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Biomaterials and Contraception: Promises and Pitfalls

ISABELLA CLAURE,[1] DEBORAH ANDERSON,[2,3] CATHERINE M. KLAPPERICH,[1,4,5] WENDY KUOHUNG,[2] and JOYCE Y. WONG[1,5]

[1]Departments of Biomedical Engineering, Boston University, Boston, MA 02215, USA; [2]Obstetrics and Gynecology, Boston University, Boston, MA 02215, USA; [3]Medicine, Boston University, Boston, MA 02215, USA; [4]Mechanical Engineering, Boston University, Boston, MA 02215, USA; and [5]Division of Materials Science and Engineering, Boston University, Boston, MA 02215, USA

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Abstract—The present state of reproductive and sexual health around the world reveals disparities in contraceptive use and effectiveness. Unintended pregnancy and sexually transmitted infection transmission rates remain high even with current prevention methods. The 20th century saw a contraceptive revolution with biomedical innovation driving the success of new contraceptive technologies with central design concepts and materials. Current modalities can be broadly categorized according to their mode of function: reversible methods such as physical/chemical barriers or hormonal delivery devices *via* systemic (transdermal and subcutaneous) or localized (intrauterine and intravaginal) administration, and nonreversible sterilization procedures such as tubal ligation and vasectomy. Contraceptive biomaterials are at present dominated by well-characterized elastomers such as polydimethylsiloxane and ethylene vinyl acetate due to their favorable material properties and versatility. Contraceptives alter the normal function of cellular components in the reproductive systems to impair fertility. The purpose of this review is to highlight the bioengineering design of existing methods, explore novel adaptations, and address notable shortcomings in current contraceptive technologies.

Keywords—Barrier technologies, Hormonal delivery devices, Bioengineering design, STI prevention, Reproductive health.

ABBREVIATIONS

SARC	Short-acting reversible contraception
LARC	Long-acting reversible contraception
MPT	Multipurpose prevention technologies
IUD	Intrauterine device
IVR	Intravaginal ring
STI	Sexually transmitted infection
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
GnRH	Gonadotropin releasing hormone
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
CFTR	Cystic fibrosis transmembrane conductance regulator
LB	Lactobacillus
PDMS	Polydimethylsiloxane
PVA	Polyvinyl alcohol
PEG	Polyethylene glycol
PVP	Polyvinylpyrrolidone
PEVA	Polyethylene vinyl acetate
PET	Polyethylene terephthalate
RISUG	Reversible inhibition of sperm under guidance
SMA	Styrene maleic anhydride

Address correspondence to Joyce Y. Wong, Departments of Biomedical Engineering, Boston University, Boston, MA 02215, USA. Electronic mail: jywong@bu.edu

INTRODUCTION

Inadequate solutions for reproductive health are a global issue continuing to affect women and men despite significant advances in medical device development. Currently forty percent of pregnancies worldwide are unplanned, and the World Health Organization estimates that 214 million women of reproductive age in developing countries who want to avoid pregnancy are not using a modern contraceptive method.[163] Barriers to prevention are typically lack of

information, access, and limited choice of methods. Concurrently, more than a million new sexually transmitted infections caused by the four leading bacterial and parasitic pathogens (chlamydia, gonorrhea, syphilis, and trichomoniasis) are estimated to occur daily worldwide.[132] The sexual transmission of viral STIs such as HIV and Herpes Simplex virus is not tracked systematically, but as the prevalence of these viruses is very high in the general population the rate of transmission of these viruses no doubt exceeds one million/year.[164] Preventative devices are important for sexual health and should encourage safe sex practice. Altogether, there exists an unmet need in reproductive and sexual wellness that has not been fully satisfied by modern contraceptive technologies due to method underuse or failure.

Contraceptive use and choice are subject to various considerations. A multitude of contraceptive methods, outlined in Table 1, are currently available on the market, differing in site of administration, effectiveness, and duration of use. Commercially available methods are disproportionately marketed toward cisgender females. A woman's age, socioeconomic status, cultural norms, marital status, childbearing goals, and personal health will dictate contraceptive suitability and use. While this review predominantly explores cisgender female-directed contraceptives, male and non-binary contraception is discussed, and its importance cannot be overstated.

Biomaterials play an important role in contraceptive design. Current contraceptive devices incorporate a multitude of materials (Table 2), with elastomers being used in many of these technologies. Elastomers are viscoelastic polymers characterized by low Young's moduli and high yield strains.[103] The major classes of elastomers are physically or chemically cross-linked with emergent properties tuned during synthesis and fabrication to suit the application. Importantly, elastomers have low production costs as well as established and well-characterized biocompatibility with male and female reproductive systems.[27,36] This review will explore the use of elastomers and other materials in contraceptives and their synthesis and material properties as it pertains to contraceptive action (Table 3). We are unaware of such a review in the literature comprehensively examining the intersection of biomaterials science and engineering and assessment of contraception performance. Recent advances in biomaterials science and engineering and nanotechnology provide a rich opportunity to re-assess contraceptive design from an integrated biomaterials and reproductive health perspective.

TABLE 1. Overview of contraceptive devices.

Product	Anatomical site	Cell behavior affected	Efficiency[a]	Duration of use
Barrier devices				
Male condom	Penis	Sperm migration	82–98%	One-time
Female condom	Vagina	Sperm migration	79–95%	One-time
Diaphragm w/ spermicide	Cervix	Sperm migration and death	92–94%	24 h
Cervical Cap w/ spermicide	Cervix	Sperm migration and death	92–96%	48 h
Spermicidal devices				
Sponge w/ spermicide	Cervix	Sperm migration and death	88–91%	24 h
Gel/Film/suppository w/ spermicide	Vagina	Sperm migration and death	72–82%	1–3 h
Intrauterine device (Inert)	Uterine cavity	Sperm death, Endometrial inflammation	> 99%	10 years
Hormonal devices				
Patch	Buttock, arm, abdomen	Endocervical mucus secretion	91–99.7%	1 week
Intravaginal ring	Vagina	Endocervical mucus secretion, Endometrial atrophy, Fallopian epithelium quiescence	91–99.7%	3 weeks
Implant	Arm	Endocervical mucus secretion, Endometrial atrophy, Fallopian epithelium quiescence	> 99%	3–5 years
Intrauterine device (Hormonal)	Uterine cavity	Endocervical mucus secretion, Endometrial atrophy, Fallopian epithelium quiescence	> 99%	3–5 years
Sterilization				
Tubal ligation	Fallopian tubes	Fallopian tissue necrosis, Fibrosis	99.5%	Permanent

[a]Range due to typical and perfect use.[152]

TABLE 2. Biomaterials utilized in recent contraceptive devices.

Contraceptive device	Biomaterial(s)
Barrier	
Male condom	Rubber latex[a], Polyurethane[a]
Female condom	Nitrile[a]
Diaphragm	Silicone[a]
Cervical cap	Silicone[a]
Spermicidal	
Sponge	Polyurethane[a]
Gel	PVP
Film	PVA[a], PEG[a]
Suppository	PEG[a]
Inert IUD	Polyethylene (Frame)
Hormonal	
Patch	Polyisobutene
Implant	PEVA[a]
IVR	PEVA[a]
Hormonal IUD	Silicone[a], Polyethylene (Frame)
Sterilization	
Filshie clip	Titanium
Falope ring	Silicone[a]
Essure	PET

[a]Indicates an elastomeric material.

TABLE 3. Relevant biomaterial properties for existing contraceptive actions.

Contraceptive action	Biomaterial properties
Barrier (short-term)	Tensile strength, Elasticity, Lubricity, Toxicity
Barrier (long-term)	Bioadhesion, Degradability, Durable, Toxicity
Hormone delivery	Permeability, Durable, Toxicity
Spermicidal delivery	Flexibility, Bioadhesion, Degradability, Viscosity, Toxicity
Sperm targeting	Viscosity, pH, Toxicity

REPRODUCTIVE SYSTEM BACKGROUND

Within the scope of contraception, there are many points of intervention, the nature of which impact the design and success of prevention technologies. In consideration of current contraceptive device design and cell impact, the binary reproductive systems most typically found in cisgender women will be discussed. For the sake of clarity, the 'female reproductive system' is the most commonly used term, but we note that the ''uterine reproductive system'' is inclusive of anyone with the ability to become pregnant, including transgender men and non-binary people. The status of male contraception has been reviewed recently.[85] Although innovative strategies including hormonal and non-hormonal methods are under development, male contraception technology lags that of females. The absence of effective and reversible male-centric contraceptive devices contributes in part to the gaps in reproductive wellness.

The female reproductive system (Fig. 1) is specialized to assist meeting of a mature egg and sperm and to support fertilized egg development. The reproductive tract consists of the vagina, cervix, uterus, fallopian tubes, and ovaries, each performing distinct roles in fertilization. These tissues undergo structural and functional changes throughout life; this review will focus on those occurring during the reproductive years.

Menstrual Cycle and Ovulation

The hypothalamic-pituitary-ovarian axis is a complex feedback network that regulates actions of the reproductive system. At the onset of puberty, the hypothalamus begins secreting gonadotropin releasing hormone (GnRH) in a pulsatile manner, triggering production of gonadotropins by the anterior pituitary gland. These gonadotropins, namely follicle stimulating hormone (FSH) and luteinizing hormone (LH), regulate production of steroid hormones by the ovaries (Fig. 2).[114]

These hormones in turn drive the proliferative and secretory phases of the menstrual cycle. Broadly, the menstrual cycle encompasses monthly changes to the uterine lining as it prepares for embryo implantation and then, if no pregnancy occurs, menstrual shedding. The proliferative phase begins when waves of follicular recruitment by FSH increases estrogen production in the ovaries. Estrogen subsequently rebuilds the endometrial lining. Specifically, estrogen exerts negative feedback on FSH production, resulting in dominant follicle selection, which produces more estrogen. At a predetermined level of estradiol, negative feedback converts to positive feedback on gonadotropin release, driving the LH surge and subsequent release of the mature oocyte by the ovary. Ovulation marks the end of the proliferative phase. In anticipation of pregnancy, a steady rise in progesterone levels produced by the corpus luteum initiates the secretory phase and ripens the endometrium. Progesterone stabilizes the endometrial lining and inhibits the actions of FSH and LH. If pregnancy does not occur, the corpus luteum regresses and declining levels of progesterone, LH, and FSH result in menstruation.[29] The interplay and transient levels of these hormones impact peripheral components of the reproductive tract and result in naturally less fertile phases of the menstrual cycle. These effects are utilized strategically in hormonal contraceptives and will be explored later. However, the menstrual cycle is susceptible to external stressors, and as such there may be variability in cycle length, symptom severity, and ovulatory sta-

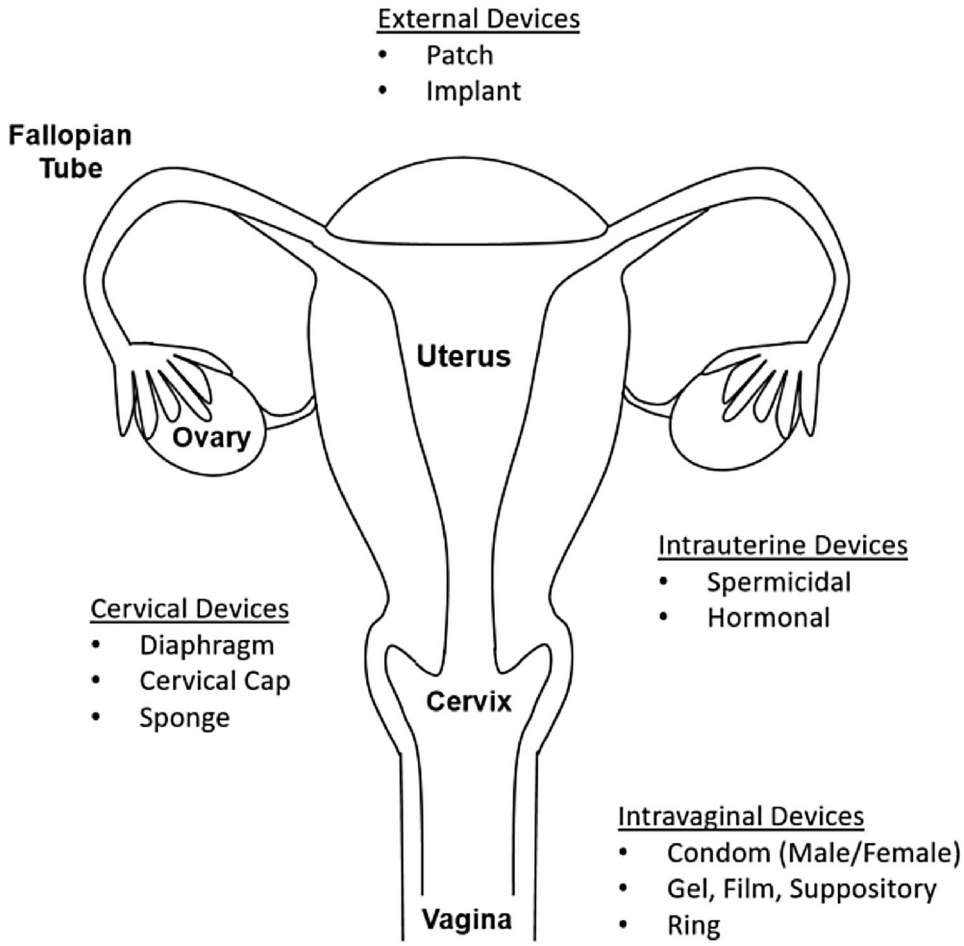

FIGURE 1. Female Reproductive Tract showing points of contraceptive intervention.

tus.[42,124,160] While current contraceptive modalities do not make allowances for these stressors, their impact on contraceptive efficiency and use cannot be underestimated.[156]

Ovary and Fallopian Tube: Anatomy and Physiology

The ovaries are the site of oocyte development and production, triggered by hormone surges of the menstrual cycle as previously discussed. The development of an oocyte is supported by the granulosa and theca cells in a follicle. The granulosa cells are responsive to gonadotropin levels, and after receptor-mediated activation begin to proliferate. Increases in FSH initiate minor and major waves of follicular development throughout the menstrual cycle.[15] Ovulation occurs after a major wave of significant follicular growth, following rising estradiol concentration, decline in FSH, and acquisition of granulosa LH receptors.[14] The LH surge induces androgen synthesis in theca cells that is converted into estrogen by granulosa cells. The LH surge drives the release of an oocyte from the dominant follicle (ovulation) into the fallopian tube by initiating protease breakdown of structural proteins in the ovary wall. Immediately following ovulation, remaining granulosa and theca cells undergo luteinization and transform into the progesterone-secreting corpus luteum.[68,165] Suppression of the LH surge and its effect on the granulosa and theca cells is a contraceptive technique effected by some hormonal devices.

Following ovulation, the oocyte travels through the fallopian tubes towards the uterus. Fertilization, the union of sperm and egg, typically occurs in the ampulla (middle) region of the tube. The fallopian tube includes an outer serosa, an intervening smooth muscle layer, and inner mucosal layer. Its epithelium is comprised of ciliated and secretory cells that assist in fertilization of the egg. As the oocyte cannot move autonomously, estrogen-triggered contractions of the smooth muscle cells drive its transport and is additionally directed by the beating of cilia. Secretory cells, abundant in the ampulla region, produce an oviductal

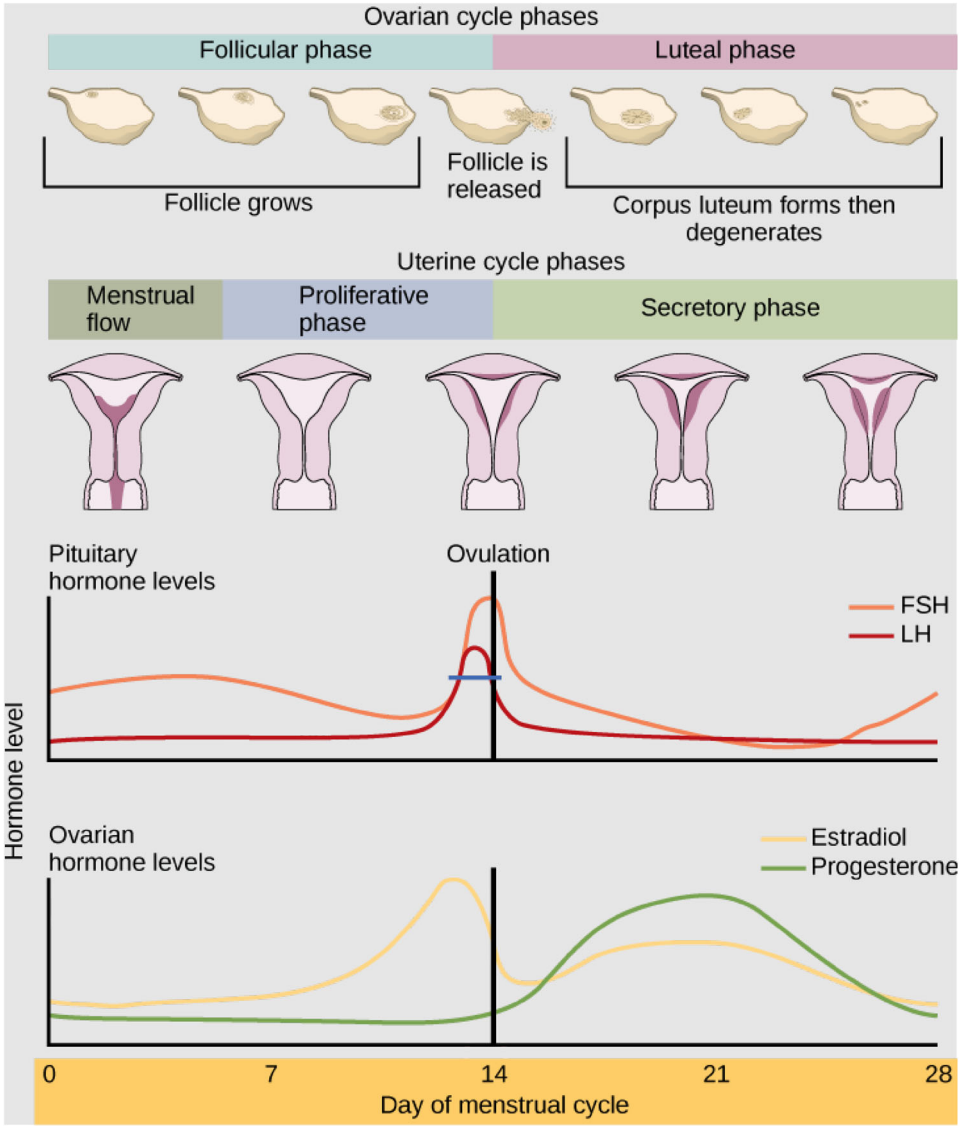

FIGURE 2. Hormone levels during the Menstrual Cycle. Work by Mikael Häggström is licensed under CC BY: 4.0.[112]

fluid rich in nutrients that enhance sperm and egg interaction.[91,114,118]

Uterus: Anatomy and Physiology

The uterus is a muscular organ located in the pelvis with three layers (perimetrium, myometrium, and endometrium) surrounding a lumen that provides lubrication, supports pregnancy, and massively expands/contracts to facilitate parturition.[114] The endometrium serves as the implantation site for a fertilized egg and plays an important role in its nourishment and development. The endometrium includes the superficial stratum functionalis layer whose receptor-mediated response to steroid hormones results in transient changes to epithelial cell proliferation and gland formation. Estrogen primes the endometrium by inducing a proliferation response with increased mitotic activity in glands and the stroma. High levels of progesterone decrease the number of estrogen receptors in endometrial cells to shift towards secretory differentiation.[46] Progesterone also prepares the endometrium for embryo implantation *via* predecidualization of the endometrial stroma.[65] The myometrium expands and contracts to facilitate parturition.

Flexible devices are placed in the uterus for long-acting, effective contraception. If properly placed, typically at the fundus, these devices can remain in the

body over several years with minimal adverse effects. Insertion into the uterine cavity does require passing the narrow cervical canal and may be invasive and temporarily painful.[1] Device migration is a major concern for intrauterine contraceptives: e.g. perforation through the uterine wall into the abdominal cavity, expulsion through the cervix/out of the vagina. These adverse events are influenced by material choice and design. In addition, intrauterine devices (IUDs) must not elicit a major foreign body response post-insertion that can negatively impact a patient's future fertility, wellbeing, and comfort.[144]

Cervix: Anatomy and Physiology

The cervix connects the vagina and uterus to permit egress of menstrual blood and sperm entry into the upper female reproductive tract. The endocervical epithelial cells regulate production and secretion of cervical mucus throughout the menstrual cycle in response to steroid hormone levels. During ovulation, the cervical mucus thins due to the estrogen rise, which allows sperm entry. However, the postovulatory rise in progesterone transforms the mucus into a thick and viscous consistency, which creates a natural barrier to sperm.[35] Endocervical cells express a gel-forming mucin (MUC5B) which, supported by the cystic fibrosis transmembrane conductance regulator (CFTR), controls rheological properties of mucus.[63] Both MUC5B and CFTR expression are responsive to serum hormone levels, with positive and negative correlations to estrogen and progesterone, respectively.[74,60] Direct modulation of MUC5B or CFTR expression *via* novel targeting platforms is an unexplored contraceptive area that could potentially benefit from biomaterials- or nano- based technologies.

Vagina: Anatomy and Physiology

Situated in the lower female reproductive tract, the vagina is a muscular structure comprising four layers: the epithelium, subepithelium, muscularis, and the tunica adventitia. The vagina is an elastic tissue with high surface area.[114] Even though there are no glands present, there is a significant buildup of vaginal secretions originating from transudation, the cervix, endometrium, and fallopian tubes. The resultant vaginal fluid is complex and includes enzymes, proteins, amino acids, and aromatic compounds. The volume and composition are affected by vaginal microflora, sexual activity and menstruation.[72] A population of commensal microorganisms inhabit the vagina and protect it against infection by pathogenic organisms. *Lactobacillus (LB)* sp. bacteria are the predominant species in vaginal secretions from many women in the US, but there is considerable diversity in the *LB* species that are present; the exact composition depends on a number of factors such as age, race, and geographical location. Common vaginal *LB* species such as *jensenii* and *crispatus* release lactic acid that creates an acidic environment (pH 3.8–4.2) that is hostile to many STI pathogens including HIV.[6] High levels of estrogen support *Lactobacilli* growth by triggering vaginal epithelial cell deposition of glycogen, a substrate for lactic acid production by *Lactobacillus*.[49,96] Another *LB* species, *iners,* does not produce as much lactic acid and is associated with a transition to vaginal dysbiosis, a condition characterized by diverse non-LB microflora and an elevated vaginal pH. Many women in developing countries have vaginal dysbiosis and pH-neutral vaginal secretions that serve as risk factors for HIV infection.[25] Following intercourse, vaginal secretions show a transient elevation in pH due to buffering effects of semen, which has a slightly alkaline pH.[162] It is largely unknown how biomaterials used in contraceptives influence the balance of the bacterial composition in the vaginal microbiome.

In the development of contraceptive devices targeting the vagina, many parameters must be considered that could alter the vaginal environment and impair product success.[127] Physiologically, the vagina is a mucous membrane with a complex mixture of fluids: their respective concentrations can fluctuate and dilute the presence of a contraceptive agent. Both the acidic environment and mucus may affect device adherence, position, and retention even during short-term use.[117] The vaginal epithelium is important for delivery of steroid hormones, as its thickness affects the degree of absorption.[72] The vagina can be easily irritated or inflamed if exposed to unsuitable materials or chemicals. Vaginal devices will also undergo shear forces from penetrative sexual intercourse at an estimated rate of 10–100/s.[89] Acceptability of devices may be reduced if the device is easily dislodged during intercourse. As a result, the design of intravaginal devices must comprehensively assess how these variables might influence its efficacy.

Sperm Physiology

Sperm are reproductive cells produced and transported by the male reproductive system. Terminally differentiated sperm do not have repair mechanisms and are subject to physical and chemical stresses in their attempt to fertilize a mature oocyte. These cells are comprised of a compact head and tail conducive to migration and survival in the female reproductive tract. Millions of sperm are ejaculated into the anterior vagina and protected from the acidic vaginal tract by adherent glycoproteins and the buffering capacity of

seminal plasma. They must migrate through the cervical canal and uterus to fertilize an oocyte in the fallopian tube. Motility of these cells is dependent on a functional flagellum with an intact plasma membrane. Changes to the fluidity or integrity of the plasma membrane may result in permanent dysfunction. Only a few thousand sperm reach the fallopian tubes, and typically only one sperm can fertilize an oocyte.[54,90,113,146] Direct targeting of sperm motility and survival along the reproductive pathway is a key contraceptive strategy.

BARRIER DEVICES

General Concepts and Biomaterials

Barrier contraceptives are intended to prevent fertilization by physically or chemically blocking sperm and egg interaction. Some are often intended as temporary birth control methods to increase user accessibility, while others extend as far as permanent sterilization. Examples include the male and female condom, diaphragm, cervical cap, contraceptive sponge, tubal ligation, and vasectomy.

The effectiveness of a barrier contraceptive is dictated by its ability to inhibit the movement of healthy sperm to fertilize the mature egg in the fallopian tube. As such, a major design consideration is the material's mechanical properties. The material must have high durability and flexibility for ease of application or insertion. Tensile strength is particularly important if it must withstand the shear forces of coitus.[152,157] Many elastomers have been used in barrier devices and are described below.

Natural rubber is extracted from plants and trees as a latex composed of cis-poly (isoprene) molecules, proteins, and phospholipids. Rubber latex is an ideal material for barrier protection due to its inherent high tensile strength, elasticity and durability.[126] Additionally, rubber latex is cheap to manufacture with post-processing for stability including compounding and vulcanization. Although generally compatible with human tissues, the protein in the latex can trigger an allergic reaction in some users.[78,107,126]

The synthetic elastomer polyurethane is a widely used biomaterial in the medical device industry because of the availability of many compositions and material characteristics. Polyurethane is a linear block co-polymer with synthesis involving the chemical linking of urethane groups through the isocyanate and polyol hydroxyl groups. The type of isocyanate or polyol monomers dictates the exhibited strength and stiffness of the polyurethane. Moreover, incorporation of chain extenders with appropriate terminal groups (–OH or –NCO) can affect the branching and crosslinking. This permits adaptability of its material properties to a specific application.[5,36,66]

Nitrile rubber is a synthetic alternative material comparable to natural rubber. Known as nitrile butadiene rubber, the material is a copolymer mixture of butadiene and acrylonitrile fabricated using emulsion polymerization. Inherent properties of the material include good resilience and puncture resistance. However, the ratio of butadiene to nitrile content can be used to further tailor physical and chemical properties of the material. Higher nitrile content increases the polarity, which improves resistance to oil and swelling but reduces flexibility.[57,73,122]

Silicone elastomers are chemically cross-linked polymers with backbones composed of repeating silicone and oxygen units. The range of properties of silicone elastomers depend on the functional groups bound to silicone. Within the scope of contraceptive devices, the most commonly used silicone rubber is polydimethylsiloxane (PDMS). The strong, inorganic backbone makes PDMS a candidate material for prolonged use in the body as it is relatively inert and nontoxic. The addition of two methyl groups to the cyclic siloxane group in PDMS in a ring opening polymerization assists in shielding the polar Si–O chain to avoid interfering intermolecular interactions. The mechanical properties of PDMS are sometimes tuned with the addition of silicone fillers that modify the hardness, strength, and tensile strength.[36,78,138]

Existing Modalities: Condom, Diaphragm, and Cervical Cap

The condom is a thin nonpermeable sheath placed on the erect penis and typically composed of rubber latex or polyurethane for latex allergic users. In addition to being a contraceptive device, condoms protect against STI transmission, due to the very small pore size that blocks transmission of even small virus particles. Condom design is centered on the protective layer being comfortable for the users, while withstanding stresses applied throughout its use. Condoms fail due to a break or tear in the membrane. Studies have shown that polyurethane-based condoms have a higher breakage rate compared to latex condoms.[55]

Similarly, the female condom is a soft sheath inserted into the vagina before intercourse with external and internal flexible rings for easy insertion and to anchor the device.[140] In its initial introduction to the market FC1 or "Reality" (Chartex) was polyurethane-based. After a redesign in 2006, FC2 switched to a nitrile-based composition.[150] Intended as a single-use preventative method by receptive partners, the internal condom is widely accepted internationally but is little

used in the United States. As of September 2018, the FDA reclassified the female condom from a Class III to Class II device, the equivalent classification as the male condom.[87] This change reduces the stringency of regulatory approval, which advocates hope will lead to expanded product development and user access in the United States.

The diaphragm and cervical cap are similar devices that cover the cervix as a mechanical barrier against sperm entry into the uterine cavity. Composed of medical-grade silicone, they are used with a spermicide coating for maximum protection. The original diaphragm was a flexible disk with a circular spring in the rim for anchoring against the vaginal walls. The Caya diaphragm (KESSEL) is a smaller cup with a nylon spring rim that is anatomically contoured and fits universally, as opposed to earlier diaphragm designs that needed to be fitted by an experienced provider.[84] The FemCap is a small, flexible cup with a round raised rim for snug placement against the cervix.[52] The devices are inserted hours before sex and can safely remain inside for 24 (Caya) or 48 (FemCap) hours. Both the cervical cap and diaphragm are considered reusable and maintain their effectiveness with proper care and spermicide reapplication.

SPERMICIDAL DEVICES

General Concepts and Biomaterials

Delivery of spermicide to the site of sperm entry is a contraceptive technique with many modes of implementation. The general principle of spermicidal devices is to have a uniform distribution of spermicide in the vagina, cervix, or uterus coupled with a protective barrier. Most spermicidal contraceptives are available over the counter for immediate use. Spermicides are chemicals or materials that disrupt normal sperm activity by causing irreversible cell damage or death. Regardless of the administration route, spermicides come into contact with sensitive tissues, and their off-target effects and tissue reactivity should be considered. Additionally, stability and duration of activity of the spermicide influences the characteristics of the delivery device.[136,140]

Nonoxynol-9 is a nonionic surfactant that immobilizes sperm *via* disruption of sperm membranes and is commonly incorporated into existing barrier methods. As an amphiphilic compound, nonoxynol-9 has a characteristic hydrophobic moiety and hydrophilic chain, nonylphenol and ethylene oxide units, respectively.[110,166] Nonoxynol-9 is recommended as an applied coating on both the diaphragm and cervical cap. Various foams, gels, films and suppositories also include nonoxynol-9 as a primary ingredient. A major drawback of nonoxynol-9 is its tendency to irritate the vaginal epithelium in some users, which can increase the risk of STI transmission.[149]

Copper is an alternative contraceptive material that exhibits spermicidal qualities. The release of copper ions into the uterine cavity results in a localized inflammation that creates a microenvironment unsuitable for fertilization.[121] Copper has been found to induce molecular changes in endometrial cells that reduce receptivity, specifically reducing intracellular ATPase levels and gene expression essential for human embryo implantation.[33] The endometrial inflammatory response recruits leukocytes and macrophages whose degradation products may contribute to this effect as well.[101,141] Concurrently, the buildup of copper ions in the cervical mucus and luminal fluids reduces the motility and viability of sperm due to direct toxicity.[115,129,144]

Spermicide delivery can occur in the vagina or in the uterine cavity. Vaginal delivery requires a vehicle or device with easy insertion/removal, short-term adhesion, and quick distribution of the spermicide.[62,140] Suitable biomaterials should be flexible and durable with an extended duration of spermicidal vaginal retention. Typically, these materials are produced in the form of sponges, gels, suppositories, and films. Common examples of biomaterials that have been used for these applications, and their characteristics are given below.

Polyurethane, as mentioned earlier, is a biocompatible material used in barrier devices. Another characteristic of polyurethane is its ability to be formed into foams with tunable properties based on the catalysts, processing conditions and starting chemicals (isocyanates and polyols) used. These foams retain the favorable mechanical properties previously determined, with the high loading and quick release advantages of a sponge-like product.[137]

Polyvinyl alcohol (PVA) is a synthetic polymer known for its general biocompatibility and biodegradability due to its hydrophilic nature. The synthesis of polyvinyl alcohol relies on the polymerization of vinyl acetate with a partial hydrolysis reaction.[13] As a result, PVA's melting point and viscosity can be modified based on the degree of hydrolysis and its molecular mass. PVA has excellent wetting and spreading properties coupled with tensile strength and flexibility ideal for the generation of films or membranes.[62]

Polyethylene glycol (PEG) is another well-known biomaterial with a long history of use in medical devices or interventions. This inert and biocompatible polymer is chemically stable and ideal for vaginal use. The molecular weight of the polymer can be altered to

tailor its firmness and melting point and create application specific compositions. Derived from repeating units of ethylene oxide, PEG is a water-soluble polymer capable of delivering intravaginal spermicidal agents.[36,44]

Existing Modalities: Sponge, Gel, Film, Suppository, and Inert IUD

The contraceptive sponge is a soft, polyurethane-based material intended to be inserted into the vagina. The TODAY Sponge (Mayer Laboratories) is a currently marketed disposable contraceptive sponge loaded with 1000 mg of nonoxynol-9. Functionally, it serves to physically block the cervix, capture sperm, and kill sperm through the addition of nonoxynol-9. Combining the foaming properties of polyurethane with nonoxynol-9 absorption, the contraceptive sponge is designed as a preventative suitable for short-term (maximum 24 h) use.[100,102]

Vaginal contraceptive gels are a semi-solid system composed of a three-dimensional polymeric matrix containing a dispersed spermicidal agent, commonly Nonoxynol-9. Principally these gels are synthesized using gelling agents, preservatives, humectants, and mucoadhesive agents.[45] The main contraceptive gels available are Gynol II (Caldwell Consumer Health), Conceptrol (Caldwell Consumer Health), and VCF Gel (Apothecus Pharmaceutical).[12,30,31], These gels are similar in composition and are distinguished by slight modifications in the quantity of spermicide and other inert ingredients. Polyvinylpyrrolidone is a water-soluble polymer included as a gelling agent due to its excellent wetting properties.[81] Carboxy methylcellulose is another gelling polymer included in contraceptive gels due to its bio-adhesive properties necessary for *in vivo* retention in the vaginal mucus.[76] The main advantages of gels are acceptability, low cost, and local pharmacological effects. The rheological properties of the gel dictate the spreading and retention in the vagina and are formulated to suit the application. Viscous gels exhibit high retention and resist sperm migration to site of fertilization.[62,89] However, contraceptive gels may be considered messy or leaky by users, likely due to poor mucoadhesive properties.[72]

Both contraceptive films and suppositories are designed as dissolving devices that are inserted vaginally to deliver spermicide and provide cervical protection. Contraceptive films are thin, homogenous polymer strips that may be easily inserted vaginally. The device design includes a water-soluble polymer usually mixed with plasticizers to improve elastic properties. Polymers such as PVA and PEG are often used due to previously mentioned properties. VCF Film (Apothecus Pharmaceutical) is a contraceptive film that uses PVA loaded with 280 mg of nonoxynol-9 for short term use. The film is discrete and can be inserted up to 3 h before intercourse. Suppositories serve as a high dosage delivery mechanism for a wide range of applications as they are self-administered and offer localized treatment. The composition and shape of the inserts depend on the therapeutic agent and purpose. As a contraceptive, these vaginal inserts use a mixture of different molecular weight PEG polymers, surfactants, and preservatives. The oval-shaped suppository is designed to dissolve at body temperature at a pH of ~ 4.5 and create a spermicide-loaded barrier on the cervix. Encare (Blairex Laboratories) is currently the only US-marketed contraceptive suppository and provides 1 h of protection with 100 mg of nonoxynol-9. Suppositories suffer from low bioadhesive properties, leading to leakage.[11,26,62] Improvements in formulation characteristics (adhesion, viscosity) could extend the length of protection and potentially increase their acceptability among users.

The Paragard (CooperSurgical) is a non-hormonal intrauterine device that functions as a spermicidal contraceptive. Structurally similar to drug-eluting IUDs with a T-shaped frame, the Paragard has a copper wire coiled around its vertical base (176 mg) and arms (68.7 mg each). The release of copper ions serves to lower fertilization rates by creating a sterile inflammatory environment inhospitable to the egg and toxic to sperm. The copper IUD affects pre-fertilization conditions, specifically the viability of gametes in the uterine microenvironment and impacts sperm transport such that few spermatozoa reach the site of fertilization (fallopian tube).[33] Paragard is indicated for up to 10 years of continuous use.[41] However, increased menstrual bleeding, cramping, and pain results in discontinuation of use in approximately 15% of users during the first year.[71]

HORMONAL DELIVERY DEVICES

General Concepts and Biomaterials

An alternative to barrier contraceptives is intervening in the female reproductive cycle *via* hormone regulation. As previously described, the reliability of hormonal contraceptives arises from physiological changes to a woman's reproductive system that prevent pregnancy. Steroid hormones delivered through oral methods are still widely used in the United States.[82] However, for some women it is difficult to remember to take the oral contraceptive pill daily, and missing pills compromises effectiveness. Consequently, steroidal hormones have been incorporated into short-acting contraceptive modalities such as the patch and

intravaginal ring (IVR), and long-acting methods such as the intrauterine device (IUD) and subdermal implant for improved ease of use.

The development of synthetic sex hormones in the 1950s expanded the performance capabilities of contraceptives. Currently, synthetic progestins and estrogen analogs are used in hormonal contraceptives, either combined or progestin-only. Combined contraceptives use progestins and estrogen together to amplify their anti-gonadotropic effects to target ovarian function. Together, these hormones inhibit the mid-cycle surge of FSH and LH from the pituitary gland and prevent ovulation. Follicular growth is halted through directed quiescence of granulosa and theca cells, and as a result the corpus luteum formation is prevented. However, ovulation can still occur if hormones are initiated in the late stages of a major wave of follicular development, typically corresponding to the first seven days of the menstrual cycle.[15] Progestin-only contraceptives incite physiological changes to the reproductive tract that occur transiently during the menstrual cycle. They primarily function by thickening the cervical mucus to prevent sperm migration. Continuously keeping plasma levels of progestins above a contraceptive threshold is thought to reduce the abundance of CFTR such that cervical mucus produced by the endocervical cells remains viscous.[74] Additionally, progestin-only contraceptives downregulate endometrial estrogen receptors and create a quiescent endometrium with atrophy of the epithelium and glands.[10,61] Progesterone is known to suppress ovulation during pregnancy, and so progestin-only contraceptives may prevent ovulation as well. However, the dosage is lower in progestin-only contraceptives such that inhibition is not consistent in all users, making this method slightly less reliable.[35,128] Progestins, specifically levonorgestrel, are thought to be effective at a plasma concentration of at least 0.3–0.4 ng/mL.[37] However, the therapeutic threshold for hormonal contraceptives remains an area of uncertainty and is highly dependent on mechanism of delivery and target outcome. For example, parenteral delivery maintains more uniform levels of levonorgestrel compared to oral dosing by utilizing comparatively lower doses.[139]

The stability of steroid hormones is a primary concern for successful therapeutic use. Relevant physicochemical properties of hormones for delivery include hydrophobicity and low molecular weight.[79] Parenteral delivery is advantageous for increasing the bioavailability of hormones by circumventing obstacles of conventional delivery systems. Transdermal, subcutaneous, intravaginal, and intrauterine routes provide greater opportunity of control over the duration of action.[18] Utilization of these delivery routes permits the development of short- and long-acting reversible contraception. The design of hormone delivery devices centers on the compatibility of the biomaterial with the hormone(s) of interest, site of administration, and appropriate release profile. Important material properties include durability and flexibility while being non-biodegradable. The most commonly used polymers are silicone elastomers and polyethylene vinyl acetate (PEVA).

As previously discussed, polydimethylsiloxane elastomers are flexible and durable materials with established usage in medical devices. PDMS is relevant for implanted devices as it has good biocompatibility for use in target delivery environments.[2] The material also demonstrates high permeability to organic substances and permits the diffusion of steroidal hormones.[48] PDMS-based devices are suitable for both short- and long-term interventions.

Ethylene vinyl acetate copolymers are non-toxic, flexible materials with tunable mechanical properties. Changing the vinyl acetate content affects the strength, melting point, and polarity of ethylene vinyl acetate.[116] The synthesis of PEVA involves high pressure free radical polymerization of ethylene and vinyl acetate monomers. Elastomers like PEVA are inexpensive to manufacture as they are processed similarly to thermoplastics.[135] PEVA has stable extended release characteristics due to its hydrophobic chain segments and permeability.[53]

The design of polymers for transdermal delivery must consider familiar principles of appropriate mechanical properties, hormone compatibility and release and adhesion to the skin at the site of delivery. Adhesive polymers are characterized based on their strength, duration of skin adhesion, and peel adhesion, i.e. the amount of force required to remove the patch from the skin. Polyisobutene, an elastomer currently used in contraceptive transdermal systems, is a pressure-sensitive adhesive with a strong holding force, tackiness and flexibility.[3] The cationic polymerization of polyisobutene from isobutylene monomers of different molecular weights dictates its physical properties.[120] Polyisobutene is inert, stable, and chemically compatible with steroid hormones.[148]

Existing Modalities: Short-Acting Reversible Contraceptives

The principle of short-acting reversible contraceptives is to provide women with greater control over their fertility. These devices provide non-invasive prevention for a limited period suitable for different contraceptive preferences.[133] Short-acting methods are widely used worldwide and have a significant impact on sexually active adolescents because although more

than half of sexually active girls in low income countries never use contraception, those who do choose to use short-term contraception.[77] Short-acting methods on the market (and within the scope of this review) are the transdermal patch and intravaginal ring.

Transdermal Delivery

The primary consideration for transdermal delivery contraceptives is penetration of the hormones through the skin for systemic delivery. The pharmacokinetics of absorption impact the efficacy of these devices and are determined by the design of the delivery system (Fig. 3). A matrix-based delivery system is used in most of the currently marketed transdermal contraceptive patches.

The matrix system in the patch consists of the suspension of a drug target in a polymeric matrix or adhesive without an internal reservoir. A highly concentrated patch will generate a hormone gradient that drives a zero-order kinetic release profile in which hormones are released at a constant rate. An advantage of these kinetics is a higher level of overall estrogen exposure coupled with reduced variability in plasma concentration compared to the oral pill. Minimizing peaks in estrogen concentrations can avoid typical side effects like nausea and headache.[56,120]

The Xulane patch (Mylan Pharmaceuticals) uses matrix-based delivery in a three-layer patch to deliver 4.86 mg norelgestromin and 0.53 mg ethinyl estradiol over a 1-week period. The patch includes a protective outer layer composed of polyethylene and polyester, and a removable inner layer of polyester film that serves as the release liner. The middle layer includes the active components (hormones) with the stabilizing inactive ingredients crospovidone (improves steroid bioavailability), oleyl alcohol (surfactant), dipropylene glycol (permeation enhancement) and polyisobutene adhesive in polyester fabric.[17,80,106,111]

Intravaginal Delivery

Intravaginal rings (IVR) are designed to be inserted into the vagina near the cervix and to remain in place and release a therapeutic agent over a longer timeframe. The flexible ring releases hormones at a constant rate to the vaginal epithelium from which they enter the circulation. The rings are composed of PEVA for the same properties as detailed earlier. Broadly, the ring can have a matrix or shell design that dictates its drug release profile. The matrix design involves uniformly loading the hormone into the polymer matrix. The shell design consists of a hormone-loaded polymer core sandwiched by two membrane layers that further control the zero-order release rate. Release is dictated by the quantity of hormone and solubility, diffusivity in matrix, and ring surface area.[62,98,140]

Recognized as a semi-long acting contraceptive, IVRs are user-controlled, easy to use, and relatively noninvasive with the vagina as the insertion site. NuvaRing (Merck) has two active ingredients, an etonogestrel (progestin) and ethinyl estradiol (estrogen) in a PEVA and magnesium stearate (lubricant) composite "shell" ring.[67] With 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol in each ring, the hormones are released during a 3-week period at an average rate of 0.120 and 0.015 mg/day respectively. Recommended use of NuvaRing is 3-week insertion followed by an optional 1-week withdrawal for menstruation.[105,131,159]

Existing Modalities: Long-acting Reversible Contraceptives (LARCs)

The introduction of long-acting reversible contraception (LARC) has greatly improved fertility control with high efficacy (~ 99%) and continuation rates.[161] Frequent patient compliance is not necessary, since the device is inserted once and is effective over a period of years, and complications are rare.[53] Long-acting methods on the market are the intrauterine device (IUD) and subdermal implants.

A unifying feature of LARCs is their use of a reservoir delivery design (Fig. 4). These drug delivery devices use a reservoir composed of a hollow, cylindrical PDMS polymer loaded with the steroid of interest during addition polymerization curing reac-

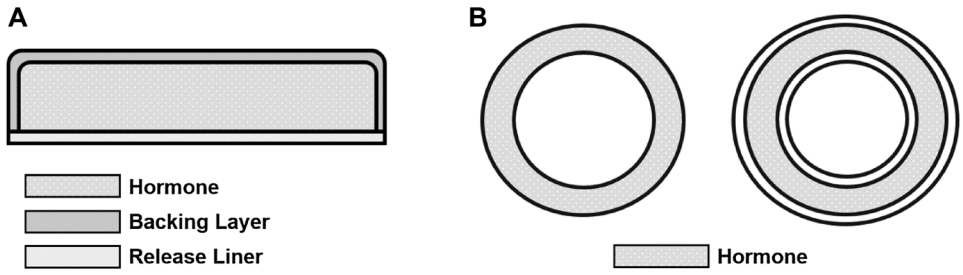

FIGURE 3. Hormone Delivery Design for Short-Acting Reversible Contraceptives (SARCs) (a) Matrix Adhesive Patch (b) Matrix (left) and Shell (right) Rings.

tions. An outer silicone membrane encapsulates the reservoir and acts as a release rate-controlling mechanism. These systems follow zero-order release kinetics with initial hormone loading and membrane determining the daily release rate.[16] Progestin-only LARCs with levonorgestrel delivery are predominately represented on the market at this time.

Subcutaneous Delivery

The subdermal implant is a small, flexible, and non-degrading implant with a drug reservoir design. The rod-shaped implant is designed to be inserted just under the skin in the patient's upper arm for three years of use, followed by replacement as needed. Nexplanon (Merck) is a PEVA core dispersed with 68 mg of etonogestrel with a corresponding membrane layer. Post-insertion, the release rate is 60–70 mcg/day with progressive decline to approximately 25–30 mcg/day at the end of the time course. Notably, Nexplanon is an adaptation from Merck's Implanon and is distinguished by the inclusion of the radiopaque barium sulfate.

Intrauterine Delivery

IUDs, briefly described earlier, serve as a semi-invasive method of delivering local, continuous contraceptive agents. Hormonal IUDs, like copper IUDs, utilize a flexible, T-shaped plastic (polyethylene) frame but implement progestin release with a reservoir delivery system.

The Mirena (Bayer HealthCare), has 52 mg of levonorgestrel (LNG) that is designed to be released at 20 mcg/day for 5 years. The Liletta (Allergan) is similar to the Mirena in design and demonstrates the same release profile over 5 years.[7] Notably, the Liletta manufacturer is partnered with Medicines360, a non-profit women's health pharmaceutical company directed towards making Liletta an affordable option for women.[104] The Kyleena (Bayer HealthCare) has 19.5 mg of LNG with a lower average *in vivo* release rate of approximately 9 mcg/day over a period of 5 years. The Skyla device (Bayer HealthCare) has the shortest duration of use with 13.5 mg of LNG delivered at an average *in vivo* release rate of 6 mcg/day.[22–24] The smaller size of the Skyla and Kyleena is meant to increase ease of insertion in women with a smaller uterus such as adolescents and perimenopausal women. Radiopaque ingredients such as barium sulfate or silver, have recently been included in the composition of the IUD to enable device imaging, since device migration is a known issue.[95,130,144]

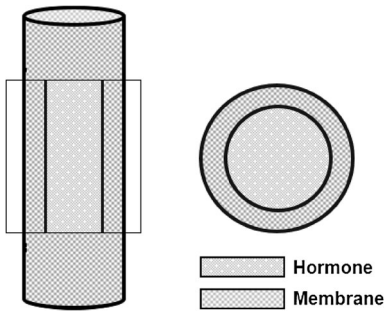

FIGURE 4. Schematic of typical Hormone Reservoir Delivery Design for LARCs. Front (Left) and Top (Right) Views.

STERILIZATION

General Concepts and Biomaterials

Sterilization is a non-reversible contraceptive method chosen by approximately 18.6% of women in the United States from 2015–2017.[43] Traditionally it is performed as a tubal ligation, where the fallopian tubes are blocked or removed. In principle, the idea is to prevent the interaction of the mature oocyte with sperm in the fallopian tube. As previously stated, the fallopian tube is the site of fertilization and so is of interest for permanent contraception.

Sterilization devices are a permanent intervention that must be durable and functional long-term. Occlusion of the fallopian tube requires an adherent material to avoid device migration and perforation of surrounding tissues. Pertinent to its extended use, biomaterials used must withstand physiological and chemical stresses to avoid deterioration. These materials should be safe, biocompatible, and minimize off target effects on the user.

Tubal ligation requires strong biomaterials that can induce dysfunction in the fallopian tube. Polyethylene terephthalate (PET) fibers are polymerized from ethylene glycol and terephthalic acid. These fibers are characteristically strong and stiff due to the large aromatic ring in its basic structure, and as such are resistant to deformation.[134] Metallic biomaterials are cheap, available, resist corrosion, and exhibit good material properties while remaining relatively inert. Combination of these metals is often seen across the medical device industry in long-term implants.[123]

Existing Modalities: Falope Ring, Filshie Clip, and Essure

Tubal ligation devices include the Falope ring and the Filshie clip, which are both mechanical devices introduced *via* laparoscopic surgery that clamp onto the tube to induce necrosis and scarring. The Falope ring (Gyrus ACMI) is composed of silicone rubber and

is designed to draw up 2–3 cm of the tube through its ring, tighten, and then stop circulation.[142] The Filshie clip (CooperSurgical) is a titanium-based device designed to occlude the mid-isthmic portion of the fallopian tube segment. A silicone coating on the device ensures continuous pressure on the tube even if metal fatigue occurs. Both are considered rapid and effective sterilization methods.[20,59,125]

Physical internal obstruction of the fallopian tube was performed with the Essure (Bayer) inserts composed of a stainless-steel inner coil, a nickel titanium expanding outer coil, and PET fibers.[39] PET fibers have been known to induce a local inflammatory response in which macrophages and fibroblasts are recruited to induce fibrosis. Tissue ingrowth is also prompted by the increase in epithelial cell proliferation around the site of implantation.[69,154] As a result, the fallopian tube microenvironment is guided towards scar tissue formation and ultimately tubal obstruction. As of April 2018, Essure was taken off the market by the FDA due to instances of perforation of the uterus/fallopian tube, insert migration into the pelvic cavity, and misrepresented risk by the manufacturer. [86]

Surgical salpingectomy (complete removal of both tubes) has also become widely used to reduce ovarian cancer risk as many ovarian cancers are thought to originate in the fallopian tubes.[58,88,147] Typically, this is performed laparoscopically, and complications are the similar to other operative laparoscopic procedures performed in gynecology. Although salpingectomy may eventually supplant tubal ligation, there is a dearth of tubal ligation devices on the market and this area may benefit from new biomaterial driven interventions.

FUTURE DIRECTIONS

Emerging Modalities

Existing contraceptive technologies have much to offer in terms of biomaterial design and protection. Current work is focused on building on and refining prior designs to better meet current contraceptive preferences and needs.

A recent publication introduced a surface-modified rubber latex condom that could increase both condom usage and patient satisfaction. The addition of a hydrophilic polymer surface coating to the traditional condom circumvents the need for a personal lubricant as it creates a "slippery" surface. Using a UV-induced reaction, the photo-macroinitiators and polyvinylpyrrolidone (hydrophilic polymer) coating is covalently bound to the latex without affecting the mechanical properties of the condom.[40]

A novel hormone-delivering transdermal contraceptive promises a rapid and self-administered alternative to traditional methods. This separable patch delivers sustained release of levonorgestrel from biodegradable microneedles inserted into the skin. The microneedles are composed of a poly(lactic-co-glycolic acid) and polylactic acid mixture, reported to be mechanically equipped to withstand the typical compression and shear forces applied to a microneedle. The steroidal hormone loaded into the polymer microneedles demonstrates a prolonged, continuous release in rat studies for more than a month.[92]

Multipurpose Prevention Technologies (MPTs)

As described above, the worldwide high prevalence of bacterial and viral STIs including HIV is a major health concern with lasting impacts on men and women. Sexual health is tightly intertwined with reproductive health, and target populations often require preventative solutions in both areas. Multipurpose prevention technologies offer integrated solutions that are women-initiated and convenient.

Amphora gel (Evofem Biosciences) is an MPT marketed as a vaginal pH regulator. Amphora is a bio adhesive gel that uses alginic acid and xanthan gum as gelling agents alongside lactic acid as the primary acidifying agent. The gel lowers the vagina's pH to be inhospitable to sperm and bacterial pathogens. The microbicidal product is reported to prevent chlamydia and gonorrhea in women.[21,83] The AMPOWER Phase III clinical trial reported 86% efficacy as a contraceptive in normal use and 98.7% when used as directed.[50]

The leading spermicidal chemical in use today, Nonoxynol-9, is a surfactant (detergent) that kills sperm but also causes vaginal and penile irritation and discomfort in users. Frequent use of Nonoxynol-9 is associated with a twofold risk of HIV acquisition and therefore is not recommended for use in women at risk of HIV infection.[155] Recent research has explored alternative sperm-targeting agents that could be incorporated into pre-existing contraceptive devices. Antimicrobial peptides play a key role in defense mechanisms as part of an organism's innate immunity. The LL-37 peptide is multifunctional with antimicrobial properties as well as spermicidal activity. LL-37 is produced by human immune and epithelial cells in the vagina 2–6 h after intercourse and interacts with the surface membrane of the sperm head leading to permanent structural damage and immobility. The peptide has demonstrated contraceptive effects on human sperm *in vitro* and *in vivo* with mouse sperm.[143]

A contraceptive film that uses monoclonal antisperm antibodies derived from plasma cells of infertile women is under development from a nationwide

research consortium with support from the National Institute of Child Health and Development,[75] Research from the Contraception Research Center at Boston University has shown that one such monoclonal antibody, "Human Contraception Antibody" or anti-CD52g, rapidly agglutinates human sperm at higher concentrations (> 10 μg/mL) and traps sperm in vaginal mucus at lower concentrations. The research consortium is also exploring HIV- and herpes simplex virus (HSV)- specific monoclonal antibodies that are intended to be combined with the sperm antibodies for a comprehensive MPT.

Male and Non-binary Contraception

While out of the scope of this review, there are some elements of male contraception that follow the themes described in this review, namely polymer-driven manipulation of local environment for contraceptive purposes. Presently, the male condom and vasectomy are the only reliable contraceptive methods a man can initiate. Condoms are useful short-term contraceptives with STI protection but moderate efficiency due to misuse or barrier failure. Vasectomies are a sterilization method with low failure rates of 0.3–9% but require follow-up semen analyses months later to ensure complete vas deferens occlusion.[109,167]

The development of long-acting and reversible contraceptive for men shows potential with research into injectable vas deferens contraceptives. The vas deferens are a target of interest for contraception since they transport sperm to the ejaculatory ducts. An Indian male contraceptive, known as Reversible Inhibition of Sperm Under Guidance (RISUG), is an alternative to the vasectomy. Whereas vasectomies traditionally cut the vas deferens, RISUG is a partially occlusive polymer injected into the vas deferens proposed to lower local pH. The copolymer styrene maleic anhydride (SMA) is dissolved in dimethyl sulphoxide, and hydrolyzes in the presence of spermatic fluid such that pH is lowered to ~ 4 to 4.5 and a positive charge is generated that disrupts sperm motility and membranes. RISUG is reversible through dissolution of the insert using sodium bicarbonate.[93,94] Presently RISUG is undergoing Phase III clinical trials in India and a similar method is in development in the United States. Vasalgel is also composed of SMA and reversible but is designed as a fully occlusive insert without any pharmaceutical effects.[158] As of January 2019, Vasalgel is being tested in preclinical studies with hopes to advance to human clinical trials.[32]

Insufficient data is available on the use of contraceptive devices by transgender and non-binary individuals. A recent survey reports 75% of transgender men and women are at risk of unintended pregnancy due to limited contraceptive use.[4] The implications of gender affirming therapies on existing contraceptives is poorly defined, leading to uncertain effectiveness or misinformation.

CONTRACEPTION PITFALLS AND CONTEMPORARY POLICY

At present, contraceptives have not fully met the needs of users worldwide. As mentioned above, the development of safe, effective, and reversible male contraception is a major contraceptive gap. There are also significant issues with female contraceptive failure intrinsic to device design (Fig. 5) reducing the effectiveness of protection. For example, barrier and spermicidal device usage is limited by moderate contraceptive effectiveness, mechanistic failure, or misuse.[108] Even if the device is effective, patient discomfort limits its use: studies have demonstrated that 35–47% of US women undergo reversible contraceptive discontinuation in their lifetime due to method-related dissatisfaction.[19,108,153] Many regimens utilizing combined hormonal contraceptives such as the patch and ring are discontinued within the first year of use due to nausea, fatigue, weight gain and menstrual irregularities.[28,108,145] In the case of the highly effective IUD, heavy bleeding and pain causes 10–20% of users to request removal.[8,9,51] Despite low effectiveness and adverse health effects, contraceptive method selection is highly dependent on cost, ease of access, client control, and privacy in resource-limited settings.[47,151] The declining trend in tubal sterilization is cited to be a result of alternative reversible methods and cost.[34,70] While the above side effects are often considered to be minor and tolerable, the statistics of discontinued use reveal less than optimal patient acceptability.[97,38,99,108]

Dissemination of many of the advances in contraception has been impeded by regulatory, cultural, and legal battles, but there is no question that advances from novel biomaterials-based technologies would

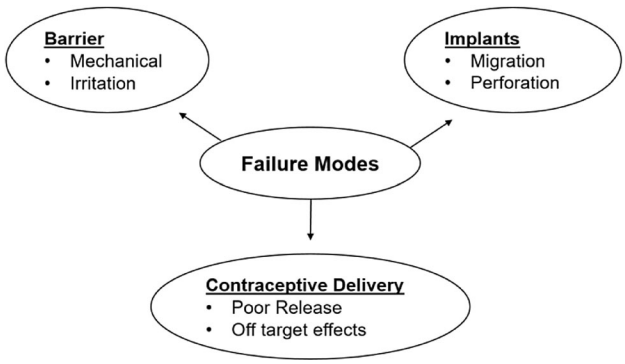

FIGURE 5. Mechanisms of contraceptive device failure.

impart significant benefit by providing more solutions and options for reproductive health.

CONCLUSION

Contraception is an integral part of reproductive health that addresses the ongoing issues of unintended pregnancy and sexual autonomy. At present, a multitude of preventative technologies exist with a wide range of efficacy, usability, and patient acceptability. These devices share similar design principles and biomaterials with a remarkable amount of success. Yet, the worldwide issues of high rates of unintended pregnancy and sexually transmitted diseases expose a still unmet need that existing methods have not sufficiently addressed. Moreover, existing devices share common mechanisms of failure that one must keep in mind for future contraceptive design (Fig. 5). New technologies must strive to address not only biomaterial properties (see Table 3) but also anatomical and physiological considerations that have hindered device success in the past. We also note that endocrine disrupting chemicals, such as parabens and phthalates, have been found in commercial personal care products and shown to alter reproductive function.[64,119] However, whether contraceptive devices contain these chemicals at sufficient levels to negatively impact health remains unknown. With ongoing advances in the fields of biomaterials, nanotechnology, and molecular biology, contraception can benefit from interdisciplinary innovation to better fulfill the needs of current and future users. Effective contraceptive solutions entail safe, affordable, and accessible technologies that enable reliable reproductive and sexual health at a global scale.

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