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CLOSED-LOOP AND ON-DEMAND CONTRACEPTIVE TECHNOLOGIES: A REVIEW OF SMART DEVICES FOR FERTILITY CONTROL IN MEN AND WOMEN

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ABSTRACT

Contraceptive technology is shifting from passive, user-dependent methods toward active, responsive systems built on advances in materials science, microelectronics, and formulation engineering. This review summarizes emerging smart contraceptive technologies for men and women, organized by mechanism of responsiveness: (1) programmable electronic implants enabling wireless, on-demand or scheduled drug release; (2) self-assembling injectable microcrystals that form a monolithic implant in situ; (3) microneedle-based systems for painless, sustained transdermal delivery; (4) on-demand, user-controlled vaginal pH regulators; and (5) ultrasound-responsive hydrogels for reversible male contraception. For each category, we describe the mechanism of action, developmental stage, available efficacy and safety data, and user-acceptability considerations, with attention to technologies that reduce dependence on surgical insertion/removal and healthcare-provider access, and that expand options for men. We conclude by identifying gaps and future directions, including biosensor-integrated closed-loop fertility monitoring and multipurpose prevention technologies combining contraception with STI prophylaxis.

KEYWORDS: Smart contraception; responsive drug delivery; long-acting reversible contraception (LARC); programmable implants; microneedles; male contraception.

INTRODUCTION

Modern contraceptives play a critical role in preventing unplanned pregnancy and empowering individuals to control their reproductive health, including the number and spacing of children.

Despite growing recognition that no single contraceptive method works well for all individuals, advances in the contraceptive market over recent decades have been largely incremental. The unintended pregnancy rate remains substantial worldwide, and unintended pregnancy is associated with significant direct medical costs and medical risk, particularly for women at both ends of the reproductive age span who are less likely to seek adequate preconception care.[1]

The limitations of existing contraceptive options are well documented. Daily oral contraceptives require consistent adherence, with typical-use failure rates substantially higher than perfect-use rates. Long-acting reversible contraceptives (LARCs), including intrauterine devices and subdermal implants, offer superior efficacy but require healthcare-provider intervention for both insertion and removal. Injectable contraceptives such as Depo-Provera offer convenience but have a limited duration of action (three months) and require repeat administration.[10] For men, options remain limited to condoms and vasectomy, neither of which combines high efficacy with reliable reversibility.

In response to these limitations, a new generation of "smart" contraceptive technologies has emerged, drawing on a broader trend toward stimuli-responsive polymer materials that change conformation or release cargo in response to defined physical, chemical, or biological triggers.[21] These systems incorporate responsive elements that enable programmable drug release, user-controlled activation, or physiological trigger-based delivery. This review provides a systematic overview of these emerging technologies, categorized by mechanism of responsiveness and stage of development.

This narrative review draws on literature identified through PubMed, Scopus, and Google Scholar for the period January 2019 to June 2026, using combinations of the terms "smart contraception," "programmable implant," "self-assembling microcrystals," "microneedle contraceptive," "vaginal pH regulator," and "male contraception." Peer-reviewed primary research articles were prioritized; regulatory announcements, company product profiles, and grant records were used only to source development-stage and funding information not available in the primary literature, and are identified as such in the text.

PROGRAMMABLE ELECTRONIC IMPLANTS FOR FEMALE CONTRACEPTION

Overview

Programmable electronic implants represent the most technologically sophisticated category of smart contraceptive devices. These systems integrate wireless communication, onboard power sources, and precision drug delivery mechanisms to enable user-controlled or scheduled drug release over extended periods, potentially decades.

The concept builds on more than two decades of work on implantable microchip-based drug delivery. Early proof-of-concept devices demonstrated pulsatile, on-demand release from arrays of individually addressable microreservoirs,[3] which was subsequently extended to chronic, programmed delivery of peptide therapeutics from multi-reservoir implants[4] and to resorbable, multi-pulse delivery platforms.[5] This microchip platform was first validated in humans in a trial of an osteoporosis therapeutic, establishing feasibility for wirelessly controlled, programmable drug release in a clinical setting,[6] and was subsequently developed further as a commercial implantable wireless microchip platform for programmable drug delivery.[7] DARE-LARC1 represents the direct extension of this platform to contraception.

DARE-LARC1: A Wirelessly Controlled Implantable Contraceptive

DARE-LARC1 (Daré Bioscience) is an implantable device designed to deliver the contraceptive hormone levonorgestrel over at least ten years.[2] Unlike existing long-acting reversible contraceptives, drug delivery can be turned on and off wirelessly, providing individuals with the ability to time and space pregnancies according to their fertility intentions.[2]

Mechanism of action: The device utilizes a microchip-based platform originally developed by Microchip Biotech, which Daré Bioscience acquired in 2019.[8] The system contains micro-reservoirs that can be individually opened to release precise doses of levonorgestrel on demand or according to a programmed schedule. The device is designed to operate without external power requirements, featuring an implant-grade battery intended to last up to 20 years. A smartphone interface is intended to enable user and clinician interaction, with firmware upgradable without device removal.[2]

Development status: As of 2025, DARE-LARC1 has received $41.8 million in non-dilutive grant funding for preclinical evaluation and Investigational New Drug (IND)-enabling research.[2,8] The underlying platform technology was previously evaluated in human studies for an osteoporosis indication, supporting feasibility for long-term programmable drug release in humans.[2]

Table 1: Comparison of programmable implants with conventional LARCs.

Feature	Conventional LARCs (e.g., Nexplanon®)	Programmable implants (e.g., DARE-LARC1)
User control	On/off requires clinic visit	Instant via smartphone
Duration	3–7 years	10+ years (proposed)
Clinician interaction	In-person for removal/reinsertion	Remote monitoring possible
Firmware updates	Not applicable	Wireless upgradable
Regulatory status	Established	Uncharted
Cybersecurity risk	None	Significant
Manufacturing cost	Low	High
Insertion procedure	Surgical (subdermal)	Surgical (subdermal)

Programmable electronic implants such as DARE-LARC1 offer several transformative advantages over conventional long-acting reversible contraceptives, but also face significant challenges that must be addressed before clinical translation.

- **Advantages:** true on-demand user control; multi-decade potential duration; remote adjustability by clinicians; firmware upgradability in situ.
- **Challenges:** complex regulatory pathway; user privacy and security concerns; cost implications for manufacturing.

SELF-ASSEMBLING INJECTABLE MICROCRYSTALS (SLIM)

Concept

A significant barrier to long-acting injectable contraceptives has been the trade-off between drug loading, injection discomfort, and duration of action. Existing long-acting injectables can be divided into two categories: microparticle suspensions and in situ forming implants (ISFIs).[10] Microparticle suspensions leverage sustained release from micrometer-sized particles, while ISFIs transform from liquid or semisolid formulations into solid-like structures at the target site.[10] However, both approaches face challenges in combining effective

long-term release with injectability through small-gauge needles suitable for self-administration.

The SLIM (Self-assembling Long-acting Injectable Microcrystals) system addresses these limitations through an innovative approach: drug microcrystals that self-aggregate in the subcutaneous space to form a monolithic implant with minimal polymer excipient.[9,10]

Mechanism of self-aggregation

The SLIM formulation consists of levonorgestrel microcrystals (average diameter 2–3 µm) suspended in a solvent (benzyl benzoate).[10] Upon subcutaneous injection, a solvent exchange process occurs: the carrier solvent dissipates into the surrounding tissue, while water from the interstitial fluid diffuses into the depot. This phase separation drives the microcrystals to compact and aggregate into a monolithic solid implant.[10]

Critically, the self-aggregation process is engineered with a low polymer-to-drug ratio of 0.0625:1 w/w — over an order of magnitude lower than previous ISFIs.[10] This minimal polymer content enables: (1) high drug loading of 293 mg/mL; (2) low viscosity, supporting injection forces below 64 N through 25-gauge needles; and (3) patient self-administration, since patients can comfortably apply the required force by hand.[10]

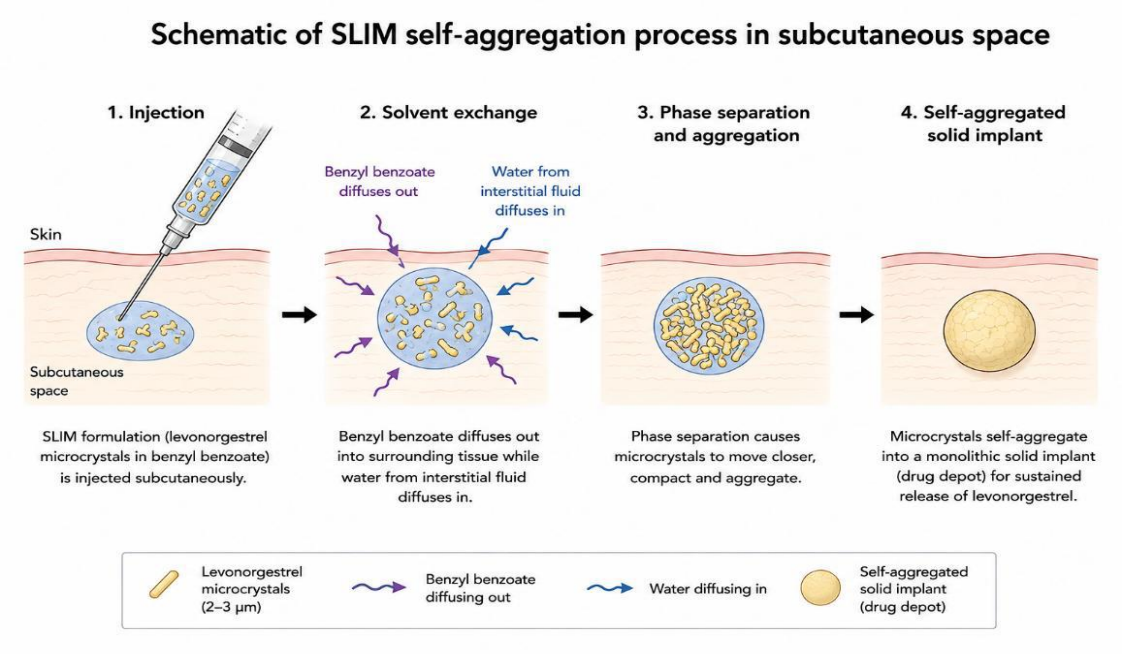

Fig. 1: Schematic Of The Slim Self-Aggregation Process In Subcutaneous Space.

Drug Release Kinetics

Because levonorgestrel microcrystals are water-impermeable solids, drug molecules are released via surface erosion rather than diffusion through a polymer matrix.[10] Release duration can be tuned by adjusting the packing density of microcrystals (higher density reduces surface area), modifying the solvent composition (slower-exchanging solvents increase compaction), and controlling implant porosity through formulation parameters. This surface erosion mechanism provides predictable zero-order or near-zero-order release kinetics, avoiding the burst release commonly observed with polymer-based systems.[10]

Development status

As of March 2025, SLIM remains in preclinical development. The technology was published in Nature Chemical Engineering (Vol. 2, pp. 209–219).[10] Lead researchers include Vivian Feig (Stanford University) and Giovanni Traverso (MIT/Brigham and Women's Hospital).[9]

Advantages and global health implications

Table 2: Advantages of SLIM and global health implications.

Advantage	Implication
25-gauge needle administration	Reduced pain, bruising, and patient discomfort
Self-administration possible	Access in low-resource settings without medical infrastructure
Minimal polymer content	Reduced risk of adverse polymer reactions
Retrievable implant	Reversibility when fertility is desired
Tunable duration	Personalized contraception (months to years)

As noted by the research team, the goal is to provide women worldwide with a variety of easily applicable contraceptive methods, particularly in regions without stable medical infrastructure.[9]

Broader applications

The SLIM platform is adaptable beyond contraception to other long-acting therapies, including HIV pre-exposure prophylaxis (PrEP) and other chronic conditions requiring sustained drug delivery,[9,10] consistent with the broader push toward long-acting injectable and implantable platforms for HIV treatment and prevention.[11]

MICRONEEDLE-BASED TRANSDERMAL CONTRACEPTIVE SYSTEMS

Rationale for microneedle delivery

Transdermal drug delivery offers significant advantages for contraception: avoidance of first-pass metabolism, improved patient compliance, and the potential for self-administration. However, the stratum corneum presents a formidable barrier to transdermal drug transport, particularly for lipophilic drugs like levonorgestrel. Microneedle technology overcomes this barrier by creating transient microchannels in the skin, enabling minimally invasive drug delivery. This approach builds on earlier work demonstrating a rapidly separable microneedle patch for sustained release of a contraceptive, which established the basic feasibility of microneedle-based long-acting contraception.[13]

Levonorgestrel-loaded microneedles with thermogelling system

Kumar and colleagues (2026) developed dissolving levonorgestrel-loaded microneedles (LMNs) incorporating a chitosan-β-glycerophosphate thermogelling system for sustained transdermal delivery.[12]

The formulation is composed of levonorgestrel (LNG) as the active pharmaceutical ingredient, embedded within a matrix of polyvinylpyrrolidone K90 and dextran 40, which enhance mechanical strength and modulate controlled release. To achieve sustained drug delivery, a thermogelling system of chitosan-β-glycerophosphate is incorporated, forming a stable release matrix under physiological conditions. The construct is fabricated by poly(dimethylsiloxane) (PDMS) molding, ensuring precise shaping and reproducibility of the dosage form.

Table 3: Characterization results of levonorgestrel-loaded microneedles.

Parameter	Finding
Morphology	Uniform, sharp structures (SEM confirmation)
Chemical compatibility	FTIR confirmed compatibility of LNG within matrix
Physical stability	XRD demonstrated stable formulation
Mechanical strength	Significant ($p < 0.05$)
Insertion efficiency	High ($F = 17.83$, $p = 3.03 \times 10^{-8}$) across Parafilm layers
Dissolution time	Complete within 30 minutes in porcine skin

In vitro drug release

Ex vivo studies demonstrated sustained levonorgestrel release of 70.86% ± 0.42% over 48 hours, significantly outperforming a topical gel control (42.33% ± 0.91%).[12] Release followed first-order kinetics ($R^2 = 0.996$), and the release exponent ($n = 0.79$) indicated a non-Fickian, combined diffusion-erosion mechanism.

In vivo efficacy

In vivo evaluation in Wistar rats demonstrated significant contraceptive efficacy: implantation sites were reduced to 0.5 ± 0.55 compared to controls, uterine thickness was reduced to 3.66 ± 0.51 mm ($p < 0.0001$), and comparative efficacy was similar to oral levonorgestrel.

Three-layer microneedle systems for extended delivery

Permana and colleagues (2025) developed a three-layer microneedle system for controlled and sustained levonorgestrel release.[14] This approach uses layered fabrication with different polymer compositions in successive layers to achieve more extended release durations, potentially weeks to months.

Advantages and limitations

- **Advantages:** painless, minimally invasive administration; potential for self-administration; no sharp waste generation; improved patient compliance; avoids gastrointestinal side effects and first-pass metabolism.
- **Limitations:** current duration limited to ~48 hours for single-layer systems; patch size for extended duration remains challenging; further optimization needed for truly long-acting (monthly+) delivery.

ON-DEMAND, USER-CONTROLLED VAGINAL PH REGULATION

Phexxi: first-in-class non-hormonal vaginal pH regulator

Phexxi (lactic acid, citric acid, and potassium bitartrate) received FDA approval in May 2020 as the first non-hormonal, vaginal pH regulator contraceptive.[15] This on-demand, woman-controlled gel represents a fundamentally different approach to smart contraception, one that leverages the body's own physiological environment rather than delivering exogenous hormones.

Mechanism of action: The gel maintains vaginal pH within the normal range of 3.5 to 4.5, an acidic

environment that is naturally spermicidal, as sperm cannot survive under these conditions.[15] Unlike traditional spermicides containing nonoxynol-9, Phexxi does not disrupt the vaginal epithelium or increase HIV risk.

Administration: The gel is applied vaginally up to one hour before each act of intercourse, providing pericoital contraception that is entirely user-controlled and hormone-free.[15]

Efficacy data

Table 4: Phase 3 AMPOWER study results (single-arm, open-label, multicenter, ages 18–35).

Outcome	Result
7-cycle cumulative pregnancy rate (typical use)	13.7% (95% CI: 10.0–17.5%)
User satisfaction	>80% "very satisfied" or "satisfied"

Sexual satisfaction outcomes

A post-hoc analysis of the AMPOWER study, published in the Journal of Sexual Medicine, examined patient-reported outcomes related to sexual satisfaction.[16] 85.8–98.4% of women reported same or improved sexual satisfaction scores compared to baseline, and 93.6% reported their sex life was improved or maintained (mean impact-on-sex-life score improved significantly, $p < 0.001$). Significant improvements ($p < 0.005$) were seen in 7 of 10 Sexual Function Questionnaire domains, including vaginal dryness, lack of sexual interest/desire, vaginal tightness, pain, anxiety, inability to orgasm, and vaginal bleeding/irritation. Mean Female Sexual Function Index (FSFI) scores also improved significantly from baseline to Visit 5 ($p = 0.037$).[16]

Safety profile

The most common adverse event was vulvovaginal burning sensation (20.0%). Cases of cystitis, pyelonephritis, and upper urinary tract infections were reported in 0.36% of participants, with one serious case of pyelonephritis resulting in hospitalization.[15] Consequently, the product is not recommended for women with a history of recurrent urinary tract infections or urinary tract abnormalities.[15]

Multipurpose prevention technology (MPT) potential

Phexxi's mechanism of maintaining acidic vaginal pH may also provide protection against sexually transmitted infections, since the acidic environment is inhospitable to several bacterial and viral pathogens. Phase 2B/3 studies demonstrated a 50% relative risk reduction for chlamydia and an 80% relative risk reduction for gonorrhea; a Phase 3 trial for chlamydia and gonorrhea prevention is ongoing (NCT04553068).[15]

EMERGING MALE CONTRACEPTIVE TECHNOLOGIES

The unmet need in male contraception

Male contraceptive options remain limited. The two mainstays, condoms (typical-use failure rate ~13%) and vasectomy, are highly effective but neither combines high efficacy with reliable, on-demand reversibility, and vasectomy reversal success rates decline over time.[20] Two non-hormonal candidates in earlier-stage development illustrate alternative approaches: Vasalgel, a polymer hydrogel vas occlusion device shown to be reversible in a rabbit model;[17] and RISUG (Reversible Inhibition of Sperm Under Guidance), an intravasal, one-time injectable polymer that has progressed through clinical safety and efficacy evaluation in India and is described as having moved from bench to bedside.[18,19] An ideal male contraceptive would combine high efficacy, rapid onset, reliable reversibility, and minimal side effects — characteristics that have proven challenging to achieve.

Ultrasound-induced self-clearance hydrogel

Wang and colleagues (2022) developed an ultrasound-responsive hydrogel system for reversible male contraception, published in ACS Nano.[20]

The hydrogel formulation consists of sodium alginate conjugated with reactive oxygen species (ROS)-cleavable thioketal (SA-tK), which provides the primary structural framework and confers responsiveness to oxidative environments. Titanium dioxide (TiO_2) nanoparticles are incorporated as ROS generators upon ultrasound stimulation, enabling controlled degradation of the thioketal linkages. Hydrogel formation is triggered by calcium chloride ($CaCl_2$), which induces ionic crosslinking of the alginate chains, resulting in a stable three-dimensional network.[20]

Contraception mechanism: The liquid precursor mixture is injected into the vas deferens, where it transforms into a hydrogel within 160 seconds. The formed hydrogel physically blocks the vas deferens, inhibiting sperm motility and providing effective contraception.[20]

Reversal mechanism: When fertility is desired, noninvasive therapeutic ultrasound is applied to the site. Ultrasound exposure causes TiO_2 nanoparticles to generate reactive oxygen species, which cleave the thioketal linkages in SA-tK, destroying the hydrogel network and restoring fertility.[20] Diagnostic ultrasound (22 MHz) can monitor both the occlusion and recanalization processes in real time.[20]

Efficacy data

Table 5: Ultrasound-responsive hydrogel — efficacy data.

Outcome	Result
Gel formation time	<160 seconds
Fertility restoration rate	100% following ultrasound treatment
Monitoring capability	Real-time via diagnostic ultrasound

Advantages and remaining challenges

- **Advantages:** non-invasive reversal (no second surgery required); real-time monitoring capability; on-demand reversibility when fertility is desired; potential for outpatient administration.
- **Challenges:** requires specialized ultrasound equipment for reversal; long-term safety of TiO_2 nanoparticles in the reproductive tract is unknown; further preclinical and clinical validation needed.

COMPARATIVE ANALYSIS AND TECHNOLOGY READINESS

Technology readiness levels

Table 6: Technology readiness comparison.

Technology	Mechanism	User control	Invasiveness	Reversibility	Current stage
DARE-LARC1	Programmable electronic	High (wireless)	Moderate (implant)	Removal required	Preclinical
SLIM	Self-assembling microcrystals	Low (constant release)	Low (25G needle)	Retrievable	Preclinical
LMN microneedles	Transdermal patch	High (self-apply)	Minimal	N/A	Preclinical (animal)
Phexxi	Vaginal pH regulator	High (pericoital)	None	Immediate	FDA-approved (2020)
Ultrasound hydrogel	ROS-cleavable hydrogel	Low (one-time)	Moderate (injection)	100% reversible	Preclinical

Comparative efficacy

Table 7: Comparative efficacy across technologies.

Technology	Efficacy measure	Result
Phexxi	7-cycle pregnancy rate	13.7% (typical use)
SLIM (rat study)	Duration	>3 months
LMN (rat study)	Implantation sites	0.5 ± 0.55
Ultrasound hydrogel (animal)	Fertility restoration	100%

User acceptability considerations

The AMPOWER study of Phexxi provides the most robust user-acceptability data among these technologies: more than 80% of women reported satisfaction, 93.6% reported improved or maintained sex life, and improvements were seen across multiple sexual function domains.[16]

For injectable technologies, needle gauge is a critical acceptability factor, since patient acceptance increases as needle size decreases, likely because smaller needles cause less bruising and bleeding.[10] The SLIM system's compatibility with 25-gauge needles represents a significant advantage over existing ISFIs, which typically require 18–20-gauge needles.

FUTURE DIRECTIONS

Closed-loop fertility monitoring and drug delivery

The next frontier in smart contraception involves integrating biosensors for real-time fertility monitoring with automated drug delivery. Potential sensing modalities include hormonal sensors for real-time detection of luteinizing hormone, estrogen, or progesterone to predict ovulation; continuous basal body temperature monitoring; and vaginal or cervical electrical impedance changes across the menstrual cycle.

A concrete step in this direction is the development of a wearable aptamer-based nanobiosensor for non-invasive monitoring of female reproductive hormones,[22] illustrating the kind of continuous, non-invasive sensing that could eventually be coupled to on-demand release platforms such as DARE-LARC1 or SLIM. A truly closed-loop system would detect the fertile window and automatically trigger drug release, or prompt the user to activate contraception, potentially achieving efficacy comparable to LARC with user control similar to on-demand methods.

Multipurpose prevention technologies (MPTs)

The dual public health burdens of unintended pregnancy and sexually transmitted infections create a strong rationale for MPTs — single products providing simultaneous contraception and STI prophylaxis. Phexxi's potential for chlamydia and gonorrhea risk reduction demonstrates the feasibility of this

approach,[15] and broader nanotechnology platforms developed for global infectious disease prevention and treatment offer a template for combination delivery.[23] Future MPTs could combine hormonal contraception with HIV PrEP (e.g., dapivirine or cabotegravir), non-hormonal contraception with broad-spectrum antivirals, or physical barrier methods with sustained drug release.

Male contraceptive development

The ultrasound-responsive hydrogel, alongside RISUG and Vasalgel, represents a proof-of-concept for reversible, non-hormonal male contraception, but significant work remains. Priority areas include translation to humans (safety and efficacy studies in men), alternative reversal triggers (light, magnetic fields, or endogenous biochemical signals), and combination approaches pairing hormonal and physical methods for enhanced efficacy.

Access and equity considerations

Several technologies discussed in this review have been developed with low-resource settings in mind; the Gates Foundation's funding of SLIM reflects this priority.[9] Key access considerations include self-administration, which eliminates the need for healthcare infrastructure (SLIM, LMNs); long duration, which reduces visit frequency for resupply (DARE-LARC1, SLIM); low manufacturing cost, aided by SLIM's minimal polymer content; and non-hormonal options such as Phexxi, which provide an alternative for women with contraindications or preference.

CONCLUSION

The field of smart contraceptive technology is rapidly evolving, with several promising approaches at different stages of development. Programmable electronic implants (DARE-LARC1) offer unprecedented user control over multi-decade durations but require surgical insertion and face complex regulatory pathways. Self-assembling injectable microcrystals (SLIM) address a key limitation of existing long-acting injectables — the need for large-gauge needles — through a solvent-exchange mechanism that enables self-administration. Microneedle systems provide painless transdermal delivery with improved patient compliance, though current formulations are limited to short durations. The FDA-approved vaginal pH regulator Phexxi demonstrates that non-hormonal, on-demand approaches can achieve acceptable efficacy with high user satisfaction and potential STI protection. Finally, ultrasound-responsive hydrogels, alongside RISUG and Vasalgel, offer a glimpse of reversible male contraception that may help overcome the efficacy-reversibility trade-off of existing methods.

Significant challenges remain, including regulatory pathways for combination products, long-term safety data, and manufacturing scale-up. Nonetheless, the diversity of approaches in development suggests that the future contraceptive landscape will offer more choices than ever before, empowering individuals to select methods aligned with their fertility intentions, lifestyle, and values.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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