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Contraceptive Technologies: Looking Ahead to New Approaches to Increase Options for Family Planning

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Abstract: With persistently high global rates of unintended pregnancy and contraceptive nonuse, nonadherence and discontinuation, new contraceptive methods must address the needs of women and men who seek alternatives to their current options. Methods under development aim to reduce potential side effects, improve access and ease of use, ensure safety, increase secondary benefits associated with method use and expand options for both women and men. Developmental approaches employed to enhance current methods utilize new delivery systems and novel active pharmaceutical ingredients. This will improve overall user satisfaction with the methods used while expanding the number of options available to provide choice and value user autonomy in the highly diverse contraceptive markets around the world.

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Approximately half (49%) of all pregnancies around the world are unintended, with recent estimates from 2015 to 2019 of 121 million unintended pregnancies annually.[1] Elimination of the global unmet need for contraception, comprising of an estimated 218 million women, would prevent 76 million unintended pregnancies, $6.6 billion costs associated with pregnancy care for these pregnancies, and 70,000 maternal deaths.[2] Furthermore, it would fulfill the global commitment to reproductive justice enshrined in the Sustainable Development Goals for 2030 by ensuring reproductive health and reducing related inequalities across social and national groups.

Inadequate access to safe, effective, and acceptable contraception is a key contributor to this unmet contraceptive need. However, even when contraception is relatively accessible, rates of unintended pregnancy can remain high, for example, in North America (48%) and Europe (43%).[1] Currently, available contraceptive options are not adequately meeting many women's needs, as is evident by high levels of typical use failure, method nonuse, switching, and discontinuation.[3] New methods are needed to support the reproductive health needs of both women and men, recognizing that these needs may change over their reproductive life-course. Methods under development aim to reduce potential side effects, improve access and ease of use, ensure safety, increase secondary benefit associated with method use. Moreover, in developing countries, some products may provide relief for overburdened supply chains by offering longer term methods that do not demand regular resupply, may be obtained through pharmacy networks, and are also highly safe and effective. This will improve overall satisfaction while expanding the number of options available to provide choice and value patient autonomy globally. In addition, there is a move towards making newer "green" methods where their potential environmental impact is minimized during manufacturing through packaging, transportation and supply chains, delivery, use, and disposal.[4]

There are many products at different stages in the contraceptive development pipeline. An ongoing database maintained by the Contraceptive Technology Innovation Exchange provides a tool to access knowledge on contraceptives in development (https://pipeline.ctiexchange.org). With over 200 results, this database highlights the many products in development and the diverse approaches, and broad but clearly insufficient investment occurring in this arena given the full cost of product development. In pursuit of greater market penetration globally, developers are employing user-informed design approaches to shape the ultimate profile of the methods they are developing to maximize their benefit and deliver a product that priority clients want to use. End-user engagement is crucial to ensure that product characteristics that can be modified during product development are considered before the final design of the product.

The development of contraceptive methods remains a priority at several nonprofit, academic, governmental, and nongovernmental organizations. The Population Council, a global nonprofit research organization, has been a pioneer in the field of contraceptive research and development for over 60 years and developed a number of highly effective long-acting reversible contraceptives (LARC) including implants, Norplant and Jadelle (Bayer OY, Turku, Finland), intrauterine devices (IUDs) such as the copper IUD ParaGard (The Cooper Companies Inc., San Ramon, CA) and medicated intrauterine systems such as Mirena (Bayer OY) and Annovera 1-year contraceptive vaginal system (TherapeuticsMD Inc, Boca Raton, FL).

FHI360 has improved access to highly effective methods in low- and middle-income countries (LMICs) is by reducing costs of contraceptive products with Sino-implant (II), a 2-rod levonorgestrel implant Similarly, Medicines360 is providing an avenue for extended access with their lower cost levonorgestrel containing IUD Avibela, Sayana Press, a subcutaneous depot medroxyprogesterone acetate, is an important advancement to provide an option for self-administration on a progestin-only contraceptive. These newer advancements are proving critical to enhancing individuals' access, specifically in LMICs, where new technologies are often initially a substantial barrier to broad distribution. We aim to provide an

overview of contraceptive technology development approaches while highlighting some of the methods in the development pipeline, as well as some of the obstacles that must be overcome to get new methods into the hands of users in dramatically diverse cultural and economic contexts.

Development Approaches

Contraceptive developers are pursuing different avenues to address user needs that are not filled by currently available contraceptive options. Developers are seeking to improve upon the profile of existing methods to increase acceptability and reduce side effects while controlling the costs of goods, facilitating global distribution, and eventually securing affordable prices to users in highly diverse markets around the world. New technologies under development will increase options including methods for women with contraindications to hormones, methods for men, and will expand secondary medical benefits, such as prevention of human immunodeficiency virus (HIV) or other sexually transmitted infections (STIs). In addition, new delivery systems can expand the way individuals receive contraception, favoring user-controlled methods to allow easy access in regions, such as LMICs, where access to health providers trained for LARC insertion or removal may be limited. Examples of such an approach is Annovera, a 1-year, the user-controlled intravaginal system recently approved by the Food and Drug Administration (FDA) in the United States, and the 3-month progesterone vaginal ring (PVR) for birth spacing among breastfeeding women included in the World Health Organization (WHO) List of Essential medicines and most recently approved by regulatory agencies in Nigeria and Senegal (see below).

METHODS FOR WOMEN

Enhancement of Existing Hormonal Contraceptives

Multiple products under development aim to enhance existing methods by improving the product profile for women. One approach is *altering the hormonal composition* of existing methods to develop products with improved safety. This can be done by lowering doses of the same hormonal formulation, for example, having a lower dose of ethinyl estradiol in newer oral contraceptive pill formulations, or by including a safer steroid. For example, newer formulations with potentially safer estrogens, such as estradiol (E2) or estetrol (E4), could potentially decrease venous thromboembolic risks or reduce hemostatic changes in comparison to ethinyl estradiol.[5–7] Newer progestins may have reduced side effects due to less androgenic activity of these progestins.[8,9] A new intravaginal ring (IVR) currently in a phase 2b trial has replaced the ethinyl estradiol with 17β-estradiol, the endogenous estrogen that is less potent with decreased impact on clotting factors. This ring combines estradiol and segesterone acetate (trademark name Nestorone), which is a potent progestin with no androgenic properties.[9]

New progestin-only options, such as progestin-only patches and IVRs, are under development. While progestin-only approaches expand access for women with contraindications to estrogen-containing methods, the altered bleeding profiles that occur with these methods may not be acceptable to all users. Further, progestin-only options may be able to promote breastfeeding, especially critical in LMICs, while extending the interpregnancy intervals. The PVR is used to extend the contraceptive effectiveness of lactational amenorrhea among breastfeeding women, which is favorable for many women. The PVR is a donut-shaped, soft, flexible silicone ring;

58 mm in outer diameter and 2.4 mm in cross-section, containing 2 g micronized progesterone releasing ~10 mg/d. Progesterone enhances the prolactin response to breast suckling that suppresses ovarian function.[10] It also thickens the cervical mucus, inhibiting sperm penetration into the uterus. Clinical trials have demonstrated that the PVR is 98.5% effective in preventing pregnancy when used correctly, is safe for mother and baby, and does not affect a woman's ability to produce breast milk, unlike estrogen-containing oral contraceptives.

The PVR was added to the 2015 updated WHO Medical Eligibility Criteria (fifth edition) and to the WHO Model Essential Medicines List. In a recently published 1-year study conducted in Indian family planning research centers comparing the PVR with the Copper-T IUD in postpartum breastfeeding women, efficacy and safety outcomes were comparable among women in both groups. Continuation rates for the PVR, a woman-controlled method, were lower than IUD rates while PVR users maintained lactational amenorrhea significantly longer than IUD users. Infant breastfeeding and growth patterns/well-being were favorable in both groups.[11] The PVR can address the unmet need for birth spacing among lactating postpartum women while encouraging breastfeeding that is essential for infant's health in many countries including LMIC where breastfeeding up to 1 year is popular.

Enhancement of Existing Contraceptives

For nonhormonal contraceptives, including condoms, diaphragms, and IUDs, developers are exploring different materials, shapes, and designs to enhance the user experience and better facilitate insertion and prevent adverse events, such as uterine perforation or expulsion. Complications like these are more likely to occur in delivery systems where task-shifting requires that general physicians and paraprofessionals with small caseloads provide the bulk of clinical family planning services. IUDs are a great example where significant investment is working toward enhancing the design for a range of clients including adolescents and women immediately postpartum and altering the formulation to reduce side effects and improve safety. One approach is altering the delivery profile for copper by lowering the doses or release of copper ions from the IUD or integrating copper nanoparticles in the device to decrease the burst of copper release.[12,13] Another approach is to add an additional active pharmacologic ingredient (API) with the goal of improving the bleeding profile, either in terms of volume, frequency, or predictability. An example of this is a copper IUD that releases indomethacin,[14] a nonsteroidal anti-inflammatory drug. Another approach is to include a progesterone receptor modulator in a small reservoir to prevent bleeding associated with IUDs. An ulipristal acetate-Copper IUD was tested in a proof-of-concept dose-finding study and confirmed the feasibility of decreasing the expected copper-associated bleeding (Brache V, Vieira CS, Plagianos M, Lansiaux M, Merkatz R, Sussman H, Cochon L, Tejada AS, Kumar N, Loeven D, Blithe DL, Aprem AS, Williams ARW, Kannan A, Bagchi IC, Sitruk-Ware R, revision under review). Advancing models that employ new materials, such as nitinol where shape memory and elasticity properties offer a theoretical advantage in terms of retention, ease of insertion or comfort over the current models or different shapes and sizes may overcome some of the side effects or resistance to existing methods, especially among sexually active youth. Veracept low-dose Copper IUD and Levocept IUS currently in clinical trials exemplify this approach.[15] Another example is the intrauterine ball, where the classic T-shape is replaced by a series of copper "pearls" on a frame that are

inserted and through shape memory develop the shape of a ball.[16] Last, new inserters are designed to simplify insertion and reduce risks of pain and perforation, including those with single-handed and 2-handed inserters as well for immediate postpartum use.[17] Enhancing the ease and safety of IUD placement can further support task-shifting to increase access in LMICs, while in-service training opportunities increase the development and maintenance of required clinical skills.

Novel Delivery Systems

New delivery systems can potentially enhance user control and increase the duration of contraceptive effectiveness to reduce the need for repeat clinical visits and associated barriers associated with some methods. Examples of newer delivery systems include biodegradable contraceptive implants and longer acting injectable methods that can provide extended periods of contraceptive effectiveness without the need for a trained provider for removal. Longer acting injectables under development allow the user to go 6 months or 1 year between injections compared with current products every 1 to 3 months, yet provide a rapid return of fertility. Recent donor interest in MedinCell's[18] BEPO technology may make it possible for a subcutaneous injectable to deliver the optimal therapeutic dose of a progestin-based contraceptive for 6 months. The possible drawback of such long-acting methods is that it could not be withdrawn if someone is dissatisfied with the method or in case of a serious adverse event requiring immediate removal.

Microneedle (or microarray) patches are being developed to provide an alternative approach for the delivery of hormonal contraception. These differ from typical transdermal patches as they contain an array of microneedles built into the patch that can release drug through the dermis via differing approaches such as dissolution of the needles or as hollow needles to deliver the drug from a reservoir in the patch that is removed after application. These are user-administered, and appropriate for community distribution along with products under development for vaccination, HIV prevention as well as recently for contraception. Individuals in theory would place the patch for a few minutes and then remove it. This interesting approach may be preferred by women who favor discreet options over the classic transdermal patches that remain in place and visible. Also, there is no risk of patch detaching from the skin in high humidity areas. Different progestin-based products under development include an on-demand patch that would provide protection for 5 to 7 days and a long-acting patch that would provide pregnancy protection for several months.

The advancement of IVR technologies are allowing for newer approaches to include multiple drug moieties in a single device. Oak Crest Institute of Science and its collaborators have developed a novel pod IVR: a core IVR in which multiple API reservoir "pods" are contained within the IVR scaffold. The ring scaffold is an unmedicated supporting structure for the pods and can be composed of silicone elastomers or thermoplastics like ethylene-vinyl acetate and polyurethane. This novel design has successfully delivered hydrophilic APIs (small and large molecules) and small-molecule hydrophobic APIs. Each API is encapsulated in its own pod, the polymers/excipients of which can be tailored to the properties of the drug, and each pod is coated with a release-controlling polymer membrane with the core content released through a delivery window in the ring scaffold. The potential for combining multiple APIs with different properties opens new avenues for multipurpose prevention technologies (MPTs) and products combining different active ingredients that had

previously been challenging to coformulate. This pod-ring approach is being pursued at the Population Council as an MPT combining hormonal components, ethinyl estradiol, and etonogestrel, with a nonantiretroviral lectin with potent anti-HIV activity, Q Griffithsin, to address the concerns of women and policymakers aiming to reduce both unwanted pregnancy and unwanted transmitted infections without increasing antiretroviral drug resistance.[19]

Microchip technology is under development as a long-acting, user-controlled approach for pregnancy prevention. The goal of the microchip is to have an insertable device with a controlled drug release that can be turned off and on through a remote device. The Bill and Melinda Gates Foundation recently invested in funding the development of a device that would release levonorgestrel with activity up to 16 years, that can be turned off when someone wants to conceive or is abstinent and turned back on postpartum or when one resumes sexual activity. Innovations such as these have the potential for reducing the current burden on supply chains and potentially may lower the long-term costs of method use. This approach, however, is not without controversy as it raises concerns regarding security, the extent of reliable user control, and contraceptive coercion.[20]

While there are some on-demand methods for use around the time of intercourse that may be sought by individuals with infrequent sex where the use of a daily pill or LARC is undesirable, the current options are limited, and the effectiveness is lower than desired. Phexxi (Evofem, San Diego, CA), a nontoxic spermicide that maintains the pH within the vagina at levels < 5 to immobilize and kill sperm and likely many sexually transmitted pathogens. However, the pearl index of this method is higher than usually required by regulatory authorities or expected by clients desiring highly effective methods. This is a common challenge with on-demand approaches, where the typical use effectiveness is much lower than perfect use effectiveness largely due to challenges in adherence. Nonetheless, many women seek an on-demand approach.[21] New approaches aim to improve the delivery of on-demand methods to enhance acceptability and provide an extended window of effectiveness by using a combination of different APIs with differing mechanisms of action in one method. Electrospun drug-eluting fibers/fabrics can combine several molecules delivered at different doses and pace. Laboratory tests showed a steady delivery from different fibers delivering levonorgestrel and tenofovir from a fabric to be used vaginally.[22] Fast-dissolving inserts are a solid dosage form that are placed inside the vagina and quickly dissolve to form a viscous gel that can deliver the active agents, without leakage that may be observed with vaginal gels. Fast-dissolving inserts are inexpensive, discrete, and portable with demonstrated high acceptability in surveys and with use in currently marketed products for other indications.[23,24] Bioadhesive films can be placed within the vagina and maintain protective activity for a longer period of time by adhering to the mucosal wall.[25–27] These discrete approaches can expand options for user control with no interference with the woman's cycle, a minimal effect on the bleeding profile, and the potential for added secondary benefits such as HIV or other STI prevention.

MPTs

As discussed above, some of the methods under development aim to incorporate drugs that have activity against HIV and/or STIs. There is an undeniable need for MPTs in many parts of the world. In 2019, ~1.7 million people became newly infected with HIV, > 3 times the target 2020 goal set by the 2030 Agenda on Sustainable

Development and articulated in the United Nations General Assembly 2016 Political Declaration of Ending acquired immunodeficiency syndrome (AIDS).[28] Uptake of preexposure prophylaxis has been slow particularly among women in developing countries. While STIs including HIV are found worldwide, the bulk of new HIV infections and cases of AIDS are reported in East and Southern Africa. For example, adolescent girls and young women (ages 15 to 24) account for about 25% of new HIV infections in sub-Saharan Africa, despite making up only 10% of the population, and AIDS is the second leading cause of death among this population. There are over 1 million new cases daily of curable STIs worldwide[29] with treatment costs exceeding $2 billion annually.[2] Despite national efforts to reduce STIs, the STI epidemic in the United States has experienced steep and sustained increases for the fifth consecutive year, reaching an all-time high in 2018 with 1.7 million cases of chlamydia (increased 22% since 2013) and 555,608 cases of gonorrhea (increased 67% since 2013).[30] Increasing antibiotic resistance exacerbates these concerning trends.[19] STIs have a broad-reaching impact on women's health and maternal-child health, including increasing the risk of HIV acquisition and transmission, chronic pelvic pain, infertility, and preterm delivery, the leading cause of infant morbidity and mortality. MPTs that can reduce the risk of STI acquisition have huge potential for public health impact as they aim to tackle these overlapping burdens. Unfortunately, condoms – a method plagued by low adherence and poor typical use contraceptive effectiveness – are the only MPTs currently available.

It is anticipated that combining these prevention strategies will not only increase uptake of interventions that can reduce the global burden of these diseases but also increase adherence, where the motivation to prevent one outcome can help drive the prevention of another. Furthermore, recent studies conducted both in the United States and in Sub-Saharan Africa, have highlighted that women will likely prefer and use an MPT product that prevents pregnancy and STI/HIV acquisition over a product that prevents only pregnancy or only STI/HIV.[31,32] These recent findings are of high relevance for women who desire an STI/HIV prevention product that could be used discretely (either not noticed by the partner or where contraception could be the stated/disclosed reason for product use).

One approach towards advancing MPTs is combining an approved contraceptive with another approved STI or HIV prevention strategy. Currently, only Truvada is approved for preexposure HIV prophylaxis for women, thus developers are aiming to combine this molecule with a hormonal contraceptive pill to develop one pill for dual prevention. With additional HIV prevention options soon becoming available to women, including a ring delivering dapivirine and a long-acting cabotegravir injectable, new approaches for combination products are becoming feasible in the foreseeable future. An example of this approach is an MPT IVR that delivers dapivirine and levonogestrel.[33] As with other family planning approaches, offering different delivery approaches is imperative to enhance uptake by providing choice to the user and enhancing efficiency in service delivery for providers.

Nonhormonal Methods

Nonhormonal contraceptive technologies are being developed to address the needs of women who want to avoid pregnancy without using hormonal approaches. The varied reasons women may want to avoid hormonal methods include contraindications and/or increased health risks associated with ethinyl estradiol use (such as venous thromboembolism, thrombophilias with increased risk of thrombosis, migraines with aura, and breast cancer),

concerns regarding hormonal methods during the postpartum period or while breastfeeding, a general dislike of these methods, side effects and/or fear of adverse effects related to hormones. There are also women who desire predictable regular menses without unscheduled or irregular bleeding experienced with the use of some progestin-only methods.[34] As the only nonhormonal options are provider-dependent copper IUDs, which have the risk of increased monthly bleeding, or pericoital approaches with low typical use effectiveness, such as condoms or spermicides, it is critical to fill this gap in the method mix.

Expanded technologies for on-demand methods will increase the number of options in the future. In addition to Phexxi, polyphenylene carboxymethylene, is being explored by Yaso Pharmaceuticals as a potential on-demand nonhormonal approach. Another such approach is through a nonhormonal vaginal ring under development which releases ferrous gluconate or ascorbic acid that impedes sperm motility. Ovaprene (Daré Bioscience, San Diego, CA) under development is a monthly vaginal ring with a semi-permeable polymer mesh barrier that physically blocks sperm from entering the cervical canal; releases of ferrous gluconate from the main ring body, which acts locally to impede sperm motility. A phase 1 safety-and-tolerability study concluded that the Ovaprene device is well-tolerated and acceptable to sexually active women and their partners[35]; and Daré began a clinical trial of Ovaprene in 2018. Bayer recently entered into a license agreement with Daré Bioscience to commercialize the product in the United States and this approach is now entering clinical trials through the NICHD clinical trials network so more data should soon be available on safety and efficacy.

Nonsurgical Permanent Contraception

Globally, permanent contraception represents the one of the leading methods of family planning for women, particularly for those who completed their family either at an early age or over age 35. Inadequate availability of surgical facilities and trained personnel in overburdened health systems present significant barriers to access that may contribute to the unmet need for permanent contraception in many low-resource settings.[36] Research is ongoing to develop an effective and safe nonsurgical approach that could improve access and even allow task-shifting to allow skilled midlevel providers to perform permanent contraception procedures without compromising appropriate counseling, informed consent, or the quality of the clinical outcome.

METHODS FOR MEN

The only current options for male contraception, condoms, withdrawal, and vasectomy, limit choice for half of the world's population. Studies indicate that $> 50\%$ of men say they would be interested in an effective reversible contraceptive method.[37] Developing male contraception can provide an opportunity for individuals to take control of their reproductive decisions and improve the efficacy of existing methods if both partners are using a contraceptive. These methods also offer an opportunity for shared responsibility for the prevention of unintended pregnancy within the couple.

Considering the disadvantages of the traditional male contraceptive methods, the prerequisites for an ideal pharmacologic male contraceptive should be applied independently of the sexual act, be highly effective, be acceptable for both partners, have minimal interference with libido, have neither short-term nor long-term toxic side effects, have no impact on eventual offspring, be rapidly effective and fully reversible and be as safe and effective as comparable female methods.[38]

Male hormonal contraception is one approach as the efficacy of hormones for suppressing spermatogenesis is well

established. Similar to women, testosterone levels in the testes that are required for spermatogenesis are regulated by the hypothalamic-pituitary axis. Exogenous androgens alone or in combination with progestins suppress gonadotropin secretion leading to reduced testicular testosterone production. Low testosterone levels may lead to other effects such as low libido, erectile dysfunction, and reduced muscle mass, thus add-back testosterone is needed to reduce these symptoms while maintaining sperm suppression. One challenge with these approaches is a delayed onset of action, as it can take several weeks to fully suppress spermatogenesis. Several formulations are being evaluated including pills, transdermal gels, and implants. Previous trials have used combinations of long-acting injectable or implantable forms of testosterone with progestogens, which can be administered orally, by injection, or by a long-acting implant. Such combinations suppress spermatogenesis to zero or below the threshold required for pregnancy in 80% to 90% of men, with near-complete suppression in the remainder of individuals without severe side effects and are always fully reversible. Progestin coadministration suppresses gonadotropins and increases both the rate and extent of sperm suppression.[39]

Some of these approaches aim to employ androgens that are not metabolized via 5-alpha reductase which may be helpful for prostate health and male pattern baldness. An androgen with high tissue selectivity has been developed by the Population Council for both male contraception and treatment of hypogonadism in men. MENT (7α-methyl-19-nortestosterone) is not converted to 5α-dihydrotestosterone and therefore had less effect on prostate growth in different animal models.[40] In the first clinical trial in male volunteers, MENT acetate implants delivering 400 μg/d of MENT, were administered for 1 year and 4 implants (1600 μg/d) were sufficient to suppress gonadotropins and spermatogenesis, that is, azoospermia or sperm counts <1 million/mL in 82% of subjects.[41] Full recovery was reached between 2 months and 1-year follow-up. New prototype implants based on a different elastomer technology intend to deliver a higher dose of MENT to decrease the number of implants. This technology needs to be refined for further clinical trials, and users will likely face similar challenges in developing country markets such as Ethiopia where women with implants have faced in getting implants withdrawn when they chose.

Currently, a nestorone/testosterone gel formulation is being evaluated for efficacy in couples enrolled in a 1-year phase IIb multinational clinical study conducted in the Male Contraceptive Clinical Trial Network of the NICHD and in collaboration with the Pop Council and including sites from 4 continents. Efficacy is suppressing the gonadotrophins has been confirmed and the dose selected for an ongoing efficacy study in volunteering couples.[42] The male pill development has been challenging given the short half-life of oral testosterone and the toxicity of modified oral androgen such as methyl testosterone that can cause hepatotoxicity. However, newer androgen, such as di-meth-androlone undecanoate (DMAU) and 11β-methyl-19-nortestosterone17β-dodecylcarbonate (11β-MNTDC), may be able to overcome this challenge. While DMAU and 11β-MNTDC are similar in structure and activity, DMAU is a more potent androgen, while 11β-MNTDC has a more balanced androgen receptor to progesterone receptor activity. Both have shown safety when administered orally. These promising compounds suggest that a "male pill" may indeed become available in the next decade.[43,44]

Another approach for men under development aims to block the passage of sperm from the testes similar to

vasectomy as a *nonhormonal male contraceptive*. Vasalgel, currently under development by Revolution Contraceptives, a Parsemus Foundation's social venture, is a polymer gel that is injected into each vas deferens that blocks sperm passage, however, this blockage is able to be reversed if the man desires with an in-office procedure.[45]

Novel Agents and Targets for Nonhormonal Contraception

In pursuit of nonhormonal contraception, there has been high interest in discovery work that has leveraged the rapid expansion in genomic and proteomic research techniques. The goal has been to identify targets, ideally those with a specific role important in male or female reproduction and located uniquely within the reproductive organs, for example, testes or ovary, or on sperm. Once these targets are identified, researchers identify agents that impact the specific target and avoid nonspecific activity, integrating approaches such as antibodies and mRNA identification. In theory, this would lead to a very focused contraceptive profile avoiding other unwanted effects. While there are several such targets identified and being worked on, it is likely that few will advance to clinical testing. For women, these approaches are aiming to block oocyte maturation or inhibit factors that influence follicular rupture. For male methods, several targets have been identified that have promise including those that block spermatogenesis and sperm differentiation and maturation, sperm motility, or the capacity of the sperm to bind to the ovary. Figure 1 highlights the multiple male-specific protein or enzyme targets being explored that can potentially be antagonized to inhibit fertility by acting at different stages of spermatogenesis.[46] Some of these targets,

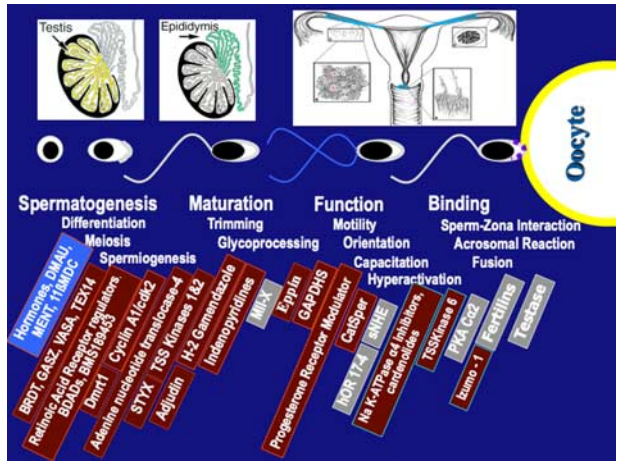

FIGURE 1. Various factors involved in sperm production, maturation, motility, and capacitation processes to fertilize an egg, that could become targets for specific blockage (in blue still hormonal; in burgundy nonhormonal approaches). 11β-MNTDC indicates 11β-methyl-19-nortestosterone17β-dodecylcarbonate; DMAU, di-meth-androlone undecanoate; GAPDHS, glyceraldehyde-3-phosphate dehydrogenase, spermatogenic; MENT, 7α-methyl-19-nortestosterone. Figure courtesy from D. Blithe and adapted from Gottwald et al[46] with permission. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. full color online

specifically those involved in blocking sperm function and binding, may also be employed as innovative vaginal female contraceptives as well.

Challenges to Method Approval and Expanding Into a Global Market

While there are many products in development, many of these will fail to advance due to technical, regulatory, or cost issues, and never get in the hands of providers or users. These failures to progress are sometimes due to issues related to safety or efficacy recognized during the course of drug development, however, often it is due to failure to obtain the needed funding required to complete product development or manufacturing in small batches until large procurements are realized. There are multiple stages in the discovery phase before a product can begin clinical trials, and then once clinical trials begin, the cost of running these trials can be substantial given the regulatory requirements for female contraceptives to provide data for 20,000 cycles of use and 400 women completing 1 year of use for any new chemical entity or a new device. Regulatory requirements for male contraceptives are not specified by regulatory authorities as pregnancy in women is the usual endpoint, rather than sperm suppression, but maybe similar with 400 couples completing a 1-year trial. Upscale manufacturing under Good Manufacturing Practice conditions is another challenge and requires commercial entities to conduct these steps for quality-assured, mass-manufacturing, and future distribution. Challenging issues of regulatory approval, procurement, and market penetration are common with all new technologies, particularly in developing countries with limited human resources for delivery.

Several multinational pharmaceutical companies abandoned a large portion of their drug discovery research and development programs in contraception in the early 2000s. Much of the progress especially in male contraception has been then driven by government, nongovernment and philanthropic organizations. However, any new product ultimately emerging from this nonpharmaceutical model will require considerable financial, manufacturing, and commercialization capabilities of the pharmaceutical industry to reach the diverse and often informal markets that service men's health around the world. Along with this, the high cost of new methods even for the private sector will require ongoing investment and a demonstrated market at a significant scale to reduce the marginal costs of delivery. As the field explores the implications of task-shifting and telemedicine, new technologies need to be developed to fit the new models of delivery. Ensuring that new technologies are included in plans for Universal Health Coverage and emerging national health insurance plans will indeed be a requirement for long-term scale-up of delivery and complex distribution and supply chain reliability.

In addition to the actual cost of moving these technologies forward, additional barriers persist. Newer contraceptives tend to have higher Pearl indexes, a metric of contraceptive effectiveness, in comparison to methods that were previously studied and approved. This relates to changes in the diversity of the populations included in studies such as those with obesity, younger participants, and the inclusion of cycles with documented sexual activity and no other method use. This is even more challenging for on-demand products where perfect use is not reflected in this metric.

For male contraceptive development, the regulatory pathway globally is not clearly developed. A large potential barrier exists in defining what will be considered safe enough for a male contraceptive. Long-term safety will need to be demonstrated and very few side effects would be acceptable as users do not face

the medical risks associated with pregnancy; thus, the risk/benefit ratio differs. We must consider the risks to the individual versus the potential health consequences in another individual. One approach to alter this ratio may be developing methods that have additional health benefits for men, without constraining the benefits for women. This may be a long-term issue as the key element for the moment is efficacy and safety for the user and his partner. Male contraception has been an unfulfilled promise for many years, so there are many issues in the delivery of new male methods that will take a great deal of time to address, for example, where will men go for information and care? Health clinics in developing countries are not particularly designed for men, apart from emergency rooms, so policies may have to focus on other sources of care.

For MPTs, a challenge will be to proving effectiveness against HIV and/or other STIs. Designing adequate studies that show reduced incidence is becoming more challenging to ethically conduct given the effectiveness of newer approaches for HIV prevention and the benefits of antiretroviral therapy treatment on reducing transmission to an uninfected partner. New studies may need to be extremely large to prove a marginal benefit to the user and their partner(s), where an index of protection, similar to the pearl index for pregnancy, will likely need to be defined. It is possible that for some of these MPT products seeking regulatory approval may be complicated due to multiple indications, where there may be delays in the seeking of approval for the secondary benefit or the inclusion of an active pharmaceutical ingredient that does not directly impact the primary indication, for example, pregnancy prevention, may lead to challenges in approval. The impact of male contraception will be significant internationally as it could reduce unintended pregnancies by 3.5% to 5% in the United States and by > 30% in low-resource settings.[44,47]

Conclusions

In summary, considerable effort is being expended despite extremely constrained funding to broaden the contraceptive method mix. Methods are being developed to increase user control, as some individuals do not want to rely on a provider for initiation and discontinuation, and to offer newer long-acting reversible contraception or nonhormonal choices with secondary benefits, such as prevention of STIs or HIV. This will lead to more choices for users and provide options for individuals who may be currently dissatisfied with their method. This may be an issue in health systems with a high turnover in skilled providers such as in LMICs. As more men are expressing willingness to share the contraceptive burden, new options for men are essential. Male contraception would enable men to take responsibility for their sexual and reproductive behavior—a critical step towards reproductive justice and greater equity in global family planning.[44,48,49] That said, insufficient resources are dedicated to support these endeavors and to provide the essential ongoing commitment to get these methods reliably to users globally. It almost goes without saying that only a small number of these promising and potential leads will ever get to rapidly evolving market in developed countries, and only a few will contribute significantly to meet the needs in developing markets. But there is hope that improved applied contraceptive science now may have a longer benefit stream for all men and women seeking to fulfill their reproductive and health goals well into the future. This clearly is an example of a public good.

While great strides were achieved through the public sector, nonpharmaceutical channels, these successes build off of partnerships between government, researchers, and potential manufacturers. To get products to the market, more viable public-private partnerships are needed. And lastly, while progress is slow and many

of these methods may never reach the global market, there is hope, demonstrated by the recently FDA-approved new methods, such as Phexxi, Twirla (Agile Therapeutics Inc., Princeton, NJ), and Annovera. There is also potential hope in expanding channels in the post-COVID environment for getting methods into LMICs and achieving regulatory approval and procurement by national authorities in emerging health insurance schemes and private sector health systems.

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