Emerging approaches to male contraception

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Despite significant interests in contraception by men, effective methods of male contraception are limited to vasectomy and condoms. Recently, there have been several promising advances in male contraceptive research. This review will update readers on recent research in both hormonal and nonhormonal approaches to male contraception. Hormonal approaches to male contraception have been stymied by adverse effects, formulations requiring injections or implants, a 5% to10% nonresponse rate, as well as poor understanding of user acceptability. In the last several years, research has focused on novel, orally bioavailable androgens such as dimethandrolone undecanoate and 11β-methyl-19-nor-testosterone. Additionally, combinations of a topical testosterone gel combined with a gel containing segesterone acetate, a potent progestin, have shown promise in clinical trials recently. Simultaneously, significant preclinical progress has been made in several approaches to nonhormonal male contraceptives, including compounds that inhibit sperm motility such as eppin, compounds that inhibit retinoic acid binding or biosynthesis, and reversible approaches to obstruction of the vas deferens. It is imperative for these areas of research to continue making strides so that there is a gamut of contraceptive options for couples to choose from. Some of these approaches will hopefully reach clinical utility soon, greatly improving contraceptive choice for couples. (Fertil Steril® 2021;115:1369–76. ©2021 by American Society for Reproductive Medicine.)

Key Words: Dimethandrolone, male contraception, nestorone, RISUG, spermatogenesis

The development of female contraceptive methods had great impacts on fertility rate, women's health, the role of women in society, and sexual practices of adults and adolescents (1). Failure rates of these methods range from <1% to >20% (2), depending on the method, with numerous reversible options. However, a significant proportion of women have contraindications to the currently available female contraceptives or experience adverse effects from the use of these methods, resulting in method discontinuation. The only effective and reversible male contraception option is condoms, the use of which is associated with a 13% on year failure rate of unintended pregnancy (3). As a result of the shortcomings of the current female contraceptives and very limited male contraceptive options, the rates of unplanned pregnancy have largely remained at approximately 44% globally for some time (4, 5), accounting for roughly 100 × 10^6 unintended pregnancies yearly. Interestingly, surveys of couples have shown that most men and women would be likely to accept and use safe and effective male contraceptive methods were they to become available (6–9). In this article, we will review the most recent advances in the field of male contraceptive research, work aimed at reducing the currently high rate of unintended pregnancy.

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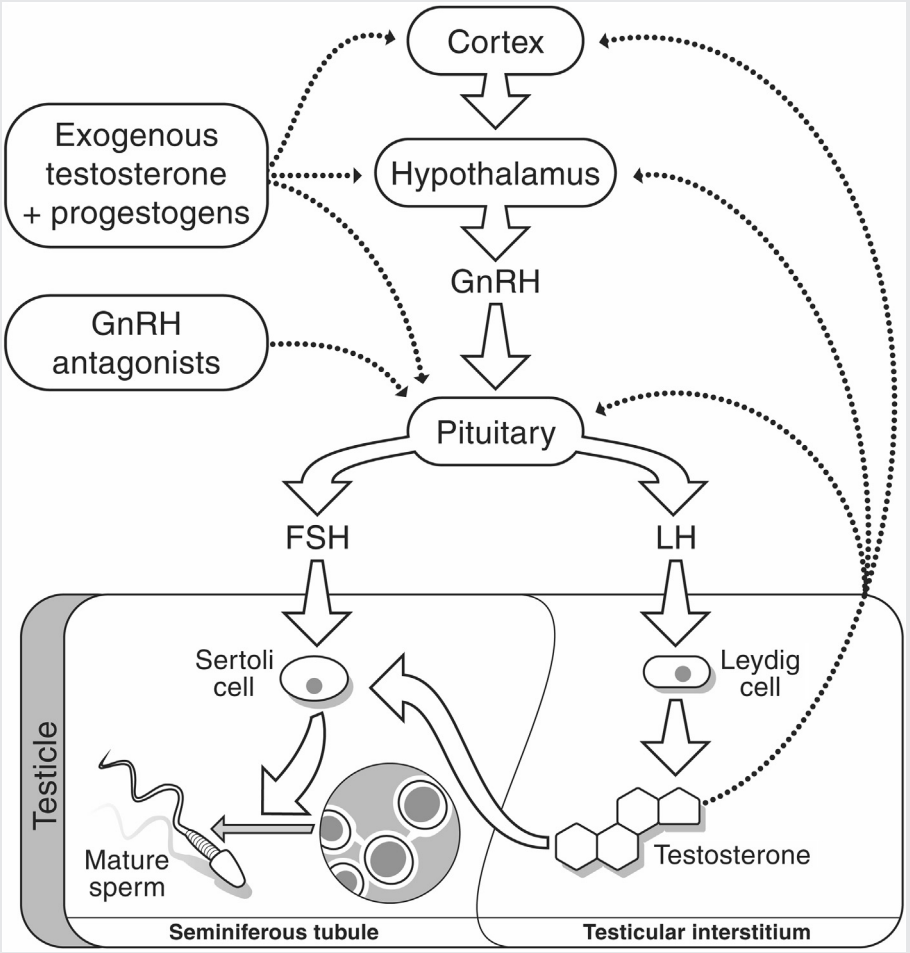
MALE REPRODUCTIVE PHYSIOLOGY

In men, the hypothalamic-pituitary-testicular axis regulates the production of testosterone (T) and sperm (Fig. 1, left panel). The hypothalamus releases gonadotropin-releasing hormone, which stimulates the pituitary to release gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates the Leydig cells of the testes to produce T and FSH stimulates the Sertoli cells, the function of which is necessary for sperm production. In addition, testosterone binds to androgen receptors (ARs) in the pituitary that suppress the release of LH and FSH in a highly regulated feedback loop. Hormonal contraceptive methods exploit this feedback inhibition (Fig. 1, right panel) by providing exogenous androgens that bind to ARs in the brain and inhibit the release of LH and FSH. Gonadotropin suppression turns off the stimulation of the Leydig and Sertoli cells in the testes, markedly lowering intratesticular T biosynthesis and Sertoli cell function, leading to a cessation of spermatogenesis in most

FIGURE 1



The normal hypothalamic-pituitary-testicular axis is depicted on the *left*. *Green arrows* are stimulatory and *red arrows* inhibitory. On the *right* is the situation induced by hormonal male contraceptives in which exogenous androgens and progestins suppress the release of FSH and LH from the pituitary (*dotted green arrows*), depriving the testes of the local signals required for spermatogenesis. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Thirumalai. Emerging methods of male contraception. Fertil Steril 2021.

men. At the same time, the exogenously administered T binds to ARs in other tissues, preventing the development of signs and symptoms of hypogonadism. Clinical trials of various hormonal male contraceptive regimens have revealed that the addition of a progestin to the androgen enhances the speed and magnitude of gonadotropin suppression (10) and may even directly inhibit spermatogenesis (11). As a result, most male contraceptive regimens use both androgens and progestins. It takes approximately 72 days to produce mature sperm from the spermatogonial stem cells (12), which is why male contraceptives that inhibit sperm production, such as hormonal methods, are associated with a 2 to3 month delay in the onset of efficacy. Similarly, sperm production is only restored several months after discontinuation of a hormonal method. After sperm are produced, they are stored in the epididymis until ejaculation, only gaining their full motility and capacity to fertilize the egg once within the female urogenital tract. Nonhormonal approaches to male contraception have focused on interrupting different steps in these processes, ranging from interfering with sperm production to blocking sperm transport during ejaculation or impairing the ability of the sperm to gain motility after ejaculation.

HORMONAL MALE CONTRACEPTIVE METHODS—WHAT IS KNOWN

The clinical trials testing androgen/progestin male contraceptive trials conducted to date have been elegantly summarized in prior reviews (13–15). The lessons learned from these trials were that marked gonadotropin suppression to concentrations well below the lower limit of the normal range is required, but not sufficient, for effective suppression of spermatogenesis. For one regimen, only men who suppressed FSH and LH serum levels to ≤ 1 IU/L had suppression of sperm concentrations to $< 1 \times 10^6$ sperm/mL of ejaculate (16), a concentration of sperm associated with a

roughly 1% rate of unintended pregnancy (17). Normally, sperm concentrations in men exceed 15×10^6 sperm/mL of ejaculate. Ideally, male contraceptive regimens would suppress sperm production to zero (azoospermia); however, achieving high rates of azoospermia has proven very difficult. For example, only 70% of men achieved this target in 1 large male hormonal contraceptive trial (17, 18). The good news is that the efficacy at prevention of unintended pregnancy is <1% when azoospermia is achieved, a rate similar to the most effective female methods available currently (2). In the most recent male hormonal contraceptive trials, sperm concentrations of $<1 \times 10^6$ sperm/mL of ejaculate (severe oligozoospermia) have been achieved in approximately 95% of men (19–21), a contraceptive efficacy similar to that of female oral contraceptives (3).

CHALLENGES FACING MALE HORMONAL CONTRACEPTION

Male hormonal contraceptive trials have reported a number of adverse side effects, including signs such as acne and weight gain and symptoms such as depression and reduced libido (22), although the rates of these symptoms are similar to those reported by women using female hormonal methods of contraception (23). Women using hormonal contraception experienced more headaches and weight gain than men did, but the decrease in libido was comparable across genders. In contrast, men in hormonal contraceptive trials experience more acne, increases in libido, and depression (23). Women were more likely to discontinue the use of the contraceptive agent than men (23), but this may be because of the fact that the data from women came from real-world use (24), whereas the male data come from a contraceptive efficacy trial (21) in which the men were self-selected volunteers. The issue of depression in men in male contraceptive studies is particularly worrisome. A recent, large efficacy study (21) of testosterone undecanoate and norethisterone enanthate injections in men was terminated early after an external safety review by the World Health Organization because of an undue number of adverse events related to depression, including one suicide, increased libido, and injection site pain. As a result, future male hormonal contraceptive studies will need to follow the subjects' moods very closely to ensure no harm comes to the study subjects.

To date, most male hormonal contraceptive studies have administered the hormones via injections or implants, and this comes with both the requirement of medical visits for dosing and significant discomfort to the subjects from the injections or implants procedures (14). Previously, oral androgens were not frequently studied either because of concern for hepatotoxicity or the need for multiple daily doses (25). Survey data suggests that men might prefer a pill over other delivery methods for hormone delivery (6).

One challenge that male hormonal contraceptives may not be able to address is the 2–3 months it takes to suppress the sperm concentrations to contraceptive thresholds (10), and the equally long time it takes for recovery of the numbers to normal when the method is discontinued. These times depend somewhat on the method of hormone delivery and duration of use (26), but reassuringly, hormonal contraception appears to be fully reversible in almost all men. The biggest mystery in the field of male hormonal contraception is why 5%–10% of men in most clinical trials fail to have their sperm concentrations fully suppressed. Although explanations such as persistent intratesticular T (27) and/or persistent gonadotropins (28) have been invoked, the true cause for the suboptimal response in a small number of subjects remains unclear. In addition some men (1%–2%) experience "sperm rebound" during efficacy trials, wherein their sperm concentrations transiently rise above the thresholds set for contraceptive efficacy, despite treatment compliance. This phenomenon is not understood.

NOVEL AGENTS FOR MALE HORMONAL CONTRACEPTION

Recent male hormonal contraceptive research has focused on oral and topical methods for self-administration to increase the convenience of use. There are several exciting new oral and topical drugs—segesterone acetate, dimethandrolone, and 11β-19-nor-testosterone—that are being tested in male hormonal contraceptive clinical trials. These agents, should they prove to be effective and well tolerated, have the potential for clinical utility. In the following sections, we will review their development in detail.

Segesterone Acetate

A novel progestin, segesterone acetate (brand name Nestorone), has been formulated as a transdermal gel for daily use in combination with a topical T gel in male contraceptive trials. Segesterone acetate is a "pure progestin", with no androgenic, estrogenic, or glucocorticoid activity in vitro (29). It is currently approved for use in women, along with ethinyl estradiol, as a vaginal ring and is well tolerated (30). The first male hormonal contraceptive study in men had participants apply once-daily segesterone acetate gel (variable dose groups of 2–8 mg/day) along with once-daily T gel (10 g/day) for 20 days. This study demonstrated that >80% of men who received 8 mg/day of segesterone acetate along with T had suppression of their gonadotropin levels to ≤1 IU/L, 69% of whom suppressed their gonadotropins levels to <0.5 IU/L (31). A subsequent 20-week study showed that among men who received segesterone acetate gel (8–12 mg/day) along with T gel (10 g/day), >88% had their sperm concentrations suppressed to $<1 \times 10^6$ sperm/mL of ejaculate, in contrast to only 23% of men receiving T gel alone (32). The gel was largely well tolerated without significant safety concerns. Five of 99 men in the study discontinued treatment because of adverse events—one for irritability and nightmares, one for decreased libido, one for increased appetite, one for mood swings, and one for an asthma exacerbation (32). Acne was reported by 21% of men, headache by 17%, weight increase by 7%, and insomnia by 6% of men during drug exposure (33). Next, segesterone acetate was formulated as a combination gel (segesterone acetate 8.3 mg and T 62.5 mg), and the combination product demonstrated gonadotropin

suppression similar to that of the two gels used alone after 28 days of treatment (84% men with FSH and LH levels ≤ 1 IU/L)(34). Given the promising results of this product, a phase IIB efficacy trial using the combined segesterone acetate/T gel is currently underway in 13 sites spanning 4 continents: North America, South America, Europe, and Africa. To our knowledge, this trial is the first large-scale, male hormonal contraceptive efficacy trial using a self-administered product. The trial is recruiting 400 couples who will undergo an initial period of sperm suppression until they exhibit a sperm concentration of $<1 \times 10^6$/mL of ejaculate. At this point, men with adequate sperm suppression will enter a 52-week efficacy phase in which they will only use the study product for contraception. The primary outcome of the study is the rate of unintended pregnancy, with key secondary outcomes being mood and sexual function as assessed by validated questionnaires.

Novel Oral Androgen: Dimethandrolone

Dimethandrolone undecanoate (DMAU) is a modified T derivative that is being studied as a once-daily oral male hormonal contraceptive. Orally dosed DMAU is cleaved by esterases in vivo to the active drug dimethandrolone (DMA). The undecanoate ester both enhances oral absorption when ingested with a fat-containing meal and extends the half-life. DMA does not require 5α-reduction for its action (35) and is not aromatized to an estrogen in vivo (36). Another unique aspect of DMA is that it binds both ARs and progesterone receptors (PRs) with a relative binding affinity 4 times that of T at the AR and 18% that of progesterone at the PR (37). Animal studies showed that orally administered DMAU was able to reversibly suppress gonadotropins, spermatogenesis, and fertility in rodents while still preserving androgenic characteristics (38–40). A first-in-men study of single doses of DMAU (at doses ranging from 100 to 800 mg/orally/day) showed that the drug was well tolerated when dosed once daily. Similar to oral testosterone undecanoate, oral DMA requires coadministration with a fat-containing meal to optimize absorption (41, 42). A subsequent 28-day daily oral dosing study of DMAU showed suppression of T serum levels to castrate levels in treated men and suppression of gonadotropin serum levels to ≤ 1 IU/L in all treated groups (43). In addition, this study showed the drug to be mostly well tolerated by trial participants. DMA is a potent androgen. Therefore, androgenic effects such as weight gain (1.5–3.8 kg), increase in hematocrit (up to 2%), and reduction in high-density lipoprotein-cholesterol level (6–15 mg/dL) were noted among study subjects (43). Among the participants who received the active drug, 11% reported headache, 11% reported decreased libido, and 7% reported acne (43). No participants discontinued treatment because of adverse events (43). Given these results, DMAU holds the promise of being a once-daily orally bioavailable prototype "male pill". A 12-week study of DMAU alone and in combination with an oral low-dose progestin, levonorgestrel, has since been completed and the results are forthcoming. In parallel, DMAU has also been formulated as an intramuscular injection and is being studied at various doses as a potential long-acting reversible contraceptive injection.

Novel Oral Androgen: 11β-Methyl-19-Nortestosterone

11β-Methyl-19-nortestosterone dodecylcarbonate (11βMNTDC) has many features similar to those of DMAU, in that it also can be dosed orally once daily, is active at both ARs and PRs (37), is not aromatized (36), and does not require 5α-reduction for its action (35). Preclinical studies of 11βMNTDC demonstrated gonadotropin suppression, while body composition and bone mineral density were preserved (38). It has no obvious hepatotoxicity (40). The first human study of 11βMNTDC, similar to DMAU, was a single-dose, dose-escalating study, which revealed that the drug did not have obvious toxicity, could be administered once daily, and required administration with a fat-containing meal for optimal absorption and suppression of gonadotropins and T (44). A subsequent 28-day daily dosing study tested 11βMNTDC (200 mg and 400 mg doses) and revealed profound suppression of T serum level with both doses but greater suppression of gonadotropins serum levels to ≤ 1 IU/L at the 400 mg once-daily dose (45). Changes in hematocrit, high-density lipoprotein-cholesterol level, and weight were similar to those seen with DMA. In addition, a small but statistically significant increase in serum creatinine and low-density lipoprotein-cholesterol levels were observed (45). Adverse events in drug-treated men in this study included headache (29%), acne (16%), decreased libido (16%), mood changes (13%), fatigue (13%), and decreased erectile/ejaculatory function (10%) (45). Further studies with this product are still being designed, and it is also being considered as a possible long-acting reversible contraceptive injection.

EXPERIMENTAL NONHORMONAL MALE CONTRACEPTIVES

In addition to the previously described work attempting to develop hormonal male contraceptives, there has been great interest in trying to develop novel nonhormonal male contraceptives. Nonhormonal male contraception can be defined as an approach to male contraception that does not utilize the administration of T or compounds that block T secretion (46). Nonhormonal contraception may have some advantages compared with hormonal male contraceptives as they would likely avoid any impact on T concentrations and therefore not impact sexual function, sex drive, or body composition. In addition, the use of T could lead to disqualification from high-level sporting events. The following sections will describe past and future efforts to develop nonhormonal male contraceptives.

Gossypol

The first widely clinically studied nonhormonal male contraceptive was gossypol. Gossypol is a large molecule purified from the seeds of a cotton plant grown in China. Gossypol was extensively studied in the 1980s in 2 large phase III studies in China that enrolled >8,000 men (47, 48). In these studies, gossypol reduced both sperm production and sperm motility and induced abnormal sperm morphology via an

unknown mechanism. Most men developed azoospermia, and gossypol had a 90% efficacy in pregnancy prevention. Unfortunately, side effects including hypokalemia and hypokalemic periodic paralysis occurred in approximately 1% of treated men. In addition, spermatogenesis in almost 20% of men did not fully recover. Despite significant efforts to modify the structure of gossypol to reduce the risk of side effects and improve efficacy, the study of gossypol for nonhormonal male contraception has been largely abandoned (49).

Triptolide

A second naturally derived male contraceptive compound studied in China was the herb *Tripterygium wilfordii*, the active compound of which was called triptolide (50). *Tripterygium* had been used in traditional Chinese medicine for many centuries for the treatment of arthritis. Clinical study of patients treated with this compound showed that *Tripterygium* administration impaired sperm motility and decreased sperm counts. Unfortunately, as was the case with gossypol, several men experienced irreversible suppression of spermatogenesis, causing the abandonment of work studying this compound as a reversible male contraceptive (51).

Adjudin

The compound adjudin was studied as a nonhormonal male contraceptive in animal studies in the early 2000s (52). Adjudin administered to rodents interfered with the ability of spermatids to adhere to Sertoli cells. Because of this, the spermatids underwent premature spermiation resulting in the production of nonfunctional spermatozoa that were incapable of fertilization. In rats, administration of adjudin (50 mg/kg) twice weekly induced 100% infertility after 5 weeks of treatment. Notably, the administration of adjudin did not lead to changes in gonadotropin or T serum concentrations (53). Unfortunately, several animals experienced liver inflammation in a 29-day study (54). Follow-up work with adjudin conjugated to an FSHβ mutant, specifically targeting it to Sertoli cells, reduced the systemic exposure (55). Unfortunately, this approach proved prohibitively costly (56), and further study in either animals or humans of this conjugate was not performed.

H2-Gamendazole

H2-Gamendazole is a derivative of adjudin that interferes with the normal functioning of the apical ectoplasmic specialization (57). In one in vivo experiment, all rats receiving a single oral dose of gamendazole (6 mg/kg) became infertile; unfortunately, only half recovered fertility after treatment (58). In addition, H2-Gamendazole had concerning toxicity. For example, in 1 study of H2-gamendazole, 3 of 5 rats dosed with 200 mg/kg died, concerning for the low therapeutic index of this agent. Some preclinical study of this compound was performed in the believe that eventually performing some human testing, but this has not progressed as believed.

Eppin

Eppin is a protein located on the surface of the sperm. Eppin functions in liquefaction of the ejaculate, the absence of which severely impairs sperm motility (59). Initial immunization studies in male nonhuman primates demonstrated that most could be immunized against eppin. Notably, these males were mated and were unable to father pregnancies. Importantly, the animals regained fertility after cessation of the injections (60). After this proof-of-principle immunization study, this research group has focused their work on developing small molecules that inhibit eppin binding to the protein semenogelin, which is a necessary step in sperm liquefaction (61). A recent publication demonstrated that intravenous administration of the small molecule EP055 reduced sperm motility by 80% in male macaques (62). The group is now working on the development of potent, oral compounds in animal studies. Hopefully, continued work on this approach will result in a pill that can effectively reduce sperm motility as a male contraceptive.

BRDT Inhibition

The bromodomain protein, BRDT, is required for meiosis. Intriguingly, men with mutations in the *BRDT* gene have infertility, and semen analysis revealed abnormal sperm heads and poor motility (63). In 2012, a group showed that JQ1, a small molecule that potentially inhibited BRDT function, reversibly suppressed fertility in a murine model (64). Unfortunately, JQ1 inhibits other bromodomain proteins, which led to toxicity. This group is performing structure-activity modeling of JQ1 in efforts to develop a BRDT-specific inhibitor, retaining the contraceptive action while minimizing the potential for side effects (65).

Retinoic Acid Receptor Antagonists

It has been known since 1925 that vitamin A (retinol) is essential for sperm production and male fertility (66). All of the effects of retinol appear to be mediated by retinoic acid. Retinoic acid was shown to be necessary spermatogenesis (67, 68). Retinoic acid functions via binding to a family of retinoic acid receptors (RARs), which serve to regulate gene expression. Gene knockout experiments have shown that mice with deletion of one of several of the RARs are sterile (69, 70). Based on these observations, several groups are working on developing nonhormonal approaches to male contraception based on the blockade of retinoic acid function or biosynthesis.

One example of such a compound is BMS-189453, which was described in the early 2000s. This compound is an oral RAR pan-antagonist. Initial 1-month studies of BMS-189453 (15, 60, or 240 mg/kg) in rats led to marked testicular degeneration and infertility, but also liver toxicity (71). A second group of investigators followed up on these earlier studies, testing lower doses of BMS-18945 and demonstrating efficacy at sperm suppression without the liver toxicity observed with higher doses (72). For example, mice treated with BMS-18945 2.5–5 mg/kg for 4 weeks were completely sterile by 4 weeks of treatment with a return to fertility 12

weeks after the cessation of treatment (73). A specific retinoic acid-alpha antagonist has been reported in the literature (74), more recent versions of which may hold some promise for nonhormonal male contraception (75).

Retinoic Acid Biosynthesis Inhibitors

Almost 60 years ago, the administration of WIN 18,446 was shown to dramatically suppress sperm production in men, and it was studied in almost 100 men as the first nonhormonal male contraceptive (76, 77). Unfortunately, it was discovered that men taking WIN 18,446 had serious "disulfiram reactions" characterized by vomiting, sweating, and palpitations when they drank alcohol while taking WIN 18,446. Because of these severe disulfiram reactions, further study of WIN 18,446 as a male contraceptive stopped. In 2011, it was shown that WIN 18,446 functioned via inhibition of testicular retinoic acid biosynthesis (78). It was further demonstrated that WIN 18,446 inhibited 2 aldehyde dehydrogenase enzymes called ALDH1A1 and ALDH1A2 that are the final step in retinoic acid production (79). Work in this area is now focused on the production of novel products that specifically inhibit ALDH1A1 and ALDH1A2 without causing disulfiram reactions, which are mediated by a similar enzyme, ALDH2 (80).

CatSper

In 2001, an investigative group identified a novel sperm-specific calcium channel (81). Genetic deletion of the gene encoding the "CatSper" protein leads to infertility (82). The structure of a candidate CatSper antagonist, HC-056456, has been published (83). When tested In vitro, HC-056456 significantly suppressed sperm motility; however, no in vivo data are available. Nevertheless, inhibition of CatSper function and research into inhibition of other sperm ion channels necessary for sperm motility as an approach to male contraception is ongoing (84).

Gendarussa

An Indonesian traditional medicine called *Justicia gendarussa* has been reported to be used as a traditional form of contraception by men in Papua New Guinea. The active ingredient is thought to be a flavonoid called gendarusin A (85). Some data on the contraceptive efficacy of this compound were reported in abstract form, but not published. In addition, the mechanism of action remains unclear. Therefore, additional information will be needed to determine whether this is a viable approach to developing a nonhormonal male contraceptive.

Vas Occlusion Methods

Since the 1970s, several research groups have conducted research directed toward developing methods to reversibly plug the vas deferens. Reversible vas occlusion is an attractive approach to male contraception, as the initial vasal obstruction could provide long-lasting contraception. Later, the man could have the obstruction removed and have his fertility restored when desired. An Indian vas occlusion device called RISUG (reversible inhibition of sperm under guidance) was studied in several clinical trials in men (86, 87). The initial procedure is performed under ultrasound guidance. Specifically, a solution of styrene maleic anhydrate is injected into the vas deferens bilaterally, effectively occluding the vas and preventing the passage of sperm during ejaculation. Data from several small clinical trials of RISUG are available (86). Taken together, these studies demonstrated effective contraception over periods of up to 1 year in men. Unfortunately, no data from large-scale trials or demonstration of reversibility have been published (87).

A reformulation of RISUG, called "Valsalgel" in the United States, was tested as a contraceptive for 1 year in rabbits (88) and monkeys (89). After reversal, however, the sperm of the rabbits no longer had acrosomes, possibly because of inflammation in the vas, and no return to fertility data on these animals were reported (90). Therefore, as was the case with the Indian studies, it remains unclear if RISUG is truly reversible. Vas occlusion devices using medical-grade silicone and polyurethane were studied in China in the 1990s (91). In addition, these devices were associated with incomplete recovery of sperm parameters after attempted reversal (92), leading the investigators to abandon this approach to male contraception.

CONCLUSION

Contraception provision is essential for the prevention of unintended pregnancy. Given the limitations of the currently available methods of contraception, there is a great deal of interest in the development of novel male contraceptive methods. Numerous hormonal approaches to male contraception tested in human studies and newer studies with novel oral androgen/progestin compounds and topical gels are showing promise. Several nonhormonal approaches have been studied in mostly preclinical studies, but human studies to determine their safety and efficacy are lacking. Ongoing work in male contraceptive research is required to meet the unmet need of male-driven methods of birth control.

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