Citation: Clin Transl Sci (2020) 13, 228–237; doi:10.1111/cts.12708

REVIEW

Development of Novel Male Contraceptives

John K. Amory[1,*]

Unintended pregnancy is surprisingly common, accounting for 40–50% of pregnancies worldwide. Contraception is the most effective means of preventing unintended pregnancy. Seventy percent of all contraceptives are used by women; however, some women are unable to use contraceptives due to health conditions or side effects. Many men wish to take a more active role family planning, but currently have only two effective male contraceptive options, condoms and vasectomy. Therefore, work to develop novel male contraceptives analogous to popular female methods, such as daily pills or long-acting shots and implants, is underway. This paper will briefly discuss the pros and cons of condoms and vasectomies, and then review the research into novel methods of male contraception.

The world's population currently exceeds 7.7 billion and is increasing by 80 million per year and will likely reach 9.6–12.3 billion by 2100.[1] Population growth is the leading cause of environmental degradation.[2] Forty to 50% of this population growth is unintended. In the United States between 2008 and 2011, 45% of pregnancies were unplanned, and 42% of these pregnancies ended in abortion, accounting for 1.2 million abortions in the United States annually.[3] Worldwide, 41% of pregnancies were unplanned and 20% of these pregnancies ended in abortion.[4] These high rates of unintended pregnancy are due to inadequate use of or access to modern methods of contraception. Use of an effective contraceptive dramatically reduces abortion rates, and also results in improvements in newborn and maternal health from better child spacing.[5] Therefore, there is a great need for better access to contraceptives, and more contraceptive options. Male contraceptive options are particularly limited.

Nevertheless, in the United States, 30% of couples use an effective male method of contraception, with 20% of couples relying on condoms for contraception and 10% of couples using vasectomy.[6] Men not in couples have an even higher reliance on condoms, with 47% of single men reporting condoms as their primary method of contraception.[6] However, both condoms and vasectomy have significant drawbacks. On the plus side, condoms do provide some protection against sexually transmitted infections, but they have a less than ideal contraceptive efficacy.[7] Vasectomy can be expensive and require surgery. Perhaps, more importantly, vasectomy can be difficult to completely reverse in all cases.[8] Additional male contraceptive options, in particular a male contraceptive analogous to the estrogen-progesterone pills used by women, would be of interest to a large majority of men.[9,10] Importantly, the available data suggest that women in stable relationships would trust their partner to use a male contraceptive were one available.[11] Therefore, greater access to male contraceptives would greatly improve contraceptive choice for both single men and men in couples, allowing men to take a more active role in family planning and the prevention of unintended pregnancy.

In order to discuss what types of male contraceptives are possible, it is first necessary to describe the process of spermatogenesis. The production of sperm (spermatogenesis) takes 64–72 days in humans.[12] After puberty, men make sperm continuously, which results in the production of ~ 1,000 sperm a second. Spermatogenesis occurs in four phases: (i) a mitotic phase, wherein the spermatogonial stem cells divide giving rise to diploid spermatocytes; (ii) a meiotic phase wherein spermatocytes double their number of chromosomes and complete two rounds of cell division leading to haploid spermatids; (iii) spermiogenesis, wherein the spermatids condenses its nuclei and forms the flagellum; and last, (iv) spermiation, wherein the spermatozoa is released into the tubular lumen.[13] The sperm completes its maturation in the epididymis. Indeed, sperm taken from the cauda epididymis are capable of fertilization, whereas sperm from the caput epididymis are unable to fertilize an egg *in vitro*.[14] The testes also synthesize testosterone, the primary male sex steroid. High concentrations of intratesticular testosterone are necessary for sperm production,[15] whereas circulating testosterone supports healthy sexual function and maintains muscle mass and bone density.[16] Testosterone is produced by the Leydig cells in the interstitium of the testes, under the stimulation of luteinizing hormone (LH). Spermatogenesis occurs in the seminiferous tubules, nurtured by Sertoli cells, the function of which is stimulated by follicle-stimulating hormone (FSH) and intratesticular testosterone.[16] With knowledge of the physiology of sperm production discussed above, it is apparent that a novel male contraceptive could work in one of the following three ways:

1. By preventing sperm from reaching the egg using a physical barrier such as a condom, or by occluding the vas deferens with a surgical vasectomy or another type of vas occlusion method.

[1]Department of Medicine, Center for Research in Reproduction and Contraception, University of Washington, Seattle, Washington, USA. *Correspondence: John K. Amory (jamory@uw.edu)
Received: August 9, 2019; accepted: September 3, 2019. doi:10.1111/cts.12708

2. By completely inhibiting spermatogenesis.
3. By killing the sperm or inhibiting an essential sperm function (e.g., sperm motility) either before ejaculation or inside the female reproductive tract.

In this review, we will first describe the advantages and disadvantages of current methods of male contraception and second, we will review some of the research into the development of novel hormonal and nonhormonal methods of male contraception that function by one of these three mechanisms.

CURRENTLY AVAILABLE MALE CONTRACEPTIVE METHODS

Vasectomy

Vasectomy is a surgical procedure in which the vas deferens is physically severed bilaterally through a small scrotal incision. Approximately half a million vasectomies are performed in the United States annually and over 60 million men around the world have undergone the procedure.[17] Vasectomy is a highly effective method of male contraception with a failure rate under 1% and few serious complications.[18] The "no-scalpel technique," developed in China, that uses a single midline puncture in the scrotal raphe using scissors has been widely adopted.[19] The main drawback to vasectomy is the delay in the onset of azoospermia and, hence, contraceptive efficacy of 3–4 months, as sperm in the vas distal to the site of surgery still appears in the ejaculate. In addition, postoperative pain can be an issue. Although most operative pain resolves quickly, 10–15% of men have some chronic testicular discomfort after vasectomy.[20] Of these men, most have relief of their discomfort with reversal of the vasectomy,[21] suggesting that obstruction of the vas was causing their pain.

Vasectomy is only appropriate for men who do not wish any future fertility. However, ~ 3–5% of men who have a vasectomy eventually request reversal, usually due to remarriage or the death of a child.[22] For this reason, some urologists recommend collection and freezing a semen sample prior to the procedure, although this is not done commonly in practice. Vasectomy can be surgically reversed by a procedure called a vasovasostomy, which restores fertility in most cases. Unfortunately, the rates of pregnancy after vasovasostomy vary from 50–75% in previously fertile men. The risk of postvasectomy infertility seems to depend on the length of time between the vasectomy and the vasovasostomy.[23] Some of these men's infertility is thought to be due to the presence of antisperm antibodies.[24] For these reasons, vasectomy cannot be recommended as a reliably reversible method of contraception, although it is very useful for men who are not interested in fathering pregnancies. In addition, some men remain cautious about a negative impact of vasectomy on sexual performance[25]; however, there is no evidence for such an association.

Condoms

Condoms have been used for contraception by men for several hundred years. Originally made of animal intestines, since the 1920s, condoms have been mostly made from latex rubber. Latex condoms are effective in protecting against several sexually transmitted diseases, such as human immunodeficiency virus, syphilis, gonorrhea, papillomavirus, and the herpes simplex virus. Unfortunately, condoms are not a highly effective method of contraception. Pregnancy rates for couples using condoms for contraception are 10–15% per year,[26] and rates of pregnancy are higher in younger couples with greater fecundity. Condom failure can result from improper usage, or breakage, which occurs up to 4% of the time.[27] In addition, some men dislike condoms because they find them difficult to use or feel that they diminish sexual pleasure.[28] Last, some people have allergic reactions to the latex, which is allergenic and can lead to penile or vaginal irritation and even anaphylaxis, although this is rare. Polyurethane condoms are an alternative for couples who have latex allergies, although polyurethane condoms are less effective at pregnancy prevention than latex condoms due to their looser fit, which can cause them to slip off more frequently.[29]

Withdrawal

Withdrawal or coitus interruptus is sometimes considered a male method of contraception, and is mentioned as the primary method of contraception by 3–5% of couples in the United States.[6] Withdrawal is not endorsed by the medical community as an effective method of contraception as the stated 1-year failure rate of withdrawal in couples using it as a sole method of contraception is 20–30%.[26] However, it must be noted that little research has focused on this method of contraception, and its true efficacy may be higher or lower depending on how it is practiced. Another male-related method of contraception is fertility awareness, also known as "natural family planning." Using this method, while driven by the female partner's knowledge of the timing of her ovulation, the man plays a crucial role in honoring the cycle-related limitations of vaginal intercourse and, thus, contraceptive efficacy of this option, which has a failure rate similar to that of withdrawal.[6]

In summary, in the United States, 30–35% of couples use an existing male method of contraception (**Table 1**). This demonstrates that men are interested in contraception and willing to use available methods. However, each of these methods has significant drawbacks. Therefore, novel approaches to male contraceptive development are needed. Research into novel methods of male contraception is underway. The remainder of this chapter will focus on these efforts to develop novel male contraceptives for the prevention of unintended pregnancy.

EXPERIMENTAL MALE CONTRACEPTIVES

Hormonal male contraceptives

The suppressive effect of exogenous testosterone on sperm production has been recognized for over 80 years. Testosterone works as a male contraceptive by suppressing the secretion of LH and FSH by negative feedback at the pituitary and hypothalamus (**Figure 1**). Very low circulating levels of LH and FSH mean that the testis lack the signals needed for endogenous steroidogenesis and spermatogenesis. Low levels of FSH and LH leads to marked reductions

Table 1 Percent of couples using a method of male contraception and efficacy of each of these methods in the prevention of unintended pregnancy in the United States[6]

Contraceptive method	Year				Unintended pregnancy rate per year (%)
	1992	1995	2002	2008	
Vasectomy	11	11	9	10	0.1
Condoms	12	20	18	16	10–15
Withdrawal	2	3	4	5	20–30
Total male contraceptive usage	25	34	31	31	–

Couple are only included in the right-hand column if they used the method as their sole means of contraception.

in sperm production in most men after 8–12 weeks of testosterone administration. When the testosterone is discontinued, sperm counts return to pretreatment levels in 3–6 months.[30]

Sperm concentrations in normal men are usually between 15 and 150 million sperm in a milliliter of ejaculate. The absence of sperm, a condition called *azoospermia*, makes pregnancy impossible; however, a male hormonal

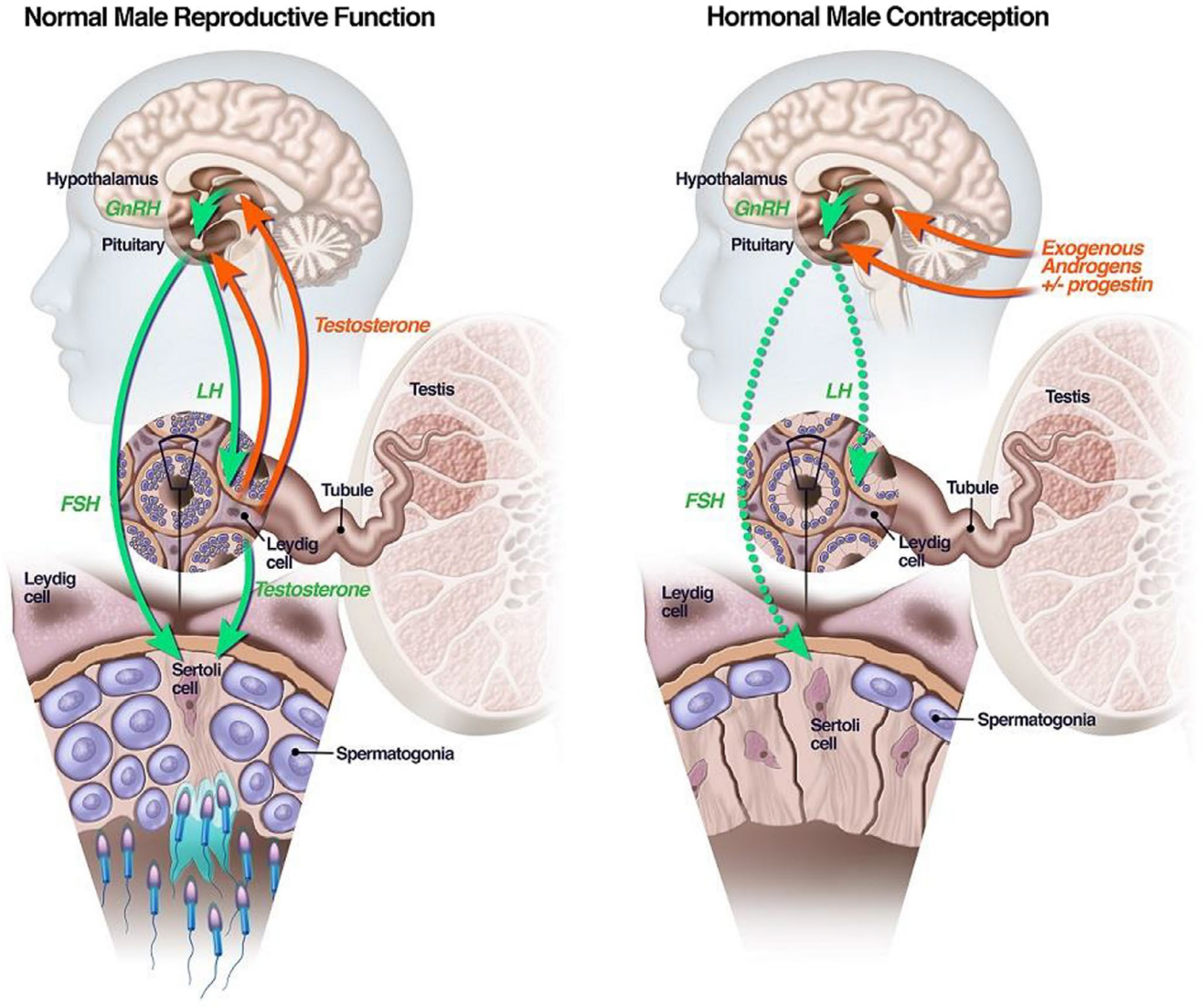

Figure 1 The normal function of the male hypothalamic-pituitary-testicular axis (left). Green arrows stimulatory, red arrows inhibitory. Male hormonal contraceptives suppress secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary leading to a cessation of spermatogenesis (right).

contraceptive that induces azoospermia in all men testing has not yet been described. For reasons that remain a mystery, some men have only partial reduction of their sperm counts with male hormonal contraceptives.[31] Suppression of sperm counts to < 1 million sperm per milliliter (severe oligozoospermia) decrease the chances of conception to < 1% per year.[32] Therefore, suppression of 100% of treated men to sperm concentrations < 1 million sperm/mL is considered reasonable in male contraceptive research, as this would be comparable to the efficacy of female hormonal contraceptives.[33]

Interestingly, men in different racial groups respond differently to male hormonal contraception. Men receiving male hormonal contraceptives in Asia seem to be more susceptible to suppression of spermatogenesis by testosterone, with azoospermia rates in the 90–100% range, whereas men studied in America and Europe have rates of azoospermia of 70–85% on the same regimens.[31,32] The reason for this difference is unknown, but it is important to consider when interpreting trial results from trials performed in different geographic areas.

Administration of testosterone by the oral route is ineffective because oral testosterone is quickly degraded by the liver. Therefore, most male hormonal contraceptive regimens have utilized long-acting testosterone esters, such as testosterone enanthate (TE; **Figure 2a**), which are administered by an intramuscular injection on a weekly basis. The World Health Organization (WHO) conducted two large multicenter trials of weekly TE injections as a male contraceptive. The first of these studies enrolled 271 men and treated them with 200 mg of TE weekly via intramuscular injection.[31] Of these men, 60% became azoospermic, and an additional 30% suppressed their sperm concentrations to fewer than 3 million sperm/mL. One hundred nineteen of the men who achieved azoospermia with this regimen were instructed to discontinue other birth control for 1 year. During that 1-year period, only one pregnancy occurred, demonstrating that azoospermia induced by testosterone was a highly effective method of pregnancy prevention.

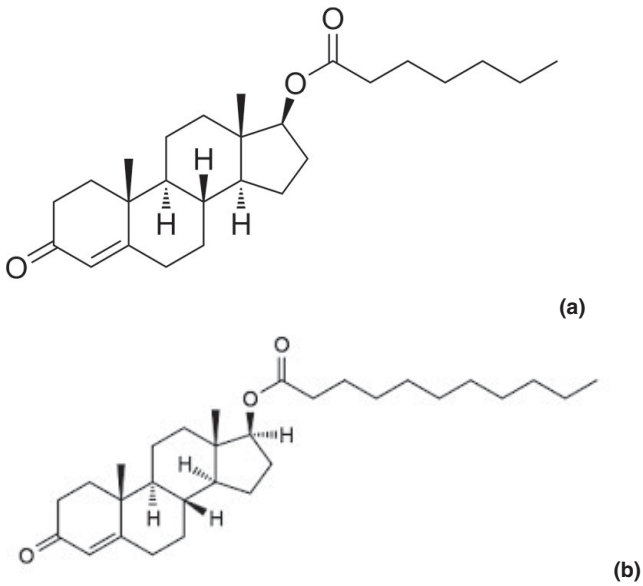

Figure 2 Androgens used in trials of male hormonal contraception: (**a**) testosterone enanthate, (**b**) testosterone undecanoate.

The second male hormonal contraceptive study conducted by the WHO examined contraceptive efficacy of TE injections in men who either became azoospermic or severely oligospermic with TE injections.[32] Of 399 mostly Asian men, 391 (98%) became azoospermic or oligospermic. Similar to the earlier WHO study, there were no pregnancies caused by the men who became azoospermic. Among the oligospermic men, fertility was reduced to 8 pregnancies per 100 person-years. This equaled an overall failure rate of 3.4%, or a contraceptive efficacy rate of 96.6%. All men had a return of normal spermatogenesis after completing the injections, and there were no serious adverse side effects.

The two WHO studies demonstrated that intramuscular testosterone injections administered weekly are an effective form of contraception in a large majority of men. However, a small percentage of men fail to suppress their sperm production low enough to be considered effectively contraception and are, thus, potentially fertile. In addition, the weekly intramuscular injections were unpopular with subjects. Indeed, 12% of the enrolled men discontinued involvement in the study because of the need for the weekly intramuscular injections. The other side effects besides injection pain were minor and relatively well-tolerated. One concern with this regimen was significant decreases in serum high-density lipoprotein (HDL) cholesterol, which may accelerate the development of atherosclerosis.[34,35]

A newer form of injectable testosterone called testosterone undecanoate (TU; **Figure 2b**) has been introduced in the last 10 years to treat men with hypogonadism. An injection of TU normalizes serum T levels in hypogonadal men for 6–12 weeks.[36,37] Two large male hormonal contraceptive trials of TU injections were conducted in China in the late 1990s and early 2000s.[38,39] In the first study, volunteers were administered monthly injections of 500 or 1,000 mg TU for 6 months in an induction phase. Of these men, 95% eventually had sperm concentrations below 1 million sperm/mL. These men then relied on their injections for contraception for a year. Only one pregnancy was reported and the overall efficacy was ~ 95% (**Table 2**). A second study enrolled over 1,000 men and reported a 94% overall contraceptive efficacy.[39] Side effects in these studies included a 7% increase in hematocrit and a 23% decrease in HDL cholesterol, but none of these changes led to subject discontinuation and there were no serious adverse events. Despite these promising results, the method was not approved for clinical use by the Chinese drug regulatory agency for unknown reasons.

In the hopes of achieving 100% azoospermia in men on hormonal contraceptive trials, more recent male contraceptive studies have combined progestins with testosterone. Progestins additively suppress FSH and LH secretion from the pituitary.[40] The first of these combinations used depot medroxyprogesterone acetate, which induced azoospermia in half of the study subjects; however, the contraceptive efficacy reported in this study was poor, with several couples conceiving while receiving therapy.[41]

Table 2 Male hormonal contraceptive efficacy trials

Study (ref.)	Regimen/length of treatment	Number of couples enrolled	Number of couples entering efficacy phase[a]	Number failing to suppress sperm production[b] (%)	Number of unintended pregnancies (%)	Total failures[c] (%)	Overall efficacy (95% CI)
WHO[32]	TE 200 mg i.m. weekly Suppression: up to 6 months Efficacy: 12 months Recovery: 12 months	399	357	8 (2.0)	5 (1.4)	19 (5.3)	94.7 (92–97)
Gu *et al*.[38]	TU 1,000 mg i.m. once, then 500 mg i.m. monthly Suppression: up to 6 months Efficacy: 6 months Recovery: 12 months	305	296	9 (2.9)	1 (0.1)	16 (5.2)	94.8 (91–97)
Gu *et al*.[39]	TU 500 mg i.m. monthly Suppression: up to 6 months Efficacy: 24 months Recovery: 12 months	1,045	855	43 (4.8)	9 (1.1)	52 (6.1)	93.9 (92–96)
Turner *et al*.[46]	Testosterone pellets 400–600 mg s.q. every 4–6 months & DMPA 300 mg i.m. every 3 months Suppression: up to 6 months Efficacy: 12 months Recovery: 1 year	55	53	2 (3.6)	0 (0)	2 (3.6)	96.4 (86–100)
Behre *et al*.[47]	TU 1,000 mg i.m. every 8 weeks & noresthisterone enanthate 200 mg i.m. every 8 weeks Suppression: Up to 26 weeks Efficacy: 56 weeks Recovery: 12 months	320	266	11 (4.1)	4 (1.5)	20 (7.5)	92.5 (89–95)
Totals		2,124	1,827	73 (4.0)	19 (1.0)	109 (6.0)	94.1 (93–95)

CI, confidence interval; DMPA, depot medroxyprogesterone acetate; TE, testosterone enanthate; TU, testosterone undecanoate; WHO, World Health Organization.
[a]For clarity, men/couples who dropped out for reasons other than failure to suppress pregnancies or sperm rebound, are omitted from the efficacy evaluable population. [b]To a predefined sperm concentration of < 1–5 million/mL depending on the study. [c]Defined as the sum of the number of pregnancies, failure to suppress sufficiently to be included in the efficacy phase, or early discontinuation due to sperm rebound.

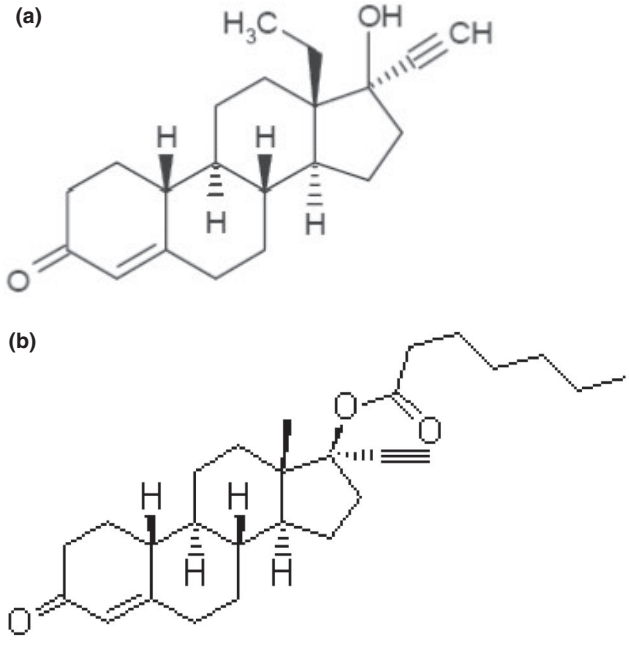

Figure 3 Progestins used in trials of male hormonal contraception: (**a**) levonorgestrel, (**b**) norethisterone enthanthate.

Several studies of the oral progestin, levonorgestrel (LNG; **Figure 3a**) have been reported in the literature. For example, in one study, LNG was administered at 500 μg daily by mouth in combination with weekly injections of TE for 6 months. This combination was better than TE alone in terms of achieving azoospermia (67% vs. 33%) and 94% of men suppressed their sperm concentrations under 1 million per mL.[42] On the negative side, the LNG-TE regimen included greater weight gain and decreases in HDL cholesterol than the TE-alone group. A second progestin, desogestrel, has also been tested in male contraceptive regimens with similar results, but with less weight gain and smaller reductions in HDL cholesterol.[43] A large industry sponsored study of testosterone decanoate injections combined with an etonogestrel implant suppressed 80–90% of men below a sperm concentration of 1 million/mL over 1 year, depending on the doses of testosterone and etonogestrel.[44] A follow-up study, one of the only placebo-controlled studies in the field, combined etonogestrel with TU with 89% of 301 treated men suppressing spermatogenesis to the goal of under 1 million sperm/mL of ejaculate.[45] The first androgen-progestin combination efficacy study with 52 couples was published in 2003.[46] This led to a WHO/CONRAD larger trial testing intramuscular injections of TU and noresthisterone enanthate (**Figure 3b**) every 8 weeks to prevent pregnancy.[47] Although

the regiment was 93% efficacious for pregnancy prevention in treated men, the study was stopped early due to concerns about side effects. In particular, a significant number of men were experiencing adverse mood effects and one suicide occurred, making this regimen unlikely to be studied further.

Nestorone is a 19-norprogesterone, which is applied as a transdermal gel daily to the skin, similar to popular testosterone gels for use by hypogonadal men.[48] A combination of daily application of Nestorone and testosterone gels was studied for gonadotropin suppression in a 1-month study,[49] as well as in a 6-month male trial for suppression of spermatogenesis.[50] In the spermatogenesis study, 89% of men achieved a sperm concentration of 1 million sperm/mL. Most subjects on this regimen were very satisfied, and indicated that they would use it if it were commercially available.[51] A large phase III international trial testing Nestorone and testosterone gels for pregnancy prevention is currently underway at nine sites around the world. Final results from this study are expected in 2022.

The last androgen of note for male hormonal contraception is called dimethandrolone undecanoate (DMAU; **Figure 2c**). DMAU is a potent 19-norandrogen that binds both androgen and progesterone receptors meaning that DMAU has the potential to be a "single-agent" male hormonal contraceptive.[52] Preclinical studies in rodents and rabbits have demonstrated reversible suppression of gonadotropins and sperm after the oral administration of DMAU.[53] Similarly, early clinical studies in men have demonstrated short-term safety and tolerability with reversible suppression of gonadotropins.[54] Phase II testing of this compound is ongoing.

Efficacy of male hormonal contraception

To date, there have been six large male contraceptive efficacy studies in which the hormonal regimen was used with the intention of preventing unintended pregnancy.[31,32,38,39,46,47] Five of these studies enrolled men with oligospermia. Taken together, these five studies demonstrate a contraceptive efficacy of ~ 94%, with a few men not progressing to the efficacy phase by virtue of unacceptably high sperm counts. In addition, there have been only a few unintended pregnancies observed in these studies (**Table 2**). Importantly, a pregnancy in these studies may not represent a failure of the tested regimen as the pregnancy may not have been fathered by a man taking the contraceptive regimen. Therefore, the reported efficacy may be even greater than reported. Given this relatively high degree of efficacy, which compares favorably to the condom, it may seem somewhat perplexing that no male hormonal contraceptive has yet to make to the marketplace. Part of the explanation for this may be uncertainly regarding the safety of using hormones for male contraception.

Indeed, the safety of a male contraceptive is paramount to regulatory approval and user uptake. In the studies performed to date, the most common side effect was acne, likely due to increased androgen exposure from the injections. Other reported side effects have varied, but have included increased body weight, changes in cholesterol profile, and mood changes. No contraceptive study conducted to date has found an increase in cardiovascular complications or blood clots, but none of these studies was powered to study this outcome, and these events are uncommon in the young men participating in these studies. The recent WHO/CONRAD trial, which used a long-acting injectable combination therapy with TU and noresthisterone enanthate, demonstrated a high degree of contraceptive efficacy, but was stopped early due to side effect concerns, particularly related to concerns about negative effects on mood.[47] Clearly, more work to understand the causes and implications of these adverse effects will be necessary before a hormonal regimen will likely be approved for widespread use.

Last, in terms of risk, it may be argued that physical risks accruing to the male partner from a male contraceptive are justifiable in terms of preventing physical harm in his female partner from unintended pregnancy, as long as the overall risk is similar to that experienced by female contraceptive users.

Experimental nonhormonal male contraceptives

Several research groups are examining approaches to nonhormonal male contraception. Nonhormonal male contraception is male contraception that does not utilize the administration of testosterone or compounds that block testosterone secretion or action.[55] Nonhormonal contraception may be more appealing to men than hormonal approaches currently in development as it would avoid any impact on testosterone concentrations and, hence, sexual function, muscle or bone mass, or sex drive. In addition, the use of testosterone would lead to disqualification from a sporting event as individuals using testosterone to suppress spermatogenesis would have a positive test in a doping analysis. Last, nonhormonal contraceptives may be more easily dosed orally than most steroid preparations, which tend to be rapidly degraded due to extensive first-pass metabolism of testosterone by the liver and intestinal wall.

Gossypol. One of the first examples of a nonhormonal male contraception was gossypol. Gossypol is a complex phenolic molecule derived from the seeds of the cotton plant (**Figure 4a**). It was extensively studied in China in the 1970s and 1980s, including in two large phase III studies that enrolled > 8,000 men.[56,57] In these studies, gossypol reduced both sperm production as well as sperm motility and induced abnormal sperm morphology by an unknown mechanism of action. After prolonged treatment, a majority of men developed azoospermia. Gossypol had an ~ 90% efficacy in pregnancy prevention, but caused troubling hypokalemia and a 1% incidence of hypokalemic periodic paralysis. In addition, ~ 20% of men did not have return of fertility. Despite attempts to lower the dose, or chemically modify the structure of gossypol to improve efficacy and reduce the risk of side effects, this approach to male contraception has been largely abandoned.[58]

Triptolide. Another potential male contraceptive compound from China is the Chinese herb *Trypterigium wilfordii*, which contains a diterpene epoxide called triptolide.[59] This herb had been used as a traditional Chinese medication for many centuries. In the 1980s an antisperm effect was identified.

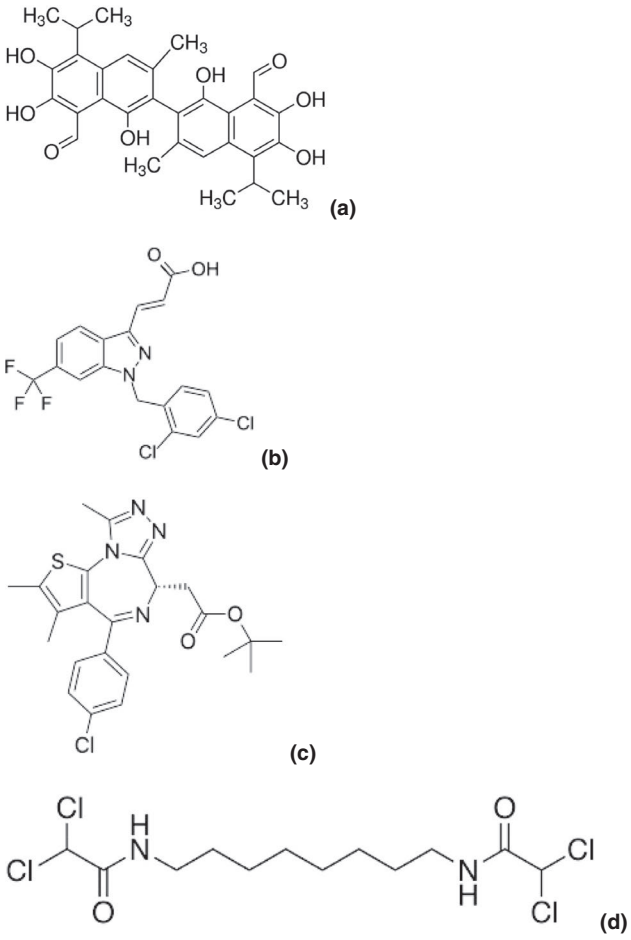

Figure 4 Nonhormonal male contraceptives (**a**) Gossypol, (**b**) H2-gamendazole, (**c**) JQ-1, (**d**) Win 18,446.

Specifically, *Trypterigium* administration impaired sperm motility and decreased sperm counts. As was the case with gossypol; however, several men taking this compound had irreversible sterility, leading to its abandonment as a reversible male contraceptive.[60]

Adjudin. A more recent example of a nonhormonal male contraceptive candidate is Adjudin, which was first described in the early 2000s.[61] Adjudin interferes with the adhesion of spermatids to Sertoli cells. As a result, spermatids undergo premature spermiation and nonfunctional spermatozoa are produced. In rats, the administration of 2 doses of 50 mg/kg of Adjudin weekly induced 100% infertility after 5 weeks of treatment without changes in serum hormones or gonadotropins.[62] However, liver inflammation was observed in a 29-day study of adjudin.[63] As a result, the researchers working with Adjudin conjugated it to an FSH-β mutant in order to target it to Sertoli cells, and reduce the dose necessary for contraception.[64] Unfortunately, this proved prohibitively costly.[65]

H2-Gamendazole. H2-Gamendazole (**Figure 4b**) is an antisperm compound related to Adjudin that also interferes with the normal functioning of the apical ectoplasmic specialization.[66] All rats receiving a single oral dose of gamendazole at 6 mg/kg were infertile, but only half fully regained fertility.[67] Unfortunately, three of five rats who received a dose of 200 mg/kg died, indicating some issues with toxicity and a low therapeutic window. Initial work was performed in hopes of moving into human testing, but this work seems to have stalled, apparently due to toxicity.

Epididymal peptidase inhibitor. Epididymal peptidase inhibitor (EPPIN) is a sperm surface protein that plays a role in liquefaction of the ejaculate.[68] It was initially shown that seven of nine male nonhuman primates could be immunized against EPPIN. These animals were unable to father pregnancies and the animals regained fertility when the immunizations were stopped.[69] This group has developed small molecules that inhibit EPPIN binding as a novel approach to the development of a nonhormonal male contraceptive.[70] Intravenous administration of one compound, EP055, reduced sperm motility by 80% in male macaques in a recently published paper.[71] The development of potent, oral compounds that can mimic this effect and fully suppress sperm motility will be an exciting area of future research.

Bromodomain testis-specific protein inhibition. A testicular bromodomain protein called bromodomain testis-specific protein (BRDT), which is testes-specific, is required for meiosis. Individuals with mutations in the *Brdt* gene have infertility from abnormal formation of sperm heads.[46] A landmark 2012 paper demonstrated that JQ1 (**Figure 4c**), a small molecule inhibitor of BRDT function, reversibly suppressed spermatogenesis in mice.[72] Unfortunately, JQ1 also inhibits other members of the bromodomain family, leading to toxicity at the doses needed for contraceptive efficacy. Therefore, this group is developing a BRDT-specific inhibitor, to minimize the potential for side effects from this approach.[73]

Retinoic acid receptor antagonists. In 1925, it was demonstrated that vitamin-A (retinol) is essential for spermatogenesis.[74] Vitamin-A and its active metabolite retinoic acid are necessary both for the initiation of spermatogenesis at puberty and continued sperm production in adults.[75,76] Retinoic acid binds one of several retinoic acid receptors (RARs), which regulate gene expression. Male RAR knockout animals are sterile.[77,78] As a result, developing approaches to block retinoic acid function or production is a promising approach to male nonhormonal contraceptive development.

BMS-189453 is an oral compound that acts as an antagonist at all three RARs. It was dosed daily by mouth at doses of 15, 60, or 240 mg/kg for 1 month to rats. In these animals, BMS-189453 produced marked testicular degeneration, but also led to some liver inflammation.[80] Lower doses of BMS-189453 seem to suppress sperm production without the liver toxicity seen at higher doses in mice.[81] For example, 2 groups of 30 mice each were administered BMS-189453 at a dose of 5 mg/kg for 2 weeks followed by a dose of 2.5 mg/kg for 4 weeks. The mice treated in this study were completely sterile by 4 weeks.[82] Twelve weeks

after treatment was stopped, fertility was completely restored in all male mice. This compound, or a more specific retinoic acid-alpha antagonist reported in the literature,[83] holds promise for nonhormonal male contraception.

Retinoic acid biosynthesis inhibitors. In 1960, the administration of WIN 18,446 (**Figure 4d**) was shown to dramatically suppress sperm production in men.[84,85] Unfortunately, men taking WIN 18,446 had "disulfiram reactions" consisting of nausea, vomiting, palpitations, and sweating, when they also drank alcohol. Because of this, further development of WIN 18,446 ended without an understanding how it so effectively suppressed sperm production. In 2011, it was demonstrated that WIN 18,446 suppressed sperm production by inhibiting the biosynthesis of testicular retinoic acid. This occurred by inhibition of enzymes aldehyde dehydrogenase ALDH1A1 and ALDH1A2.[86,87] Current work in this area is focused on the development of novel, specific compounds that inhibit retinoic acid biosynthesis in the testes without blocking with alcohol metabolism.[88] If successful, this work could result in a contraceptive that inhibits sperm production without significant side effects.

CatSper. In 2001, a novel sperm-specific calcium channel was identified.[89] Importantly genetic knockout of this protein leads to infertility.[90] One candidate CatSper antagonist, called HC-056456, has been reported in the literature.[91] *In vitro*, this compound significantly suppressed sperm motility; however, no *in vivo* data on this compound or other CatSper antagonists have been reported to date. Nevertheless, several groups are pursuing sperm ion channels as potential male contraceptives.[92]

Gendarussa. A plant commonly used in an Indonesian traditional medicine called *Justicia gendarussa* has been used as a contraceptive by men in Papua, New Guinea. The active ingredient may be flavonoids called gendarusin A and B.[93] Some data on contraceptive efficacy for this compound have been 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.

Silodosin. Recently, a group in India published a paper demonstrating that the alpha-1A-specific antagonist Silodosin, used to treat prostate hypertrophy, could function as a male contraceptive by inducing aspermia and anejaculation.[94] They had 63 men take 8 mg of silodosin 3 hours prior to intercourse and reported no pregnancies. Notably the semen volume in these men was markedly diminished, which may present issues with acceptability for some men. However, this compound may be an option for on-demand male contraception.

Vas occlusion methods. Since the 1970s, researchers in India and China have been working to develop methods to temporarily plug the vas deferens. Such a vas occlusion method could, in theory, be removed at a later date if and when the man desired a return to fertility. The Indian approach to vas occlusion device is called reversible inhibition of sperm under guidance (RISUG). Under ultrasound guidance, a solution of styrene maleic anhydrate is injected into both vas deferens, leading to occlusion and preventing the passage of sperm. Several small clinical trials of RISUG in men have been performed.[95] These studies show excellent contraceptive efficacy over periods of up to 1 year. However, data on efficacy and reversibility from large-scale clinical trials have not been published.

A nongovernmental organization called the Parsemus Foundation has acquired the rights to RISUG, now re-named "Valsalgel." This reformulated styrene maleic anhydrate functioned effectively as a contraceptive for 1 year in rabbits,[96] and also displayed efficacy in monkeys.[97] However, after reversal, the sperm of the rabbits lacked acrosomes, possibly due to residual inflammation in the vas.[98] No data on the fertility of these animals were reported. As a result, it remains unclear if this procedure is truly reversible.

In China, in the early 1990s, a vas occlusion device using medical-grade silicone and polyurethane plugs was studied.[99,100] Unfortunately, these devices had problems with recovery of sperm counts after reversal, and the investigators abandoned this approach.

CONCLUSIONS

Contraception is the best tool available for the prevention of unintended pregnancy. Thirty percent of US couples use male methods, such as condoms and vasectomies, but interest into novel male methods is high. Hormonal approaches to male contraceptives have been extensively tested in human studies; however, no regimen has been identified with sufficient efficacy and safety to reach regulatory approval. Several nonhormonal methods seem promising in preclinical studies, but more testing and refinement of these approaches will be required before human studies can be performed to determine their efficacy.

Funding. The author has received research funding from Clarus Therapeutics.

Conflict of Interest. The author declared no competing interests for this work.

1. Gerland, P. *et al.* World population stabilization unlikely this century. *Science* **346**, 234–237 (2014).
2. Speidel, J.J. & Grossman, R.A. Addressing global health, economic, and environmental problems through family planning. *Obstet. Gynecol.* **117**, 1394–1398 (2011).
3. Finer, L.B. & Zolna, M.R. Declines in unintended pregnancy in the United States, 2008–2011. *N. Engl. J. Med.* **374**, 843–852 (2016).
4. Shah, I. & Ahman, E. Unsafe abortion in 2008: global and regional level and trends. *Reprod. Health Matters* **18**, 90–101 (2010).
5. Singh, S., Darroch, M.E., Ashford, L.S. & Vlassoff, M. Adding It Up: The Costs and Benefits of Investing in Family Planning and Maternal and Newborn Health (Alan Guttmacher Institute, New York, NY, 2009).
6. Daniels, K., Daugherty, J., Jones, J. & Mosher, W. Current contraceptive use and variation by selected characteristics among women aged 15–44: US, 2011–2013. *Natl. Health Stat. Report* **86**, 1–14 (2015).
7. Trussell, J. & Vaughan, B. Contraceptive failure, method-related discontinuation and resumption of use: results from the 1995 National Survey of Family Growth. *Fam. Plann. Perspect.* **31**, 64–72 (1999).

8. Li, S.-Q., Goldstein, M., Shu, J. & Huber, D.H. The no-scalpel vasectomy. *J. Urol.* **145**, 341–344 (1991).
9. Martin, C.W. *et al*. Potential impact of hormonal male contraception: cross-cultural implications for development of novel male preparations. *Hum. Reprod.* **15**, 637–645 (2000).
10. Heinemann, K., Saad, F., Wiesemes, M., White, S. & Heinemann, L. Attitudes towards male fertility control: results of a multinational survey on four continents. *Hum. Reprod.* **20**, 549–556 (2005).
11. Glasier, A.F. *et al*. Would women trust their partners to use a male pill? *Hum. Reprod.* **15**, 646–649 (2000).
12. Heller, C.G. & Clermont, Y. Kinetics of the germinal epithelium in man. *Recent Prog. Horm. Res.* **20**, 545–571 (1964).
13. DeKretser, D.M. Morphology and physiology of the testis. In Principles and Practice of Endocrinology and Metabolism, 2nd edn (ed. Becker, K.L.) 1032–1041 (Lippincott, Philadelphia, PA, 1995).
14. Silber, S.J., Ord, T., Balmaceda, J., Patrizio, P. & Asch, R.H. Congenital absence of the vas deferens. The fertilizing capacity of human epididymal sperm. *N. Engl. J. Med.* **323**, 1788–1792 (1990).
15. Roth, M.Y. *et al*. Dose-dependent increase in intratesticular testosterone by very low-dose human chorionic gonadotropin in normal men with experimental gonadotropin deficiency. *J. Clin. Endocrinol. Metab.* **95**, 3806–3813 (2010).
16. Matsumoto, A.M. Testosterone administration in older men. *Endocrinol. Metab. Clin. North Am.* **42**, 271–286 (2013).
17. Haws, J.M., Morgan, G.T., Pollack, A.E., Koonin, L.M., Magnani, R.J. & Gargiullo, P.M. Clinical aspects of vasectomies performed in the United States in 1995. *Urology* **52**, 685–691 (1995).
18. Philp, T., Guillebaud, J. & Budd, D. Complications of vasectomy: review of 16,000 patients. *Br. J. Urol.* **56**, 745–748 (1984).
19. Li, S.-Q., Goltein, M., Shu, J. & Huber, D. The no-scalpel vasectomy. *J. Urol.* **145**, 341–344 (1991).
20. McMahon, A.J., Buckley, J., Taylor, A., Lloyd, S.N., Deane, R.F. & Kirk, D. Chronic testicular pain following vasectomy. *Br. J. Urol.* **69**, 188–191 (1992).
21. Myers, S.A., Mershon, C.E. & Fuchs, E.F. Vasectomy reversal for treatment of the post-vasectomy pain syndrome. *J. Urol.* **157**, 518–520 (1997).
22. Jequier, A.M. Vasectomy related infertility: a major and costly medical problem. *Hum. Reprod.* **13**, 1757–1759 (1998).
23. Belker, A.M., Thomas, A.J., Fuchs, E.F., Konnak, J.W. & Sharlip, I.D. Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J. Urol.* **145**, 505–511 (1991).
24. Heidenreich, A., Bonfig, R., Wilbert, D.M., Strohmaier, W.L. & Engelmann, U.H. Risk factors for anti-sperm antibodies in infertile men. *Am. J. Reprod. Immunol.* **31**, 69–76 (1994).
25. Campbell, A.D., Turok, D.K. & White, K. Fertility intentions and perspectives on contraceptive involvement among low-income men aged 25 to 55. *Perspect. Sex Reprod. Health* **51**, 125–133 (2019).
26. Sundaram, A. *et al*. Contraceptive failure from the 2006–2010 national survey of family growth. *Perspect. Sex Reprod. Health* **49**, 7–16 (2017).
27. D'Anna, L.H. *et al*. Factors associated with condom use problems during vaginal sex with main and non-main partners. *Sex Transm. Dis.* **39**, 687–689 (2012).
28. Fennell, J. "And isn't that the point?" Pleasure and contraceptive decisions. *Contraception* **89**, 264–270 (2014).
29. Walsh, T.L., Frezieres, R.G., Peacock, K., Nelson, A.L., Clark, V.A. & Bernstein, L. Evaluation of the efficacy of a nonlatex condom: results from a randomized, controlled clinical trial. *Perspect. Sex Reprod. Health* **35**, 79–86 (2003).
30. Liu, P.Y., Swerdloff, R.S., Christenson, P.D., Handelsman, D.J. & Wang, C. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet* **367**, 1412–1420 (2006).
31. World Health Organization. Contraceptive efficacy of testosterone-induced azoospermia in normal men. *Lancet* **336**, 995–1002 (1990).
32. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of induced azoospermia and oligozoospermia in normal men. *Fertil. Steril.* **65**, 821–829 (1996).
33. Aaltonen, P. *et al*. 10th Summit Meeting consensus: recommendations for regulatory approval for hormonal male contraception. *J. Androl.* **28**, 362–363 (2007).
34. Bagatell, C.J., Heiman, J.R., Matsumoto, A.M., Rivier, J.E. & Bremner, W.J. Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. *J. Clin. Endocrinol. Metab.* **79**, 561–566 (1994).
35. Meriggiola, M.C., Marcovina, S., Paulsen, C.A. & Bremner, W.J. Testosterone enanthate at the dose 200 mg/week decreases HDL cholesterol levels in healthy men. *Int. J. Androl.* **18**, 237–242 (1995).
36. Zhang, G.Y., Gu, Y.Q., Wang, X.H., Cui, Y.G. & Bremner, W.J. A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. *J. Androl.* **19**, 761–767 (1998).
37. Behre, H.M. *et al*. Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. *Eur. J. Endrocrinol.* **140**, 414–419 (1999).
38. Gu, Y.Q. *et al*. A multicenter contraceptive efficacy study of injectable testosterone undeanoate in health Chinese Men. *J. Clin. Endocrinol. Metab.* **88**, 562–568 (2003).
39. Gu, Y. *et al*. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. *J. Clin. Endocrinol. Metab.* **94**, 1901–1915 (2009).
40. Meriggiola, M.C. & Bremner, W.J. Progestin-androgen combination regimens for male contraception. *J. Androl.* **18**, 240–244 (1997).
41. Barfield, A. *et al*. Pregnancies associated with sperm concentrations below 10 million/ml in clinical studies of a potential male contraceptive method, monthly depot medroxyprogesterone acetate and testosterone esters. *Contraception* **20**, 121–127 (1979).
42. Bebb, R.A., Anawalt, B.D., Christensen, R.B., Paulsen, C.A., Bremner, W.J. & Matsumoto, A.M. Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: a promising male contraceptive approach. *J. Clin. Endocrinol. Metab.* **81**, 757–762 (1996).
43. Wu, F.C., Balasubramanian, R., Mulders, T.I.M. & Coelingh-Bennink, H.J. Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. *J. Clin. Endocrinol. Metab.* **84**, 112–122 (1999).
44. Brady, B.M. *et al*. A multicentre study investigating subcutaneous etonogestrel implants with injectable testosterone decanoate as a potential long-acting male contraceptive. *Hum. Reprod.* **21**, 285–294 (2006).
45. Mommers, E. *et al*. Male hormonal contraception: a double-blind, placebo-controlled study. *J. Clin. Endocrinol. Metab.* **93**, 2572–2580 (2008).
46. Turner, L. *et al*. Contraceptive efficacy of a depot progestin and androgen combination in men. *J. Clin. Endocrinol. Metab.* **88**, 4659–4667 (2003).
47. Behre, H.M. *et al*. Efficacy and safety of an injectable combination hormonal contraceptive for men. *J. Clin. Endocrinol. Metab.* **101**, 4779–4788 (2016).
48. Kumar, N., Koide, S.S., Tsong, Y. & Sundaram, K. Nestorone: a progestin with a unique pharmacological profile. *Steroids* **65**, 629–636 (2000).
49. Mahabadi, V. *et al*. Combined transdermal testosterone gel and the progestin nestorone suppresses serum gonadotropins in men. *J. Clin. Endocrinol. Metab.* **94**, 2313–2320 (2009).
50. Ilani, N. *et al*. A new combination of testosterone and nestorone transdermal gels for male hormonal contraception. *J. Clin. Endocrinol. Metab.* **97**, 3476–3486 (2012).
51. Roth, M.Y. *et al*. Acceptability of a transdermal gel-based male hormonal contraceptive in a randomized controlled trial. *Contraception* **90**, 407–412 (2014).
52. Attardi, B.J., Hild, S.A. & Reel, J.R. Dimethandrolone undecanoate: a new potent orally active androgen with progestational activity. *Endocrinology* **147**, 3016–3026 (2006).
53. Hild, S.A. *et al*. Development of dimethandrolone 17B-undecanoate (DMAU) as an oral male hormonal contraceptive: induction of infertility and recovery of fertility in adult male rabbits. *J. Androl.* **32**, 530–540 (2011).
54. Thirumalai, A. *et al*. Effects of 28 days of oral dimethandrolone undecanoate in healthy men: a prototype male pill. *J. Clin. Endocrinol. Metab.* **104**, 423–432 (2019).
55. Nya-Ngatchou, J.J. & Amory, J.K. New approaches to male non-hormonal contraception. *Contraception* **87**, 296–299 (2013).
56. Liu, G.Z., Lyle, K.C. & Cao, J. Clinical trial of gossypol as a male contraceptive drug part I: efficacy study. *Fertil. Steril.* **48**, 459–461 (1987).
57. Liu, G.Z., Lyle, K.C. & Cao, J. Clinical trial of gossypol as a male contraceptive drug part II: hypokalemia study. *Fertil. Steril.* **48**, 462–465 (1987).
58. Waites, G.M., Wang, C. & Griffin, P.K. Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. *Int. J. Androl.* **21**, 8–12 (1998).
59. Qian, S.Z. *Tripterygium wildfordii*, a Chinese herb effective in male fertility regulation. *Contraception* **36**, 335–345 (1987).
60. Huynh, P.N. *et al*. Long-term effects of triptolide on spermatogenesis, epididymal sperm function, and fertility in male rates. *J. Androl.* **21**, 689–699 (2000).
61. Cheng, C.Y. *et al*. Two new male contraceptive exert their effects by depleting germ cells prematurely from the testis. *Biol. Reprod.* **65**, 449–461 (2001).
62. Mruk, D.D. & Cheng, C.Y. Testin and actin are key molecular targets of adjudin, an anti-spermatogenic agent, in the testes. *Spermatogenesis* **1**, 137–146 (2011).
63. Mok, K.-W., Mruk, D.D., Lie, P.P.Y., Lui, W.Y. & Cheng, C.Y. Adjudin, a potential male contraceptive, exerts its effects locally in the seminiferous epithelium of mammalian testes. *Reproduction* **141**, 571–580 (2011).
64. Mruk, D.D., Wong, C.H., Silvestrini, B. & Cheng, C.Y. A male contraceptive targeting germ cell adhesion. *Nat. Med.* **12**, 1323–1328 (2006).
65. Chen, H., Mruk, D.D., Xia, W., Bonanomi, M., Silvestrini, B. & Cheng, C.Y. Effective delivery of male contraceptives behind the blood-testis barrier – lessons from adjudin. *Curr. Med. Chem.* **23**, 701–713 (2016).
66. Tash, J.S., Attardi, B., Hild, S.A., Chakrasali, R., Jakkaraj, S.R. & Georg, G.I. A novel potent indazole carboxylic acid derivative blocks spermatogenesis and is contraceptive in rats after a single oral dose. *Biol. Reprod.* **78**, 1127–1138 (2008).
67. Tash, J.S. *et al*. Gamendazole, an orally active indazole carboxylic acid male contraceptive agent, targets HSP90AB1 and EEF1A1, and stimulates Il1a transcription in rat Sertoli cells. *Biol. Reprod.* **78**, 1139–1152 (2011).
68. O'Rand, M.G., Widgren, E.E., Hamil, K.G., Silva, E.J. & Richardson, R.T. Functional studies of EPPIN. *Biochem. Soc. Trans.* **39**, 1447–1449 (2011).

69. O'Rand, M.G. *et al*. Reversible immunocontraception in male monkeys immunized with EPPIN. *Science* **306**, 1189–1190 (2004).
70. O'Rand, M.G., Silva, E.J. & Hamil, K.G. Non-hormonal male contraception: a review and development of an EPPIN based contraceptive. *Pharmacol. Ther.* **157**, 105–111 (2016).
71. O'Rand, M.G., Hamil, K.G., Adevai, T. & Zelinski, M. Inhibition of sperm motility in male macaques with EP055, a potential non-hormonal male contraceptive. *PLoS One* **19**, e0195953 (2018).
72. Li, L. *et al*. Whole-exome sequencing identified a homozygous BRDT mutation in a patient with acephalic spermatozoa. *Oncotarget* **8**, 19914–19922 (2017).
73. Matzuk, M.M. *et al*. Small-molecule inhibition of BRDT for male contraception. *Cell* **150**, 673–684 (2012).
74. Wolbach, S.B. & Howe, P.R. Tissue changes following deprivation of fat soluble A vitamin. *J. Exp. Med.* **42**, 753–777 (1925).
75. Vernet, N. *et al*. Retinoic acid metabolism and signaling pathways in the adult and developing mouse testis. *Endocrinology* **147**, 96–110 (2006).
76. Koubova, J., Menke, D., Zhou, Q., Capel, B., Griswold, M.D. & Page, D.C. Retinoic acid regulates sex-specific timing of meiotic initiation in mice. *Proc. Natl. Acad. Sci. USA* **103**, 2472–2479 (2006).
77. Dufour, J.M. & Kim, K.H. Cellular and subcellular localization of six retinoid receptors in rat testis during postnatal development: identification of potential heterodimeric receptors. *Biol. Reprod.* **61**, 1300–1308 (1999).
78. Lufkin, T. *et al*. High postnatal lethality and testis degeneration in retinoic acid receptor alpha mutant mice. *Proc. Natl. Acad. Sci. USA* **90**, 7225–7229 (1993).
79. Lohnes, D., Kastner, P., Dierich, A., Mark, M., LeMeur, M. & Chambon, P. Function of retinoic acid receptor gamma in the mouse. *Cell* **73**, 643–658 (1993).
80. Schulze, G.E., Clay, R.J., Mezza, L.E., Bregman, C.L., Buroker, R.A. & Frantz, J.D. BMS-189453, a novel retinoid receptor antagonist, is a potent testicular toxin. *Toxicol. Sci.* **59**, 297–308 (2001).
81. Chung, S.S., Wang, X., Roberts, S.S., Griffey, S.M., Reczek, P.R. & Wolgemuth, D.J. Oral administration of a retinoic acid receptor antagonist reversibly inhibits spermatogenesis in mice. *Endocrinology* **152**, 2492–2502 (2011).
82. Chung, S.S., Wang, X. & Wolgemuth, D.J. Prolonged oral administration of a pan-retinoic acid receptor antagonist inhibits spermatogenesis in mice with a rapid recovery and changes in the expression of influx and efflux transporters. *Endocrinology* **157**, 1601–1612 (2016).
83. Chung, S.S. *et al*. Pharmacological activity of retinoic acid receptor alpha-selective antagonists in vitro and in vivo. *ACS Med. Chem. Lett.* **4**, 446–450 (2013).
84. Heller, C.G., Moore, D.J. & Paulsen, C.A. Suppression of spermatogenesis and chronic toxicity in men by a new series of bis(dichloroacetyl)diamines. *Toxicol. Appl. Pharmacol.* **3**, 1–11 (1961).
85. Beyler, A.L., Potts, G.O., Coulston, F. & Surrey, A.R. The selective testicular effects of certain bis(dichloroacetyl)diamines. *Endocrinology* **69**, 819–833 (1961).
86. Amory, J.K. *et al*. Suppression of spermatogenesis by bisdichloroacetyldiamines is mediated by inhibition of testicular retinoic acid biosynthesis. *J. Androl.* **32**, 111–119 (2011).
87. Paik, J. *et al*. Inhibition of retinoic acid biosynthesis by the bisdichloroacetyldiamine WIN 18,446 markedly suppresses spermatogenesis and alters retinoid metabolism in mice. *J. Biol. Chem.* **289**, 15104–15117 (2014).
88. Chen, Y. *et al*. Structural basis of ALDH1A2 inhibition by irreversible and reversible small molecule inhibitors. *ACS Chem. Biol.* **13**, 582–590 (2018).
89. Ren, D.J. *et al*. A sperm ion channel required for sperm motility and male fertility. *Nature* **413**, 603–609 (2001).
90. Qi, H. *et al*. All four CatSper ion channel proteins are required for male fertility and sperm cell hyperactivated motility. *Proc. Natl. Acad. Sci. USA* **104**, 1219–1223 (2017).
91. Carlson, A.E. *et al*. Pharmacological targeting of native CatSper channels reveals a required role in maintenance of sperm hyperactivation. *PLoS One* **4**, e6844 (2009).
92. Lishko, P.V. Contraception: search for an ideal unisex mechanism by targeting ion channels. *Trends Biochem. Sci.* **41**, 816–818 (2016).
93. Widyowati, R. & Agil, M. Chemical constituents and bioactivities of several Indonesian plants typically used in Jamu. *Chem. Pharmaceut. Bull.* **66**, 506–518 (2018).
94. Bhat, G.S. & Shastry, A. A prospective double-blind, randomized placebo-controlled study to evaluate the efficacy of silodosin 8 mg as an on-demand, reversible, nonhormonal oral contraceptive for males: a pilot study. *World J. Urol.* 2019. https://doi.org/10.1007/s00345-019-02806-7(Epub May 10, 2019).
95. Guha, S.K. *et al*. Phase II clinical trial of a vas deferens injectable contraceptive for the male. *Contraception* **56**, 245–250 (1997).
96. Waller, D. *et al*. Azoospermia in rabbits following an intravas injection of Vasalgel™. *Basic Clin. Androl.* **26**, 6 (2016).
97. Colagross-Schouten, A. *et al*. The contraceptive efficacy of intravas injection of Vasalgel™ for adult male rhesus monkeys. *Basic Clin. Androl.* **27**, 4 (2017).
98. Waller, D. *et al*. Reversibility of Vasalgel™ male contraceptive in a rabbit model. *Basic Clin. Androl.* **26**, 6 (2016).
99. Zhao, S.C., Zhang, S.P. & Yu, R.C. Intravasal injection of formed-in-place silicone rubber as a method of vas occlusion. *Int. J. Androl.* **15**, 460–464 (1992).
100. Zhao, S.C., Lian, Y.H., Yu, R.C. & Zhang, S.P. Recovery of fertility after removal of polyurethane plugs from the human vas deferens occluded for up to 5 years. *Int. J. Androl.* **15**, 465–467 (1992).