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PERSPECTIVES

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Male Contraception

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Unintended pregnancy is a global public health problem. Despite a variety of female contraceptive options, male contraceptive options are limited to the condom and vasectomy. Condoms have high failure rates and surgical vasectomy is not reliably reversible. There is a global need and desire for novel male contraceptive methods. Hormonal methods have progressed the furthest in clinical development and androgen plus progestin formulations hold promise as a marketable, reversible male contraceptive over the next decade. Investigators have tested androgen plus progestin approaches using oral, transdermal, subdermal, and injectable drug formulations and demonstrated the short-term safety and reversibility of hormonal male contraception. The most commonly reported side effects associated with hormonal male contraception include weight gain, acne, slight suppression of serum high-density cholesterol, mood changes, and changes in libido. Efficacy trials of hormonal male contraceptives have demonstrated contraceptive efficacy rates greater than that of condoms. Although there has been less progression in the development of nonhormonal male contraceptives, potentially reversible vaso-occlusive methods are currently in clinical trials in some countries. Various studies have confirmed both men and women's desire for novel male contraceptives. Barriers to development include an absence of investment from pharmaceutical companies, concerns regarding side effects and spermatogenic rebound with hormonal methods, and lack of clear reversibility and proven effectiveness of nonhormonal methods. The ultimate availability of male contraceptives could have an important impact on decreasing global unintended pregnancy rates (currently 40% of all pregnancies) and will be a step towards reproductive justice and greater equity in family planning.

INTRODUCTION

There is an unmet need to address ongoing high rates of unintended pregnancies worldwide. An estimated 44% of pregnancies are unintended globally [1], with more than half of those ending in abortion. This puts women at risk for preventable medical procedures, that are many times unsafe, and for maternal death. These trends have persisted despite a variety of female contraceptive options, with millions of women undergoing unsafe abortions annually [2]. A recent World Health Organization (WHO) study found that among women facing unintended pregnancies, two-thirds were either not using contraception or not using a reliable method (*e.g.* withdrawal or the rhythm method) [3]. Common reasons for discontinuation of contraceptive use were health concerns, side effects, and contraceptive failure. Within couples where the woman discontinues contraceptive use for any of the above reasons, there are frequently limited alternative reversible methods to prevent unwanted pregnancies. The two currently available forms of male contraception are condoms and the vasectomies. Condoms have a high

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Abbreviations: WHO, World Health Organization; HPG, hypothalamic-pituitary-gonadal axis; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; IM, intramuscular; TE, testosterone enanthate; TU, testosterone undecanoate; DMAU, Dimethandrolone Undecanoate; DMA, dimethandrolone; AEs, adverse events; MENT, 7α -methyl-19-nortestosterone; RISUG, Reversible Inhibition of Sperm under Guidance; DMSO, dimethyl sulfoxide.

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failure rate, 13% with regular use [4], while vasectomies are invasive and are not reliably reversible [5]. Despite ongoing efforts to develop male contraceptive options, to date, highly effective and reversible male contraceptive methods are unavailable.

Both men and women express interest in using novel male contraceptive methods. The majority (78%) of men believe that both partners share an equal responsibility for family planning [6]. A novel male contraceptive would not only give men an additional and much needed contraceptive option but would provide a necessary alternative for couples in which the woman is unable to use female contraception due to medical contraindications or side effects.

Research on male contraception began over 60 years ago, and there have been some important advances in the last decade. Here, we review progress in male contraceptive development, the challenges and limitations the field faces, highlight recent promising studies, and speculate on future prospects.

MECHANISMS OF MALE CONTRACEPTION

Hormonal male contraception interrupts a naturally occurring hormonal feedback loop, the hypothalamic-pituitary-gonadal (HPG) axis, to suppress spermatogenesis (Figure 1a). An intact HPG axis starts at the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH). This stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). FSH supports testicular Sertoli cell function, which is required to support maturation of spermatogonia within the testes. LH stimulates testicular Leydig cells to make testosterone. A high concentration of intratesticular testosterone (approximately 100-fold that in blood) is required to support normal spermatogenesis. Circulating testosterone inhibits the release of GnRH, LH, and FSH secretion, completing the feedback loop.

Hormonal male contraception interrupts the HPG axis (Figure 1b). Exogenous testosterone, alone or with a progestin, suppresses GnRH, LH, and FSH production, leading to suppression of intratesticular testosterone production and, consequently spermatogenesis. The addition of a progestin to testosterone increases both the rapidity and extent of suppression of FSH and LH release [7], and may have additional direct, inhibitory testicular effects [8]. While intratesticular testosterone is reduced, the exogenous androgen in the male contraceptive binds to androgen receptors in the brain and non-gonadal, peripheral tissues, maintaining androgenic functions such as muscle mass and libido in the man. Suppressed spermatogenesis eventually results in reversible and often complete absence of sperm in the ejaculate.

Non-hormonal male contraceptive approaches include physically blocking sperm passage through the male reproductive tract (vaso-occlusion), altering sperm motility, and interrupting intratesticular sperm maturation, among others.

HORMONAL MALE CONTRACEPTION

Various combinations of hormonal agents and methods of hormonal delivery have been used in male contraceptive clinical trials, including injectable formulations, transdermal gels, implants, and oral formulations (Figure 2).

Testosterone-based Contraceptive Efficacy Trials

Contraceptive "efficacy studies" are clinical trials in which enrolled couples rely solely on the contraceptive method under study. Prior to reaching that stage of development, the experimental agent must first be shown to be safe with prolonged administration to men, while achieving maximal suppression of FSH and LH [9]. In addition, the hormonal method must suppress sperm production to levels low enough to be effective as a contraceptive. Healthy men have 15-200 million sperm per milliliter of ejaculate. Analyses of data from early male contraceptive efficacy studies demonstrated that azoospermia (zero sperm in the ejaculate) was not required for effective contraception [10]. "Severe oligozoospermia" (less than 1-3 million sperm per milliliter of ejaculate) is consistent with effective male contraception, resulting in efficacy rates similar to female oral contraceptives.

Male contraceptive efficacy studies are designed to both test the effectiveness of the agent as a contraceptive while minimizing the risk of pregnancy. Enrolled couples first undergo a "suppression phase," during which they are required to use alternative contraceptive agents simultaneously with the investigational product until the man achieves a predetermined sperm count threshold (usually < 1 million sperm/ml in the ejaculate). This qualifies the couple for entrance into the "efficacy phase" of the study, at which point the couple relies solely on the investigational product for contraception, with concomitant monitoring of the sperm concentration by the clinical investigators.

WHO carried out the first two efficacy studies on hormonal male contraception. In both studies, male participants received weekly intramuscular (IM) injections of 200 mg testosterone enanthate (TE), twice the dosage required for physiologic testosterone replacement. The threshold for entering the efficacy phase was azoospermia in the first study, which 70% of men achieved [10] and was severe oligozoospermia (≤ 3 million/mL) in the second, which 98% of men achieved [9]. The regimen had high contraceptive efficacy, with a 1.4% failure rate.

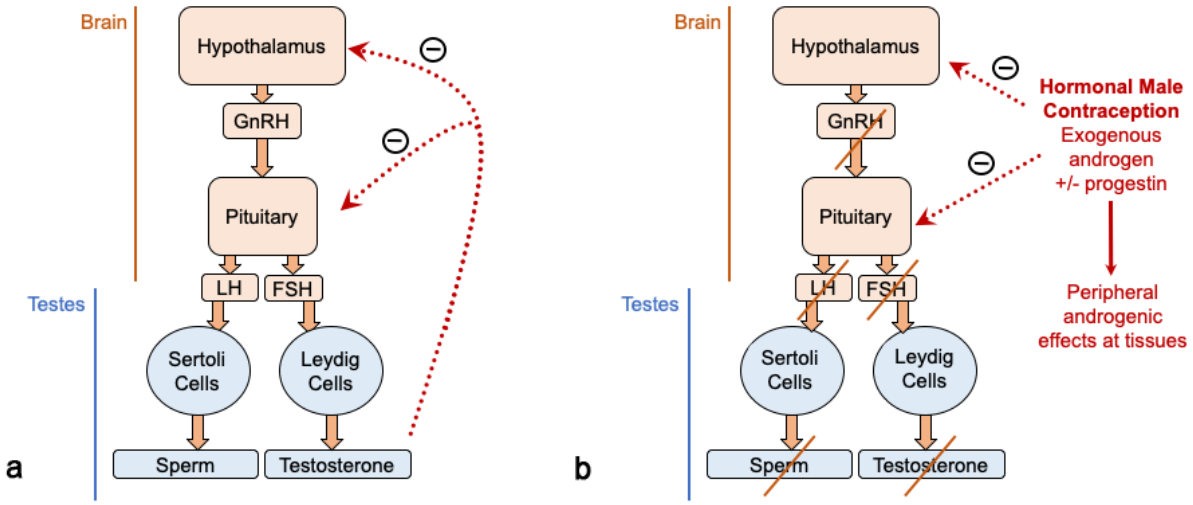

Figure 1. Mechanism of Hormonal Male Contraception. a. A normal male hypothalamic-pituitary-gonadal axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), stimulating the pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Respectively, LH and FSH stimulate Sertoli cells to promote the production of sperm (spermatogenesis) and Leydig cells to stimulate intratesticular testosterone production. Completing the classic feedback loop, circulating testosterone inhibits the secretion of GnRH, LH and FSH. **b**. The introduction of hormonal contraception (androgen +/- progestin) results in the suppression of circulating GnRH, LH, and FSH, thereby resulting in the suppression of intratesticular testosterone and spermatogenesis. Androgenic effects are maintained through the peripheral effects of the exogenous androgen at non-gonadal tissues.

Among the men whose sperm concentrations suppressed to ≤ 1 million/mL, the pregnancy rate was 0.7 per 100 person-years. These findings established the threshold target of ≤ 1 million/mL currently used in the field in order to reach the contraceptive efficacy phase of a hormonal male contraceptive trial. Common adverse events (AEs) experienced by participants included known androgenic side effects such as acne, weight gain, mood changes, changes in libido, and abnormal liver function tests. Injection site discomfort was also reported. Hence, this regimen was relatively unacceptable to users.

A longer-acting IM formulation, testosterone undecanoate (TU), aimed to reduce frequency of injections (to monthly injections instead of weekly). Two studies of this regimen targeted different sperm count thresholds – 97% of men suppressed to < 3 million/mL in the first study [11] and 95% of men suppressed to ≤ 1 million/mL in the second [12]. Good contraceptive efficacy was demonstrated (failure rates of 1.1-2.3%) but these studies underscored the phenomenon of spermatogenic rebound (when one's sperm count increases above the threshold during the efficacy phase), which was likely responsible for the few pregnancies observed. Despite the easier dosing schedule, similar androgenic side effects persisted.

Combination Testosterone-progestin Contraceptive Efficacy Trials

The addition of a progestin to an androgen not only aids in the suppression of spermatogenesis in most men, but allows physiologic dosing of the androgen, reducing potential adverse androgenic effects. The first male contraceptive efficacy study to investigate the combination utilized testosterone implants with IM depot medroxyprogesterone acetate (progestin) injections administered every 3 months. Ninety-four percent of men suppressed their sperm production to < 1 million/mL [13]. No pregnancies occurred and fewer androgenic effects were reported but implant extrusion rates of nearly 10% in pilot studies as well as inconsistent pharmacokinetics among testosterone implants halted future progression.

The most recent efficacy study was a multinational study using injectable TU along with norethisterone enanthate (progestin). Ninety-six percent of the men suppressed their sperm counts to ≤1 million/mL [14] and the approximate failure rate was 2%. The typical androgenic side effects were again noted in this study. However, an independent safety committee terminated the study early due to the perceived risk of adverse effects, chiefly depression and mood changes in some participants. Despite the study's early termination, three-quarters of participants said they were satisfied with the method and only 6% of participants discontinued use due to side effects.

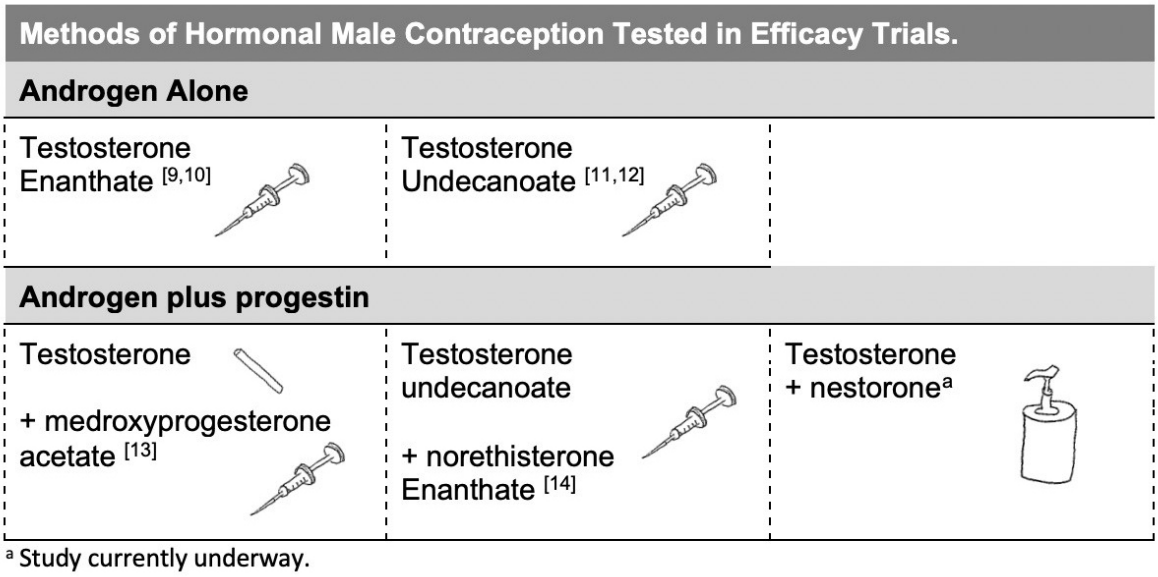

Figure 2. **Methods of Hormonal Male Contraception Tested in Efficacy Trials**.

GnRH Antagonists

GnRH antagonists suppress circulating FSH and LH levels in men, and could be adjuncts to androgen and/or progestin based male contraceptive methods. Unfortunately, most studies of GnRH antagonists (such as the short peptides Nal-Glu and acyline) have found they do not significantly enhance the spermatogenic suppression produced by the androgen/progestin regimen [15,16]. Another agent, cetrorelix (paired with 19-nortestosterone) uniformly induced azoospermia [17] but requires daily subcutaneous injections, making it undesirable. While research on GnRH antagonists has decelerated, they may still be promising adjuncts to androgen-based male contraceptive methods.

RECENT DEVELOPMENTS IN HORMONAL MALE CONTRACEPTION

When surveyed about potential contraceptives, many men report preferring a daily pill over an injection or implant [18]; however, identifying a safe and effective oral formulation of testosterone or a testosterone agonist has been elusive. Two novel androgens, DMAU and 11-βMNTDC, hold promise as potential oral male contraceptives.

Dimethandrolone Undecanoate (DMAU)

DMAU is currently under investigation as both a potential oral and injectable male contraceptive. *In vivo*, the pro-drug, DMAU is converted to the active drug, dimethandrolone (DMA), which can bind to both androgen and progesterone receptors, making DMAU a potential single-agent hormonal male contraceptive. Three studies of oral DMAU have been conducted in men to date [19-21]. DMAU requires concomitant food administration for oral absorption [22], and daily oral doses of 200-400 mg DMAU effectively suppresses serum testosterone, FSH, and LH concentrations to thresholds consistent with contraceptive efficacy [23]. Oral DMAU is well tolerated by users and the majority of trial participants experienced no side effects, despite markedly suppressed serum testosterone concentrations, confirming the androgenic potency of DMA. There was no suggestion of hepatotoxicity, and common side effects reported were weight gain, increased hematocrit, decreased HDL-cholesterol, and mild decrease in sexual desire in some subjects. A 12-week study of oral DMAU measuring effects on spermatogenic suppression has just been completed. If DMAU proves to effectively suppress sperm production, it could be a great step forward towards the development of a daily "male pill." Longer studies will also need to establish the safety and acceptability of DMAU as well as the longer-term feasibility of the food intake requirement for absorption.

11β-methyl-19-Nortestosterone17β-Dodecylcarbonate (11-βMNTDC)

Like DMAU, 11-βMNTDC is an oral male contraceptive candidate that can bind to both androgen and progesterone receptors. Pre-clinical studies were promising [19] and an initial human study showed that it also required concomitant food administration for absorption [20]. A 28-day, daily-dosing study of oral 11-βMNTDC [21] demonstrated suppression of serum testosterone,

FSH, and LH to very low levels, consistent with contraceptive efficacy in other studies. An increase in weight and LDL-cholesterol, minor increases in hemoglobin and creatinine, and a reduction in sexual desire and HDL-cholesterol in drug-treated individuals was reported. Longer studies of 11-βMNTDC are being designed to optimize desired effects while minimizing side effects. An injectable formulation of 11-βMNTDC is also being considered.

7α-methyl-19-nortestosterone (MENT)

The synthetic androgen MENT also has high androgenic potency [24]. When studied as a subdermal implant, MENT suppressed spermatogenesis in men [25] but this was not sustained in the long-term [26]. This may be due to complications with the implant's hormone release at higher doses. This agent has not moved forward in development.

Testosterone plus Nestorone gel (NES-T)

Testosterone plus nestorone (segesterone acetate), a potent progestin, is currently under investigation as a combined transdermal formulation. In contrast to other synthetic progestins which may have androgenic, anti-androgenic, or glucocorticoid binding activities in addition to activating the progesterone receptor, nestorone is considered a "pure progestin" with only progestogenic actions [27]. The combination of testosterone and nestorone successfully suppressed serum FSH, LH, and testosterone concentrations in men [28-30] with over 88% of participants in a 6-month study suppressing their sperm counts to ≤ 1 million/mL. A phase 2b efficacy study of a combined testosterone plus nestorone gel is currently underway. This multinational study is recruiting 400 couples across seven countries. The male partner applies the gel on his shoulders daily until his sperm count suppresses to ≤ 1 million/mL, after which he and his female partner enter the efficacy phase and rely solely on the testosterone plus nestorone gel contraceptive for 12 months. Results are expected in 2022-2023. This is the first self-administered male hormonal contraceptive to reach efficacy testing, and the first hormonal male contraceptive efficacy study to include a site in sub-Saharan Africa.

CHALLENGES FACING DEVELOPMENT OF HORMONAL MALE CONTRACEPTION

Adverse Effects and Long-Term Safety

Until very recently, trials of hormonal male contraceptives have typically been reassuring with regards to serious side effects. Clinical trials of male contraceptives have been without serious adverse events or persistent metabolic derangements. Yet, there is lingering concern about the safety of long-term use of androgens. Commonly reported metabolic and biochemical changes resulting from use of hormonal male contraception include modest weight gain, suppressed HDL-cholesterol, and increased hematocrit and hemoglobin [31-33]. These abnormalities can vary depending on the method of delivery, dosage, and the combination of androgen and progestin. Transdermal formulations, for example, are less likely than injectable formulations to increase hemoglobin and hematocrit [34]. The addition of progestin to a testosterone-based method is more likely to increase weight gain than testosterone-alone [35,36] and oral androgen delivery is associated with more marked reductions in HDL-cholesterol than injectable or transdermal formulations [37]. In most efficacy trials of male contraception, these changes were not associated with any adverse health events (such as blood clots or cardiovascular events). However, the implications of longer-term use of these agents remain unknown. For example, although modest weight gain is frequently reported in these trials, whether the weight gain is associated with changes in body composition, including increases in lean versus fat mass, is not clear but could have implications for longer term metabolic risk. Some of the newer androgens (DMAU, 11-βMNTDC) cannot be converted to an estrogen-like compound in the human body. The resulting decrements in serum estrogen might have long-term effects on bone mass and strength, which are not quantifiable in a shorter-term study.

A recent study [14] highlighted the importance of assessing potential mood and sexual side effects of male hormonal contraceptives. This efficacy study was halted due to concerns regarding adverse effects including mood changes and depression. Of note, there was one case of depression deemed probably related to the contraceptive agent, one suicide that was deemed not related (subject was unable to cope with academic pressure), one intentional paracetamol overdose and one tachycardia with paroxysmal atrial fibrillation, both deemed possibly related. Of the twenty men who discontinued participation in that study, 14 of them had changes in mood as the only or one of multiple reasons for discontinuation. Sexual side effects associated with male hormonal contraceptives have been mixed, with both increases and decreases in libido having been reported with the same formulation in some studies [38], and such potential side effects are difficult to determine without a placebo group. It remains unclear what drives these changes in mood and sexual desire, but these are commonly reported by women with use of female hormonal contraception. Importantly, it is not yet understood what side effects regulatory agencies and future users of male contraception will be willing to accept in exchange for the benefits of contraception. Women weigh the risks of side effects associated with female contraception in relation to the risks of pregnan-

cy. In contrast, men who would use male contraception are aiming to prevent pregnancy and possible contraceptive-associated side effects in their partner(s), while assuming the risk of potential side effects themselves.

Rates of suppression and recovery: A disadvantage of hormonal male contraception is the time it takes men to suppress and to recover normal spermatogenesis. Due to the 72-day cycle of spermatogenesis (time from first mitotic event to fully mature sperm), hormonal methods require at least 2-3 months of use for spermatogenesis to suppress to contraceptive efficacy [7]. This is a similar amount of time to the onset of effectiveness of a vasectomy [5]. Similarly, the time it takes for spermatogenesis to fully recover after suppression is a median of 3.4 months [39]. There is variability in the time it takes men to both suppress and recover spermatogenesis. This variability may be affected by age, race, baseline sperm, and/or LH serum concentrations, method of hormone delivery, and use of progestin [39]. These long "on" and "off" periods could hinder the acceptance of these methods in men seeking contraceptive options. Despite the long waiting periods, all male hormonal contraceptive methods are fully reversible.

Failure to Suppress Spermatogenesis: Across hormonal contraceptive trials, around 5-10% of men consistently fail to fully suppress spermatogenesis to ≤ 1 million/mL. While it is currently unknown why this is the case, it is possible that persistent levels of intratesticular testosterone [40] and/or FSH/LH [41] maintain low-level spermatogenesis in some men. An integrated analysis of prior studies suggests that Asian men more rapidly and uniformly suppress spermatogenesis than non-Asian men of European descent [7]. The reason for this variance is still unknown. It is possible that the mechanisms that result in those differences are also at play in "non-responders." These have been hypothesized to include: testicular histomorphometry, T concentrations and metabolism, polymorphisms within the androgen receptor, or gonadotropin suppressibility [42].

Spermatogenic Rebound: Around 1-2% of men in hormonal contraception efficacy studies show a brief rise in their sperm concentration outside of the threshold of contraceptive efficacy, otherwise known as spermatogenic rebound. Often, after sperm rebound occurs, the sperm concentration will drop back into efficacy parameters. Again, the mechanism of sperm rebound is unknown. Given that this is reported even in studies of long-acting androgens, it is not likely a regimen compliance related issue. It is correspondingly possible that persisting testosterone and/or FSH/LH concentrations aid in this momentary recovery of spermatogenesis. Emerging technologies may allow men to test their sperm concentrations at home to check their fertility status [43,44], making this hurdle more easily overcome.

In summary, the realm of hormonal male contraception is one where extensive study has established that a regimen consisting of combination androgen/progestin will likely deliver high contraceptive efficacy that is fully reversible. Research is ongoing to enhance ease of delivery and refine the dose at which the risk/benefit profile is optimized.

NONHORMONAL MALE CONTRACEPTION

By design, nonhormonal male contraceptives do not result in hormonal changes for the user, potentially resulting in fewer systemic side effects. Various nonhormonal candidates are in development, and many have reached pre-clinical development, showing promise in rodent models. However, sperm-specific targets are difficult to identify, and have not been translatable from rodent models to human trials. In particular, the issue of "off target" effects have been particularly challenging in targeting these various molecules and pathways. Mechanisms under investigation include non-hormonal molecules required for sperm maturation, inhibition of specialized sperm motility machinery, and prevention of sperm transport to the ejaculate by reversibly occluding the vas deferens.

Vaso-occlusive Methods

Reversible Inhibition of Sperm under Guidance (RISUG): Vaso-occlusive methods are the only nonhormonal male contraceptive method to reach clinical trials in men. Conceptually, these methods create a temporary physical blockage in the lumen of the vas deferens, blocking the passage of sperm, which can be reversed by introduction of dimethyl sulfoxide (DMSO) in the same space. Vaso-occlusive methods currently under investigation are RISUG and Vasalgel, both of which are administered via a one-time, bilateral intravasal injection.

RISUG is a bilateral vas intraluminal injection that has been under investigation in India for nearly three decades. RISUG utilizes a styrene maleic anhydride (SMA) to temporarily plug the vas deferens, both creating a physical barrier to sperm passage and altering the local pH thereby altering sperm morphology (resulting in disrupted fertilizing ability) [45,46]. Early studies [47,48] showed that RISUG achieved azoospermia in all men (within 1-3 months of the injection) and maintained suppression for at least a year. The most commonly reported side effect was scrotal swelling in some men. No pregnancies were reported in these studies. Most recently, a phase III efficacy study was completed in 139 men [49]. In this trial, 133 of the men achieved profound sperm suppression with 82.7% of them achieving azoospermia within 1 month and 17.3% within 3-6 months. Procedure failure was reported in six men who did not suppress

their sperm production. No pregnancies occurred during the 6-month follow up period. Again, temporary scrotal enlargement was reported in the majority of participants and 48 participants (36.2%) also reported mild scrotal and inguinal region pain (which resolved within 1 month).

While RISUG holds the promise of an effective male contraceptive with minimal side effects, reversibility has not yet been demonstrated in human trials. Reversibility was demonstrated in rats [50], rabbits [51], and non-human primate studies without side effects [52-54]. Reversal has been attempted invasively – by injecting DMSO with [51] or without sodium bicarbonate [50] – and non-invasively, by means of a multimodal approach of maneuvers [52-54]. Human studies that demonstrate full return of fertility are required before RISUG can be considered a method of reversible contraception and not permanent sterilization.

Vasalgel: Vasalgel is also a bilateral vas injection that creates a physical barrier to sperm but differs slightly from RISUG in chemical composition. It is comprised of SMA acid, which unlike SMA, does not hydrolyze in aqueous solutions. This confers on it the advantages of ease of production and longer-term stability [55]. In a pre-clinical study of Vasalgel, marked sperm suppression was achieved (all rabbits reached < 1 million/ml) within ~1 month [55]. However, when some of these rabbits were studied after reversal of Vasalgel with injection of sodium bicarbonate, it was found that while sperm concentration was restored in all of them, certain abnormalities of morphology and motility persisted [56]. This raised a serious concern about the return of sperm function. In a recent study, Vasalgel was effective at preventing pregnancy in 16 rhesus monkeys for a 2-year period [57]. Reversibility was not evaluated. Human studies of Vasalgel have not yet been performed.

Other Nonhormonal Male Contraceptive Candidates

An early nonhormonal candidate was adjudin, a lonidamide derivative that disrupted the Sertoli cell spermatid junctions and Sertoli cell cytoskeleton, resulting in loss of spermatids. Despite reversibly suppressing spermatogenesis in rats, resulting liver inflammation and skeletal muscle atrophy demanded a modification to the compound [58]. A follow-up study conjugated adjudin to a recombinant FSH mutant to target it to the testes and improve organ specificity [59]. While this improved off target effects, there was concern about high production costs, low bioavailability, and the risk of developing anti-FSH autoantibodies. Recently, the combination of an endogenously produced reversible blood-testes-barrier modifier, F5-peptide, along with low (subtherapeutic) dose adjudin, induced effective and reversible infertility in rats [60]. By using the F5-peptide, bioavailability was increased and the lower dose of adjudin reduced the systemic toxicity. Thus adjudin, and other agents that target Sertoli cells, remain promising agents in the pre-clinical pipeline.

EPPIN, a sperm-specific surface protein, is another potential non-hormonal contraceptive target. Studies in monkeys demonstrated that antibodies bound to EPPIN impair sperm motility leading to induced infertility [61,62]. Recently, a study found that the compound EP055, which targets EPPIN, suppresses normal sperm motility in macaques within 30 hours of infusion with full reversibility by 18 days [63]. Thus, EP055 may ultimately be an "on demand" contraceptive but work remains to demonstrate both safety and efficacy before human trials are undertaken.

Vitamin A, and its metabolites, are other potential targets for nonhormonal approaches to male contraception. Retinoic acid, the active metabolite of vitamin A, binds to retinoic acid receptors (RAR) to regulate the genes necessary for the maintenance of normal spermatogenesis. Infertility among RAR-knockout and vitamin A-deficient animals suggest that the administration of RAR antagonists may function to inhibit spermatogenesis [64,65]. BMS-189452, a pan-RAR-antagonist, led to 100% infertility in male rats, with full reversibility; however, adverse effects included testicular degeneration and indications of liver toxicity [66]. An ensuing study decreased the dose and increased the duration of BMS-189453, resulting in 100% induced infertility in mice, as well as full recovery, without any of the previously observed off-target effects [67]. This method holds promise as a future nonhormonal male contraceptive candidate if a more specific RAR-antagonist can be developed that inhibits only RAR-α activity in the sperm production pathway.

WIN 18,446, is an orally administered compound that inhibits testicular retinoic acid biosynthesis. WIN 18,446 was demonstrated to effectively, reversibly, inhibit spermatogenesis in men more than 50 years ago; however, men developed severe adverse reactions, such as nausea, vomiting, and malaise, when the contraceptive was taken in conjunction with alcohol (disulfiram reaction) [68]. In an effort to decouple the disulfiram reaction from the contraceptive effects, investigators determined that aldehyde dehydrogenase 1A2 (ALDH1A2) might be an effective, specific target in the retinoic acid biosynthesis pathway to target a novel inhibitor and potential contraceptive [69]. Studies are currently underway to develop a specific and bioavailable inhibitor of ALDH1A2.

There are a variety of other products under investigation in pre-clinical trials to produce a nonhormonal male contraceptive agent. These include JQ1, an inhibitor of bromodomain testes-specific protein, which is critical for chromatin remodeling during spermatogenesis [70] and

HC-056456, a calcium ion channel (CatSper) inhibitor, that prevents sperm hyperactivation [71]. These putative contraceptive targets are still in the proof-of-concept stages but hold long term promise as reversible, non-hormonal male methods. Unfortunately, none to date have reached clinical trials and thus the specificity of these inhibitors for sperm/spermatogenesis in humans remains untested.

IMPACT AND ACCEPTABILITY

Across the globe, a majority of men want novel forms of male contraception [72] and generally have positive responses to the hypothetical use of male contraceptives [18]. Studies have demonstrated that women would also support their male partner's use of a contraceptive and would trust them to use it [73,74]. Although these types of surveys demonstrate widespread interest in male contraception, it is challenging to quantify male contraceptive acceptability when no methods currently exist on the market. The closest existing data on acceptability is from men who have participated in contraceptive clinical trials who are likely to be skewed towards receptivity and acceptability. The majority of men who used injectable or transdermal methods in clinical studies reported both satisfaction and a willingness to recommend the contraceptive to others if it were commercially available [75-78]. In fact, in the male contraceptive study that was terminated early due to concerns for mood changes, 83% of participants reported they would use an analogous hormonal contraceptive if it were available, despite being aware of the safety concerns [14].

A recent study modeled the potential impact male contraception could have internationally. The results indicated that male contraception could reduce unintended pregnancies by 3.5-5% in the United States and by > 30% in the developing world [79]. This analysis suggested male contraception could most meaningfully reduce unintended pregnancy in populations where use of existing contraceptives is low. Understanding the impact of male contraception may be particularly relevant in underserved and marginalized communities, where the consequences of unintended pregnancies may be the greatest.

Further data on the potential impact and acceptability of male contraception may aid in garnering interest from the pharmaceutical industry to accelerate male contraceptive development towards market availability. Currently, research and development are sponsored mostly by the National Institutes of Health (Eunice Kennedy Shriver National Institute of Child Health and Human Development). Reasons for discontinued support are largely considered financial in nature, especially given the unclear regulatory path to approval of a new agent. However, changing global attitudes towards male contraception and gender equity may alter this situation with time, particularly if products in the pipeline demonstrate efficacy, safety, and reversibility.

CONCLUSIONS AND OUTLOOK

There is a global need and interest in novel male contraceptives. The ideal male contraceptive will be effective, safe, fully reversible, and accessible to a broad population of potential users. Not only does male contraception have the potential to reduce the high number of unintended pregnancies worldwide but could provide couples an additional family planning option. Efficacy studies of hormonal male contraception have evaluated a variety of androgen-alone and androgen plus progestin approaches. The most promising hormonal approach is androgen plus progestin regimens delivered as injections and transdermal gels, but novel oral agents are currently under investigation. Results indicate these methods are safe in the short-term, reversible, and more efficacious than condoms in the majority of men at least in the context of a clinical trial. Research is ongoing to find a regimen that will minimize side effects. Other considerations are reducing the time taken for a regimen to be effective and reversed, minimizing and identifying "non-responders" and determining long-term safety.

Efficacy studies on nonhormonal approaches have been limited to vas-occlusive methods and mandate additional research to confirm safety and reversibility. Several alternative targets for non-hormonal contraception are in preclinical development but may be many years from reaching the market.

Studies affirm the high acceptability and potential positive impact of introducing novel male contraceptives to the family planning marketplace. The development of reversible, safe male contraceptives will be a step towards reproductive justice, giving men more options to control their own fertility and to share the responsibility of family planning with their partner.

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