densely loaded with small-interfering RNA. *Nat Mater*. 2009;8:526-533.
17. Cu Y, Saltzman WM. Drug delivery: stepping out of the mucus barrier. *Nat Mater*. 2009;8:11-13.
18. Whaley KJ, Hanes J, Shattock R, Cone RA, Friend DR. Novel approaches to vaginal delivery and safety of microbicides: biopharmaceuticals, nanoparticles, and vaccines. *Antiviral Res*. 2010;88 Suppl 1:S55-S66.
19. Hoang T, Zierden H, Date A, et al. Development of a mucoinert progesterone nanosuspension for safer and more effective prevention of preterm birth. *J Control Release*. 2019;295:74-86.
20. Zierden HC, Ortiz JI, DeLong K, et al. Enhanced drug delivery to the reproductive tract using nanomedicine approaches. *Adv Drug Deliv Rev*. 2021;178:113955.
21. Yadav K, Sharma R. Nanodrug impact on female reproductive health and fetal development: From translation approaches to long-term safety concern. *Reprod Toxicol*. 2026;139:109103. doi:10.1016/j.reprotox.2025.109103.
22. Koduru R, Maity S, Das D, et al. Nanotechnology for reproductive healthcare: a comprehensive review. *J Nanobiotechnology*. 2026;24:262. doi:10.1186/s12951-025-03898-7.
23. Keyvani V, et al. The application of nanotechnological therapeutic platforms against gynecological cancers. *Curr Pharm Des*. 2024;30:975-987. doi:10.2174/0113816128291955240306112558.
24. das Neves J, Amiji MM, Bahia MF, Sarmento B. Nanotechnology-based systems for the treatment and prevention of HIV/AIDS. *Adv Drug Deliv Rev*. 2010;62:458-477.
25. Date AA, Destache CJ. A review of nanotechnological approaches for the prophylaxis of HIV/AIDS. *Biomaterials*. 2013;34:6202-6228.
26. Vanić Ž, Škalko-Basnet N. Nanopharmaceuticals for improved topical vaginal therapy: can they deliver? *Eur J Pharm Sci*. 2013;50:29-41.
27. Vanić Ž, Rukavina Z, Manner S, et al. Azithromycin-liposomes as a novel approach for localized therapy of cervicovaginal bacterial infections. *Int J Nanomedicine*. 2019;14:5957-5976.
28. Frank LA, Sandri G, D'Autilia F, et al. Chitosan gel containing polymeric nanocapsules: a new formulation for vaginal drug delivery. *Int J Nanomedicine*. 2014;9:3151-3161.
29. Knuth K, Amiji M, Robinson JR. Hydrogel delivery systems for vaginal and oral applications. *Adv Drug Deliv Rev*. 1993;11:137-167.
30. Cook MT, Brown MB. Polymeric gels for intravaginal drug delivery. *J Control Release*. 2018;270:145-157.
31. Brannon-Peppas L. Novel vaginal drug release applications. *Adv Drug Deliv Rev*. 1993;11:169-177.
32. Shattock RJ, Rosenberg Z. Microbicides: topical prevention against HIV. *Cold Spring Harb Perspect Med*. 2012;2:a007385.
33. das Neves J, Sarmento B. Drug delivery and nanotechnology: the road ahead in HIV prevention. *Future Virol*. 2014;9:605-608.
34. Rohan LC, Sassi AB. Vaginal drug delivery systems for HIV prevention. *AAPS J*. 2009;11:78-87.
35. Mesquita PMM, Rastogi R, Segarra TJ, et al. Intravaginal ring delivery of tenofovir disoproxil fumarate for prevention of HIV and HSV infection. *J Antimicrob Chemother*. 2012;67:1730-1738.
36. Katz DF, Gao Y, Kang M. Using modeling to help understand vaginal microbicide functionality and create better products. *Drug Deliv Transl Res*. 2011;1:256-276.
37. Clark JT, Clark MR, Shelke NB, et al. Engineering a segmented dual-reservoir polyurethane intravaginal ring for simultaneous prevention of HIV transmission and unwanted pregnancy. *PLoS One*. 2014;9:e88509.
38. Malcolm RK, Fetherston SM, McCoy CF, Boyd P, Major I. Vaginal rings for delivery of HIV microbicides. *Int J Womens Health*. 2012;4:595-605.
39. McConville C, Major I, Friend DR, Clark MR,

- Woolfson AD, Malcolm RK. Development of a UC781 releasing poly ethylene vinyl acetate vaginal ring. *Drug Deliv Transl Res*. 2012;2:489-497.
40. Verstraelen H, Verhelst R. Bacterial vaginosis: an update on diagnosis and treatment. *Expert Rev Anti Infect Ther*. 2009;7:1109-1124.
 41. Petrova MI, Lievens E, Malik S, Imholz N, Lebeer S. *Lactobacillus* species as biomarkers and agents that can promote various aspects of vaginal health. *Front Physiol*. 2015;6:81.
 42. Amabebe E, Anumba DOC. The vaginal microenvironment: the physiologic role of *Lactobacilli*. *Front Med*. 2018;5:181.
 43. Tyler B, Gullotti D, Mangraviti A, et al. Polylactic acid implants for sustained drug delivery. *Adv Drug Deliv Rev*. 2016;107:163-175.
 44. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers*. 2011;3:1377-1397.
 45. Sercombe L, Veerati T, Moheimani F, et al. Advances and challenges of liposome assisted drug delivery. *Front Pharmacol*. 2015;6:286.
 46. Patil Y, Sadhukha T, Ma L, Panyam J. Nanoparticle-mediated simultaneous and targeted delivery of paclitaxel and tariquidar overcomes tumor drug resistance. *J Control Release*. 2009;136:21-29.
 47. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nat Rev Cancer*. 2017;17:20-37.
 48. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov*. 2021;20:101-124.
 49. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. *Bioeng Transl Med*. 2019;4:e10143.
 50. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015;33:941-951.
 51. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013;65:36-48.
 52. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnology*. 2018;16:71.
 53. International Council for Harmonisation. ICH Q8(R2): Pharmaceutical Development. Geneva: ICH, 2009.
 54. International Council for Harmonisation. ICH Q9(R1): Quality Risk Management. Geneva: ICH, 2023.
 55. International Council for Harmonisation. ICH Q10: Pharmaceutical Quality System. Geneva: ICH, 2008.
 56. U.S. Food and Drug Administration. Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products. FDA guidance.
 57. European Medicines Agency. Reflection paper on nanotechnology-based medicinal products for human use. EMA.
 58. Paramanick D, et al. Biomaterials empowering in new era of women's healthcare system. *Reprod Sci*. 2026. doi:10.1007/s43032-026-02066-y.
 59. Breaking physiological barriers in women's health: Mucoadhesive and stimuli-responsive nanomaterials. *WIREs Nanomed Nanobiotechnol*. 2026.
 60. Nanoparticle-mediated drug delivery to treat infections in the female reproductive tract: evaluation of experimental systems and the potential for mathematical modeling. 2018.
 61. Vaginal drug delivery: strategies and concerns in polymeric nanoparticle development. *Expert Opin Drug Deliv*. 2014;11:1415-1434.
 62. Nano-sized platforms for vaginal drug delivery. *Curr Pharm Des*. 2015.