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REVIEW ARTICLE

Application of electrospun fibers for female reproductive health

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Abstract Here, we present the current challenges in women's reproductive health and the current state-of-the-art treatment and prevention options for STI prevention, contraception, and treatment of infections. We discuss how the versatile platform of electrospun fibers can be applied to each challenge, and postulate at how these technologies could be improved. The void of approved electrospun fiber-based products yields the potential to apply this useful technology to a number of medical applications, many of which are relevant to women's reproductive health. Given the ability to tune drug delivery characteristics and three-dimensional geometry, there are many opportunities to pursue new product designs and routes of administration for electrospun fibers. For each application, we provide an overview of the versatility of electrospun fibers as a novel dosage form and summarize their advantages in clinical applications. We also provide a perspective on why electrospun fibers are well-suited for a variety of applications within women's reproductive health and identify areas that could greatly benefit from innovations with electrospun fiber-based approaches.

Keywords Electrospun fibers · Contraception · STIs · Infection · Treatment · Prevention · Female reproductive health

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Current challenges in women's reproductive health

Reproductive health is a crucial part of general well-being and is particularly important for women, especially during their reproductive years. According to the World Health Organization (WHO), one third of health issues for women between the ages of 15 and 44 years are associated with sexual and reproductive health. Contraception, infertility, menopause, gynecologic cancers, and sexually transmitted infections (STIs) including human immunodeficiency virus (HIV) are the most common reproductive health concerns for women [1–4]. In particular, STIs and HIV/AIDS have disproportionally affected women worldwide. More than one million STIs are acquired every day, and there are an estimated ~500 million new infections of curable STIs (chlamydia, gonorrhea, syphilis, and trichomoniasis) each year [5–7]. Over 500 million people are living with incurable genital herpes simplex virus (HSV) infection [8], and approximately 300 million women are infected with human papillomavirus (HPV) [6]. STIs can also cause serious consequences for women's health including adverse birth outcomes, cervical cancer, and infertility [6, 9]. Women are also at greater risk of being infected with HIV during sex. Worldwide, nearly half of all individuals living with HIV are now women. In sub-Saharan Africa in 2014, women comprised 59% of the adults living with HIV [2]. Women bear the greatest burden of reproductive health problems; thus, empowering women through education and tools to control their reproductive health are an essential element to improve their lives.

Electrospun fibers for medical applications

In this section, we provide an overview of the versatility of electrospun fibers as a novel dosage form and summarize their

advantages in clinical applications. We also provide a perspective on why electrospun fibers are well-suited for a variety of applications within women's reproductive health and identify areas that could greatly benefit from innovations with electrospun fiber-based approaches (Fig. 1).

Electrospun fibers: a versatile, solid dosage form for biomedical applications

The process of using an electric field to pull a polymer solution into fibers dates back to the 1930s [10] and was later described as "electrospinning" by Reneker et al. [11]. Electrospinning has since been widely explored for biomedical applications including drug delivery and tissue engineering. A number of electrospun fiber-based products are in clinical trials and include a hemostatic wound dressing [12], a transdermal patch for treatment of leishmaniasis ulcers [13], and a patch for treatment of diabetic ulcers [14]. However, there is not yet an electrospun fiber-based product that has been approved by the FDA. Several reviews focus on electrospun fibers for biomedical applications beyond the depth of this review [15, 16].

The wide variety of polymers that can be electrospun allow for a broad design space. Many of the commonly used polymers are generally recognized as safe (GRAS) by the FDA, which could potentially ease progression into pre-clinical and clinical studies [17]. Fibers can be tailored to dissolve in seconds [18], or biodegrade over the course of months [19]. In addition, fibers have been shown to encapsulate an array of small molecules [20], nucleic acids [21, 22], and protein drugs [23, 24] that greatly expand their applications for treatment and prevention of disease [25]. Electrospinning is a proven way to achieve high drug loading of therapeutics into a solid dosage form. Furthermore, it is possible to control the architecture at both the fiber and macroscopic levels such as fabricating core-sheath morphologies [26], multilayered composites of drugs and polymers [27, 28], and various three-dimensional geometries [29]. Finally, the scale-up production of electrospun fibers has been accelerated by developments made in industries such as filtration technologies, and there are commercially available instruments that produce fibers at rates up to three orders of magnitude higher than laboratory scale electrospinning rigs [30]. The versatility of the fiber platform provides opportunities to formulate dosage forms that can be effectively used in diverse biomedical applications.

How do fibers fill a gap within women's reproductive health?

The void of approved electrospun fiber-based products yields the potential to apply this useful technology to a number of medical applications, many of which are relevant to women's reproductive health. Given the ability to tune drug delivery characteristics and three-dimensional geometry, there are many opportunities to pursue new product designs and routes of administration for electrospun fibers. For example, electrospun fibers have been used as coatings for tissue engineering implants to reduce inflammation and calcification on

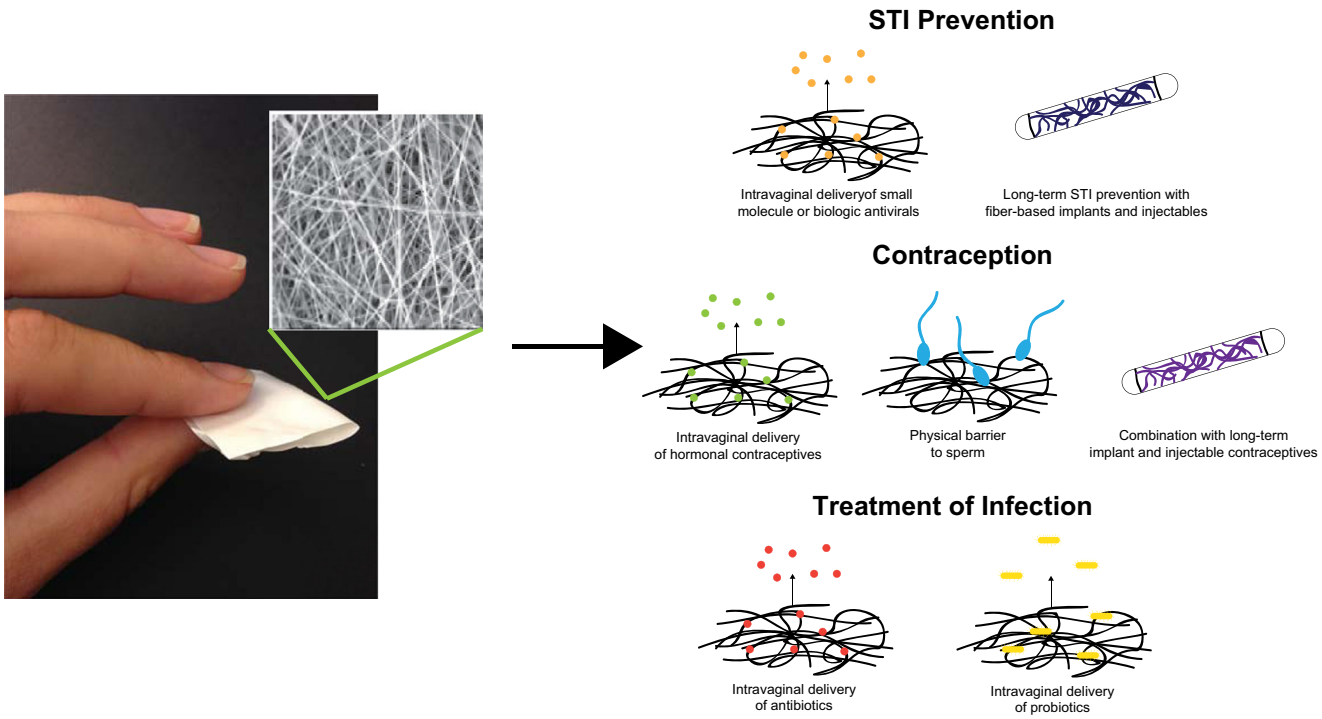

Fig. 1 Schematic of electrospun fiber-based dosage concepts for applications in women's reproductive health.

vascular grafts [31] and prevent formation of biofilms [32]. Similar coating approaches of implants commonly used in the realm of women's reproductive health such as intrauterine devices or subcutaneous contraceptive implants could augment their functionality and efficacy. Next, we discuss the three main categories of women's reproductive health that we identified as most conducive to innovations with electrospun fibers: prevention of sexually transmitted infections, contraception, and treatment of infections. For each category, we discuss the current state-of-the-art, including what products, if any, are approved and available. Then, we discuss how electrospun fibers have been applied to certain challenges within each category. Finally, we draw on parallel, relevant examples of applications of electrospun fibers, and postulate on how these ideas and findings might be applied to challenges in women's reproductive health.

Electrospun fibers for female reproductive challenges: current state-of-the-art, applications, and future directions

Prevention of sexually transmitted infections

Current state of STI prevention

STIs, including HIV, have a significant impact on women's sexual and reproductive health worldwide. More effective approaches are urgently needed for the prevention and control of STIs. The current STIs and HIV prevention strategies include education [33], abstinence [34], mutual monogamy [35], vaccination (hepatitis B, HPV) [36, 37], barrier methods (condom) [38], male circumcision [39], and pre-exposure prophylaxis (PrEP) for HIV [40, 41] (Table 1) . Although correct and consistent use of condom is highly effective in reducing STDs transmission, it is a male-controlled prevention method [42, 43]. Due to social, gender, and economical inequities, female-controlled STI/HIV prevention strategies such as topical microbicides are desirable alternatives to protect women [44]. Microbicides will fill an important gap in current prevention strategies by empowering women with a discreet tool against STIs/HIV [3, 45, 46].

Electrospun fibers for STI prevention

To date, the use of fibers as a modality for preventing sexually transmitted infections has primarily focused on intravaginal delivery of small molecule drugs and proteins for HIV-1 and HSV-2 inhibition. Ball et al. formulated fibers from poly-L-lactic acid (PLLA) and polyethylene oxide (PEO) to independently deliver maraviroc (MVC), a CCR-5-mediated entry inhibitor of HIV, 3′-azido-3′-deoxythymidine (AZT), a reverse transcriptase inhibitor of HIV, and acyclovir (ACV), which has been shown to have activity against HSV-2 [20]. These formulations achieved both burst and sustained release of all three compounds in vitro, and MVC and AZT eluted from the fibers were found to maintain antiviral activity against HIV-1 BaL, while activity of eluted acyclovir was not tested. However, Aniagyei et al. have shown release of ACV from poly(lactic-co-glycolic) acid (PLGA) and poly(lactide-co-caprolactone) (PLCL) over the course of 28 days and observed complete viral inhibition with eluted doses of 1–200 μg/mL [48]. Carson et al. showed programmable release of tenofovir (TFV), AZT, MVC, and raltegravir (RAL) from fibers composed of blends of PLGA and polycaprolactone (PCL) [49]. Huang et al. developed pH-responsive electrospun fibers composed of cellulose acetate phthalate (CAP) and loaded with etravirine (ETR). These fibers maintained their integrity at normal vaginal pH of 4.5, but dissolved and release drug upon exposure to semen (pH 7.4–8.4) [50]. Blakney et al. found that release of TFV from polyvinyl alcohol (PVA) fibers could be hindered by increasing fiber mat thickness or incorporating another hydrophobic small molecule drug into the fiber matrix [27]. Krogstad

Table 1 Strategies for STIs/HIV prevention [3, 47].

Strategies	Pros	Cons
Education/advocacy	Reduce sexual risk behaviors	More effective interventions are needed
Abstinence	The only guaranteed way to prevent STIs	Not widely accepted
Condom	Easy to use, reduce STIs	Male controlled
Vaccination	Long-term protection	Only available for HBV, HPV
PrEP (Truvada)	Reduce the risk of getting HIV-1 infection	Costly, requires a prescription and adherence, systemic dosing
Microbicide including electrospun fiber loaded with antibiotics or antiviral drugs	Easy to use, topical administration, women controlled	No effective microbicide available yet

et al. explored the scale-up of TFV-loaded PVA fibers from a laboratory-scale instrument to a production-scale instrument and found that fibers could be loaded with up to 60 wt.% TFV when the drug was solubilized in the polymer solution by adding sodium hydroxide [30]. Non-commercially available PLGA-based polyurethane polymers have also been electrospun with TFV for sustained release in vitro [51]. MVC has been formulated into both coaxial electrospun fibers with an ethylcellulose core and polyvinylpyrrolidone (PVP) shell [26], as well as amorphous solid dispersions in PVP and PEO [52]. Grooms et al. investigated the effect of incorporating griffithsin (GRFT), a protein that has been shown to have potent activity against both HIV-1 and HSV-2, by grafting the biologic onto the surface of electrospun fibers, as opposed to encapsulating GRFT within the fiber [53]. As opposed to using drug-eluting fibers to prevent infection, Huang et al. coated polystyrene fibers with poly(allylamine hydrochloride) (PAH) or dextran sulfate sodium (DSS) and observed inactivation of HIV-1 and a reduction of CD4+ TZMbl cells in the presence of replication competent HIV-1 [54]. Despite a multitude of formulations that have been investigated for prevention of HIV-1 and HSV-2, in vivo efficacy studies have yet to be reported. Overall, these studies illustrate the versatility of electrospun fibers to encapsulate both physicochemically diverse small molecule drugs, as well as biologics, for preventative drug delivery, and warrant further studies of these formulations.

Future directions of STI prevention

While electrospun fibers have been widely investigated for intended use as vaginal drug delivery systems, it may also be possible to incorporate drug-loaded fibers into implantable or injectable devices for long-acting prevention of STIs. Recently, two devices for delivery of tenofovir alafenamide fumarate (TAF) have been developed as a dermal implant for long-term HIV prevention. Schlesinger et al. achieved a 90-day linear release of TAF from an implantable with a TAF core surrounded by a thin-film PCL membrane [55]. Similarly, Gunawardana fabricated a silicone implant with a TAF core and PVA membrane and observed continuous release over 40 days in a pharmacokinetic study in beagles [56]. Electrospun fibers can be fabricated to exhibit similar mechanical characteristics as thin films but can typically incorporate a higher drug loading and combinations of physicochemically diverse drugs unachievable by films and could potentially be formulated to achieve long-acting release rates upon incorporation into an implant. The wide array of antiretroviral drugs that have been formulated in electrospun fibers could potentially be applied to an implant for long-acting prevention of HIV-1, HSV-2, or other sexually transmitted infections that can be prevented by small molecule drugs or biologics.

Contraception

Current state of contraception

Effective contraception prevents unintended pregnancy and reduces the need for abortion. According to the WHO, 67% of women who practice contraception currently use non-permanent methods such as hormonal contraceptives (the pill, patch, implant, injectable, and vaginal ring), intrauterine devices (IUD), and condoms [57] (Table 2). However, as of 2014, an estimated 225 million women in developing countries were not using any method of contraception due to either lack of resources or other socioeconomic reasons [58–61]. Every year, 52 million unintended pregnancies in developing regions could be averted if all unmet needs for discreet and female-controlled methods of contraception were met [61, 62]. Safe and long-acting reversible contraception may be the ideal first option for most women.

Electrospun fibers for contraception

Electrospun fibers have been investigated for contraceptive indications with formulations for vaginal drug delivery as both physical and chemical barriers. Ball et al. used a combination of PLLA and PEO loaded with 1 or 10 wt.% glycerol monolaurate (GML), a surfactant that is known to inactivate lipid-coated viruses but was also found to inhibit sperm motility in a dose-dependent manner [20]. Furthermore, electrospun fibers without any loaded drug were found to act as a physical barrier to sperm when fabricated at a thickness of >150 μm. Although fiber-based fabrics are porous with pores on the size of >3 μm diameter, the sperm were unable to penetrate through the materials likely due to the tortuous path created by the intermingling network of fibers. Blakney et al. loaded levonorgestrel (LNG), a hormonal contraceptive used in oral contraceptives, intrauterine devices, implants, and intravaginal rings, into both PVA and PLGA-based polyurethane fibers [27, 51]. The PVA fibers were found to release in vitro doses of LNG up to 50 mg within 1 h, rendering this formulation more suitable for an on-demand contraceptive option. On the contrary, the PLGA-polyurethane fibers loaded with LNG were found to sustain release for at least 3 days, with a total release predicted to occur after 14 days. These studies show the capacity of electrospun fibers to prevent unintended pregnancy by a variety of mechanisms, including chemical sperm inhibition, acting as a physical barrier, and delivery of small molecule hormonal contraceptives.

Future directions of contraception

There are many diverse dosage forms currently available for contraception including oral pills, intrauterine devices, intravaginal rings, injectables, implants, and spermicides. The electrospun fibers that have been developed to date with an

Table 2 Comparison of current and potential reversible contraception

Methods	Failure rate[a]	Advantages	Disadvantages
1. Hormonal birth control (HBC)			
Implant	0.05%	Most effective, long lasting	Prescription is required
Injectable	6%	Long lasting	Requires adherence (pill)
Pill	9%	Easy to use	Hormone over dose (patch)
Patch	9%	Easy to use	Requires surgery (implant)
Ring	9%	Long lasting	Needle involved (injectable)
			Potentially unwanted side effects [63–67]: bleeding, blood clot, migraine headaches, breast/uterine/cervical cancer, cardiovascular risk
2. Intrauterine devices (IUDs)	0.2–0.8%	Most effective, long lasting, topical use	Risk of uterine perforation and infection during procedure, bleeding
3. Diaphragm	12%	Easy to use	Requires spermicide, messy
4. Condom	18%	Easy to use, cheap, no prescription	Male controlled, less effective
5. Spermicide	28%	Easy to use, cheap, no prescription	Toxic, messy, less effective
Electrospun fiber with or w/o hormone	N/A	Topical use, tunable release of hormone, physical barrier to sperm, women controlled	Not yet commercially available

[a] The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method

indication for contraception have either been proof-of-concept or intended for vaginal delivery. However, the versatility of fibers lends this technology to a variety of dosage forms and routes of administration. For example, injectable fibers have been developed for applications in tissue engineering as a cell scaffold [68, 69]. The aforementioned PLGA-based polyurethane fibers may be particularly well-suited to be used as an implant as they could be tailored to release LNG over the course of many months but may improve the current dosage form by eradicating the need for removal of the implant, as the polyurethane polymers are biodegradable [51]. There is also a void in permanent contraception options for women who no longer wish to conceive. While there have been numerous studies using tablets and intrauterine devices to deliver sclerosing agents to the uterotubal junctions for tubal occlusions, none of these devices have achieved reproducible efficacy with just a single administration [70, 71]. One of the main challenges with this method is that there is often inadequate exposure of the sclerosing agents at the uterotubal junction. This could potentially be overcome by pairing electrospun fibers, which have been previously loaded with known sclerosing agents such as doxycycline [72] and tetracycline [73], with an IUD frame to achieve a longer, more consistent exposure of the agent at the uterotubal junction to improve overall efficacy. However, the combination of electrospun fibers with other technologies, such as an IUD or IVR, may alter drug release rate from the fibers or require special safety evaluation for the combined dosage form. While there is currently a diverse array of female contraceptive options available, electrospun fibers may enhance the convenience and functionality of current dosage forms.

Treatment of reproductive tract infections

Current state of treatment of reproductive tract infections

Common bacterial and parasitic STIs such as gonorrhea, chlamydia, syphilis, bacterial vaginosis, and trichomoniasis can be treated with antibiotics given either orally or by intramuscular injection. Vaginal yeast infection can also be treated by non-prescription creams [74]. Although there is no cure for viral STIs including HSV, HPV, hepatitis B virus (HBV), and HIV, these viral infections can be controlled by antiviral drugs [75]. Infection of HPV and HBV can be prevented by vaccination [76], and HIV can be treated and controlled by highly active antiretroviral therapy (HAART). HAART has significantly improved the quality of life of people living with HIV and reduced the risk of transmission [77].

Electrospun fibers for treatment of infections

Electrospun fibers have been formulated for the treatment of two common infections in the context of women's reproductive health: bacterial vaginosis (BV) and yeast infections (candidiasis). Fibers offer considerable advantages compared to the currently available dosage forms for both BV and yeast infections, which are typically treated with oral tablets/gels, including

localized drug delivery, potentially limiting side effects, and less leakage from the vaginal tract upon administration. Sharma et al. formulated mucoadhesive PVA nanofibers with fluconazole, an antifungal small molecule drug, which were shown to have activity against *Candida albicans* while having no effect on *Lactobacillus acidophilus* cultures, which are important for maintaining normal vaginal pH and health [78]. Other formulations have also been fabricated for oral candidiasis, which could also potentially be used as a vaginal dosage form [79]. While not intended specifically for bacterial vaginosis treatment, a number of fiber formulations of the two most common small molecule antibiotics used for treatment of BV, metronidazole [80–83], and clindamycin [84, 85] have been fabricated. The fibers were specifically formulated for periodontitis, but similarities between the oral cavity and vaginal reproductive tract may facilitate the use of these formulations for a more effective treatment of BV. These studies exhibit the advantages of fiber systems for local treatment of vaginal infections including BV and candidiasis, which may minimize the required drug dose and limit systemic exposure and potential side effects.

Future directions of infection treatment

In proof-of-concept studies, electrospun fibers have been formulated for vaginal delivery of antibacterial or antifungal agents intended for treatment of BV or candidiasis. Recurring BV can be a formidable clinical challenge to clear, often requiring repeated doses of antibiotics. An alternative treatment that has gained traction is the administration of beneficial strains of bacteria to equilibrate the vaginal microbiome back to its normal state. Reid et al. showed that oral administration of *L. rhamnosus* and *L. fermentum* probiotics eradicated BV in seven out of 11 patients [86]. Hallen et al. administered *L. acidophilus* vaginally and found that 16 of 28 women had normal test results following treatment, but noticed that this strand of bacteria did not adhere to the vaginal walls [87]. This treatment could be improved by using a mucoadhesive fiber matrix to increase the residence time of the administered probiotics within the vaginal cavity. Probiotic bacteria have previously been encapsulated into electrospun fibers [88–92], with viability immediately after the electrospinning process and up to 130 days when stored at 4 °C. Nagy et al. incorporated *L. acidophilus* bacteria into PVA and PVP fibers, which showed long-term storage stability of the encapsulated bacteria and postulated that their biohybrid nanowebs could at as a dosage for treatment of BV, but did not test the efficacy of the fibers [93]. Incorporating bacteria post-electrospinning is another technique that could be used to produce bacteria-laden fiber doses for treatment of infections, which may offer a greater bacterial viability than encapsulation [94]. This strategy could be used to treat BV and also potentially reduce the risk of infections that are known to have increased risk with a disrupted vaginal microbiome such as HIV [95], gonorrhea [96], or chlamydia [96]. Overall, encapsulation of small molecule drugs and/or probiotics into electrospun fibers may improve the treatment of infections in women, including BV and related opportunistic infections.

Perspective

Electrospun fibers have many advantages as a drug delivery system, including tunable drug release and the ability to encapsulate a wide variety of therapeutic agents and are poised to impact the challenges currently faced in women's reproductive health. This versatility may also enable the development of multipurpose prevention technologies (MPTs). The intention for these devices is to prevent multiple indications in a single dosage, including unintended pregnancy, HIV, and/or other STIs. MPTs are currently being investigated in the form of intravaginal rings [97], gels [98], and fibers [27] and have the potential to provide a new convenient prevention option for women in both developed and developing countries worldwide. MPTs are a particularly promising platform for progress in women's reproductive health, and as an adaptable drug delivery system, electrospun fibers may enable the development of products that improve the health of women worldwide. Though electrospun fibers have enormous potential as a drug delivery platform, they have yet to be approved as a commercially available dosage form. Current electrospinning technology must be augmented to meet the production capabilities needed for a commercial product, and these materials must be evaluated for safety and efficacy through clinical trials in order to fill voids in female reproductive health.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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