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Recent Developments in Promising Hormonal and Non-Hormonal Male Contraceptives: A Review

Nooralhuda A. Yahya[1], Farah R. Noori[2], Doaa K. Ibrahim[3*]

[1]*Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq (nooralhuda-alzarqy@uomosul.edu.iq).*
[2]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq. (farah.ramzi@uomosul.edu.iq).*
[3]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq (ph.doaa@uomosul.edu.iq).*

*Correspondence: *ph.doaa@uomosul.edu.iq*

Abstract

New male contraceptive methods would expand male and female contraceptive alternatives and enhance male contraceptive agency. Since 1969, a program for developing contraceptives has been financed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, which also continues to fund the majority of hormonal male contraceptive development today. Also, the early stages of non-hormonal techniques start to develop. The hormonal male contraceptive methods, include testosterone undecanoate injection plus norethisterone enanthate injection, implants of testosterone plus depo-medroxyprogesterone acetate injection, testosterone enanthate injection, and other testosterone-based methods. The non-hormonal methods, include novel hormone-free substances such as retinoic acid inhibitors, sperm ion channel blockers, and vasal peristalsis blockers. The review provides insights into the efficacy, safety, and potential side effects of each method, and highlights the current state of research and development in the field of male contraception.

Keywords: *Male contraception, Hormonal methods, Non-Hormonal methods, Testosterone undecanoate, Retinoic acid inhibitors.*

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I. INTRODUCTION

Despite the fact that women can use a variety of contraceptive techniques, nevertheless, the United States has an unintended birth rate of over 45% (Finer and Zolna, 2016). The only reversible methods of contraception available to men are male condoms and withdrawal, which have failure rates of typically 13% and 20%, respectively. These methods are far less effective than those available to women, including hormonal intrauterine systems, combined hormonal contraceptives (pills, rings, and patches), hormonal injections or implants, and the copper intrauterine device (Black *et al*., 2010) Studies conducted in many cultures, countries, and continents have shown that about 50% of men would use a reversible method of male contraception if one were available (Heinemann *et al*., 2005), In addition, a lot of women would be depending on their partner to take contraception (Glasier, 2010).

Men have a restricted ability to engage in reproductive decision-making because of the absence of acceptable male-controlled methods (Hamm *et al*., 2019). Nowadays, male condoms or vasectomies account for 21% of contraception use in the United States (Kavanaugh and Jerman, 2018). New reversible male contraceptives give the male partner the chance to have more reproductive control. Computational modelling indicates that if just 10% of potential users use a male contraceptive pill, the undesired birth rate in the US may drop by 3.5%, and if 15% of them do, it could drop by 5.3% (Dorman *et al*., 2018). In a survey study based on 55,890,830 fertile men, only 3340 participated and the outcome of the methods used by them for contraception were no contraception used by 23.2%, condoms used by 15.8%, withdrawal by 5.1%, and

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vasectomy used by 5.1% (Nguyen, 2024). In a retrospective global (1994-2005) study based on Africa, Asia, Europe, Latin America and the Caribbean, and Northern America Oceania have shown various outcome however it seems that condoms are the most popular (21-24%) (Table 1) (Ross and Hardee, 2017).

Table 1. Male commonly used methods of contraception

		Male sterilization	Male condom	Withdrawal	Rhythm	Share between methods
Developed countries in different continent	Africa	0.4	2.2	1.4	2.7	17.2
	Asia	2.2	7.6	2.9	2.7	22.7
	Europe	3.3	16.7	7.8	2.4	43.6
	Latin America and the Caribbean	2.6	9.6	2.6	2.8	24.2
	Northern America	11.9	11.9	4.3	1.2	39.2
	Oceania	6.3	10.2	1.7	2.1	34.2
Developing countries	China	4.4	8.3	0.5	0.5	16.4
	India	1.2	6.0	2.3	5.1	24.5
	Indonesia	0.2	1.8	2.2	1.2	8.7
	Bangladesh	0.6	4.0	0.9	5.2	16.6
	Pakistan	0.3	9.9	8.4	0.8	50.4
	Brazil	5.0	11.9	2.5	1.3	26.1
	Nigeria	0.0	2.5	2.2	2.0	41.9
	Mexico	2.2	6.5	2.0	2.1	17.6

II. HORMONAL METHODS

Male hormonal contraceptives can be just as effective as female contraceptives, according to studies from the 1970s. The understanding of how hormones can work in women is the foundation for hormonal male approaches. The production of the sex hormones required for the formation of an egg or sperm—testosterone [T] in the testes and estrogen in the ovaries—is inhibited by exogenous progestins (Noori and Althanoon, 2022a; Noori and Althanoon, 2022b). Biological similarities between male and female reproduction form the basis for the development of effective hormonal contraception for males (Wang *et al*., 2016).

Elevated intratesticular testosterone tissue levels are required for spermatogenesis to take place. In a normal male, serum testosterone concentrations are routinely 40–100 times lower than testicular T concentrations. When testicular T drops below a particular threshold, sperm production ceases. Research indicates that the administration of an exogenous steroid hormone, such as an androgen alone or with a gonadotropin-releasing hormone agonist or antagonist or a progestin, inhibits the hypothalamic-pituitary axis through feedback (figure 1). Nonetheless, other androgen-related functions like libido, erection, ejaculation, and retaining muscular mass entail sufficient blood androgen concentrations. Reintroducing exogenous androgens is necessary to keep serum levels high enough to support those activities without allowing testicular T to rise above the threshold needed to commence sperm production (Long *et al*., 2021).

Over 60 million sperm are present in a typical ejaculate, which is more than the 15 million sperm/mL required for good fertility. Early effectiveness trials explained that the pregnancy percent due to males with sperm density ranges of 0 and 3.0 million sperm/mL was 1.4 per 100 person per year (Waites, 2003). There is an approximate 2% yearly risk of pregnancy associated with severe oligozoospermia (sperm concentration of 1 million per mL) (Wu *et al*., 1996), which is equivalent to extremely successful female methods and provides support for using 1 million/mL as the goal sperm suppression level for male hormone treatments (Aaltonen *et al*., 2007). Sperm suppression has been shown in many controlled studies using progestin and T derivative combinations at levels that could consistently achieve this goal (Behre *et al*., 2016; Gu *et al*., 2004; Ilani *et al*., 2012; Meriggiola *et al*., 2003; Mommers *et al*., 2008; Wang *et al*., 2006). In these studies, sperm suppression rates of 89% to 100% were attained. It is unknown what causes certain guys to be unable to suppress. In contraceptive efficacy tests of potential male methods, sperm suppression must be verified before permitting males to rely on a product for contraception. Although it is possible to determine sperm concentration at home with commercially available sperm evaluation instruments, this confirmation is anticipated to be required for regulatory approval.

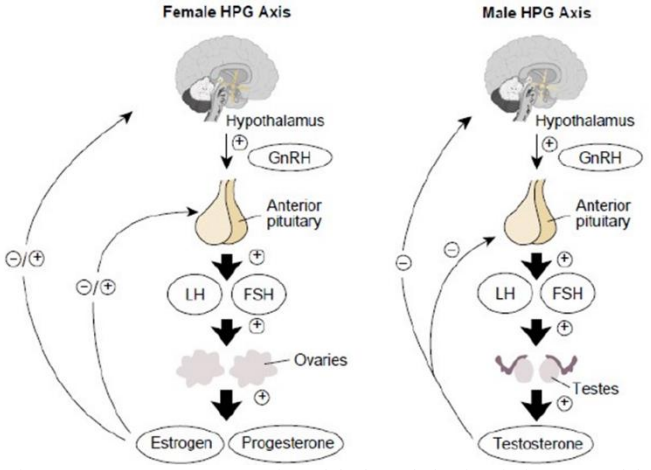

Figure 1. Schematic representation of the hypothalamic–pituitary–gonadal (HPG) axes (Kong *et al*., 2014).

The hunt for the "man pill" has stopped since there isn't a safe and effective oral androgen that can offer hormone add-back when testicular testosterone synthesis and spermatogenesis are decreased (Behre *et al*., 2016). In actuality, even when taken in conjunction with progestin, oral testosterone is cleared too quickly to be effective as a single daily dosage schedule (Gu *et al*., 2009). Taking numerous oral testosterone tablets every day for contraception would be unfeasible. Long-term usage of 17-methyltestosterone has been associated with hepatotoxicity, even though it has better oral bioavailability. Oral testosterone undecanoate has recently been approved in the US, however two daily dosages are needed (Long *et al*., 2021).

With funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), researchers are creating new androgens that bind to both progesterone and androgen receptors in the hopes that they will one day be utilized as single-agent male contraceptives (Blithe, 2016). Dimethandrolone undecanoate (DMAU) and 11-methyl-nortestosterone dodecylcarbonate (11-MNTDC) are two leading compounds in the development stage (Attardi *et al*., 2006; Attardi *et al*., 2011). If endogenous T synthesis is reduced, the drugs have the potential to lower blood estradiol levels since they do not aromatize. While 28-day research using oral DMAU showed increases in P1NP, a blood biomarker of bone production, the chronic effects on bone health remain unknown (Thirumalai *et al*., 2021). When given intravenously or orally, DMAU is hydrolyzed to the active substance dimethandrolone, a 19-nortestosterone derivative that binds to both androgen and progesterone receptors.

In phase I clinical research, the NICHD's Contraceptive Clinical Trials Network examined DMAU, and the results showed that it was well tolerated (Ayoub *et al*., 2017). Most subjects in a 28-day trial using 200 mg and 400 mg of oral DMAU daily had low blood gonadotropin levels (Thirumalai *et al*., 2019). No significant negative impacts were observed. The majority of participants (80%) found the approach to be effective, and 54% said they would use it as their main form of birth control if it were accessible (Nguyen *et al*., 2020). When administered in single dosages of 200, 400, and 800 mg, 11-MNTDC underwent its first-ever clinical trial and proved to be well tolerated with no significant side effects (Wu *et al*., 2019). After another 28-day study using 200 mg and 400 mg daily oral 11-MNTDC, the gonadotropins were effectively suppressed, but this time there were no appreciable side effects (Yuen *et al*., 2020).

A different artificial progestogenic androgen, 7-methyl-19-nortestosterone (MENT), is currently being investigated as a potential male contraceptive (Nieschlag *et al*., 2013). Early experiments with TU and MENT implants to reduce sperm production showed similar results, with roughly two-thirds of males demonstrating dose-dependent spermatogenesis suppression (Nieschlag, 2010). The MENT implant is being improved, but it still needs to be validated before it can produce continuous quantities of MENT release.

Transdermal or injectable androgens can be used as an alternative to oral medications. Testosterone gels are a common treatment for hypoandrogenism in the United States. Numerous studies have looked at the effectiveness of injectable testosterone enanthate, or TU, in reducing sperm either on its own or in combination with a progestin, with positive results (Gu *et al*., 2004; Gu *et al*., 2009; Meriggiola *et al*., 2003; Mommers *et al*., 2008). In a trial utilizing T gel and injections of the female contraceptive progestin depomedroxyprogesterone acetate, 90% of patients reported effective suppression of sperm (Page *et al*., 2006). Significantly, although they were used for off-label purposes, these two United States Food and Drug Administration (FDA)-approved medications were used in this technique.

The main studies that have examined the role of male contraceptive pills and their regimens are shown in (Table 2).

In the most current contraceptive efficacious trial, the effectiveness of injectable TU was assessed further by inhibiting sperm production with the addition of progestin.

Table 2. Main clinical trial that showed the efficacy of male hormonal contraceptives.

The used regimen	Year of study	Number of participants	Failure cases	Reference
Testosterone undecanoate injection plus norethisterone enanthate injection every 8 weeks	2016	111	4	(Behre *et al*., 2016)
Testosterone undecanoate injection every month	2009	733	9	(Gu *et al*., 2009)
Implant of Testosterone every 4-6 months plus depomedroxyprogesterone acetate injection every 3 months	2003	28	0	(Turner *et al*., 2003)
Testosterone undecanoate injection every month	2003	280	1	(Gu *et al*., 2003)
Testosterone enanthate injection every week	1996	209	4	(Wu *et al*., 1996)
Testosterone enanthate injection every week	1990	119	1	(Male, 1990)

The World Health Organization (WHO) and CONRAD clinical trial funded this phase II multisite international clinical trial, which looked at the safety and efficacy of contraception when two long-acting progestins—norethisterone enanthate and TU—were given intramuscularly at intervals of eight weeks (Behre *et al*., 2016). The 320 couples were recruited for the continuing trial; 266 males had poor sperm counts, which caused the couples to go onto the efficacy phase. On the recommendation of an outside safety evaluation committee, the experiment ceased early due to the frequent occurrence of reported mood changes, depression, injection site pain, and enhanced libido. Despite this, the overall technique failure rate was 7.5%, encompassing sperm non-suppression at the end of the suppression phase, sperm rebound during the efficacy phase and pregnancy during the efficacy phase. Compare this to the estimated 7% to 9% of women who do not complete their birth control tablet regimens (Sundaram *et al*., 2017). Significantly (>75%) of participants confirmed that they would be open to using the procedure if it were made available.

The alternative dosing schedule under investigation involves daily injections of a testosterone gel preparation and the progestin, Nestorone® (NES). In the proof-of-concept experiment, sperm concentration was reduced to 1 million/mL or azoospermia by testosterone gel preparation (100 mg) and NES gel (8 mg); however, only 23% of males who used T gel in addition to a placebo gel achieved this (Ilani *et al*., 2012). The serum levels of follicle-stimulating hormone and luteinizing hormone were quickly reduced. Treatment failure (sperm concentration greater than 1 million/mL) was predicted with 97% sensitivity by gonadotropin hormone concentrations greater than 1 IU/L four weeks following therapy (Roth *et al*., 2013). Instead of failing to respond to the treatment regimen, the majority of failures were caused by inconsistent or nonuse of the medicines. More than half of the participants who were questioned about the method's acceptability said they were satisfied or highly satisfied with it. To evaluate the dualistic gel of NES/testosterone placed together in one preparation for use as a method of contraception in men, the NICHD Contraceptive Clinical Trials Network is now undertaking a contraceptive effectiveness study (Roth *et al*., 2014).

Hormonal male contraceptives have been demonstrated to be effective in clinical trials. For a novel contraceptive drug to be approved by the FDA, women must usually undergo 20,000 cycles of safety and contraceptive efficacy testing over the course of at least a year of use. It was necessary to demonstrate the long-term safety of a male approach before a drug could be approved by regulators. Men do not face the same medical risks associated with pregnancy and childbirth, so weighing the potential benefits and risks of a male contraceptive pill can be challenging. A high safety profile is required for any systemic medicine intended for men. The benefits of pregnancy prevention from a social and biological standpoint must be considered in a shared risk model for both spouses (Campelia *et al*., 2020). Finding more health advantages for male contraceptive approaches is a desirable objective in particular. Practically, years will pass before a product is ready for the market due to long-term testing by a significant number of couples. Regulatory bodies will need to offer instructions on what is necessary for this new class of pharmaceuticals to be approved. Also, to accomplish this goal, pharmaceutical investment will be crucial (Long *et al*., 2021).

III. NON -HORMONAL METHODS

A. Novel hormone-free substances

Since the 1950s, researchers have been aware that suppressing spermatogenesis might affect the hypothalamus-pituitary-testes axis without having an immediate impact. Numerous non-hormonal medications have been found to be able to temporarily or permanently inhibit sperm maturation (Service *et al*., 2023). Because they lack the stigma associated with hormone augmentation (the use of anabolic steroids in sports), the side effects of changing hormonal pathways, and the challenges related to dosage or mode of administration, these medications may be a good alternative to hormonal contraceptives for male contraception (Service *et al*., 2023; Thirumalai *et al*., 2019). A wide range of substances that are not hormones can affect spermatogenesis at any stage. Testicular epigenetics, the testicular retinoic acid receptor, and the interactions between Sertoli cells and germ cells are common targets (Service *et al*., 2023; Thirumalai *et al*., 2020).

B. Retinoic acid inhibitors

Etinoic acid is essential for spermatogenesis because it promotes spermatogonial differentiation, spermiation, and the blood-testis barrier (BTB) (Schleif *et al*., 2022). Male mice with retinoic acid receptor (RAR) knockouts are sterile (Chung *et al*., 2005). In earlier antiparasitic studies conducted on rats in the 1950s using retinoic acid inhibitors, the rats unexpectedly became infertile. This finding has commenced the synthesis of non-hormonal male contraceptives as retinoic acid inhibitors (Heller *et al*., 1961).

WIN 18,446: At the Oregon State Penitentiary, 60 prisoners received the medication known as WIN 18,446 during the first human experiments, and 60 of them stayed azoospermic for a full year. A disulfiram response, which was later determined to have been caused by one of the prisoners who had access to illicit whiskey, unfortunately, caused them to become quite unwell (Chung *et al*., 2005). This is due to the fact that the medication functions by preventing the testes' aldehyde dehydrogenase 1A2 (ALDH1A2) from producing retinoic acid. Hepatic aldehyde dehydrogenase 2 (ALDH2) is the target of off-target actions that result in acetaldehyde accumulation in the serum and the concomitant systemic symptoms. WIN 18,446 was eventually stopped from being used, despite subsequent efforts to acquire retinoic acid receptor antagonists that are more specifically tailored to the testes (Schleif *et al*., 2022).

BMS-189453: Bristol-Myers-Squibb (BMS) has developed retinoic acid receptor antagonists with varying degrees of selectivity towards the testis. Developed in the 1990s, BMS189453 is an antagonist of the panretinoic acid receptor that works on the α, β, and γ receptors (Noman, *et al*., 2020; Schulze *et al*., 2001). Dosages of 5 to 240 mg/kg/day resulted in severe testicular atrophy and degeneration in rat models (Schulze *et al*., 2001). At doses greater than 240 mg/kg, serious toxicity led to deaths. Additional studies were conducted with lower dosages to obtain therapeutic effects. According to the Chung *et al*. study, all mice were infertile at 4 weeks, and fertility was regained by 20 weeks (Chung *et al*., 2011), which used 2.5 mg/kg for four weeks or 5 mg/kg for two weeks as doses. The 100% sterility was produced by doses as little as 1 mg/kg for 4 to 16 weeks; fertility returned when the medication was withdrawn (Chung *et al*., 2016).

YCT529: It was recently presented at the national meeting of the American Chemical Society in 2022 and is an α specific antagonist of retinoic acid (Sævareid, 2022). Taken orally for four weeks, sperm counts reduced and averted 99% of gestations in mice, alongside negligible adverse effects reported with these less selective retinoic acid receptor antagonists. After quitting the medication, mice were able to procreate for four to six weeks (Service *et al*., 2023), these findings ensures that clinical trial will be commenced soon.

C. Targeting connections between sertoli cells and germ cells

Indenopyridine derivatives: has been shown that indenopyridine derivatives, such as CDB-4022 and RTI-4587-073, restrict the formation of mature sperm in rat, primate, and stallion models (Hild *et al*., 2007a; Hild *et al*., 2007b; Pozor *et al*., 2013). These compounds primarily work by inhibiting the adhesion of juvenile spermatids to the seminiferous tubules, causing immature, non-motile germ cells to slough into the semen. Hild *et al*. (2007b), looked into the effects of a single dosage of CDB-4022 on the ultrastructure of rat testicles. They observed degenerative changes in Sertoli cells and spermatids. In the Sertoli cells, there were more vacuoles, cellular debris, more mitochondria, and larger endoplasmic reticulum. The spermatids' dispersed chromatin and nuclear envelopes were ruptured. In primate trials employing the same chemical, sperm counts decreased below 1 million/mL after 17 days and remained suppressed for 6 weeks (Hild *et al*., 2007). More unexpectedly, they found that immature spermatids completely eliminated sperm motility. Serum Inhibin B was elevated, although levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol were all within normal ranges. All blood markers and measurements of the health of the sperm were restored to normal healthy status within 17 weeks (Pozor *et al*., 2013).

Lonidamine derivatives: medication used in chemotherapy Analogs of lonsidamine are being researched as possible reversible male birth control methods. Adjudin is a derivative of lonidamine that is made from 3-carboxylic acid and 1H-indazole. The Sertoli-germ cell link is disrupted upon directing the apical ectoplasmic specialization proteins (Cheng, 2014; Mok *et al*., 2011). This leads to the exfoliation of immature spermatids. Two weekly dosages of 50 mg/kg of adjuvant were tested in rats, all of whom developed infertile (Mruk *et al*., 2006). Regrettably, the target proteins were not specific to the gonads, and their adverse effects were inflammation of the liver. To encourage testicular-directed selectivity, one group attempted to conjoin Adjudin with the vector biomolecule of FSH, the study demonstrated that by using this method, the effective dose in the rat model was reduced from 50 to 0.50 g/kg, while gonadal selectivity was greatly increased (Mruk *et al*., 2006).

D. Sperm ion channel blockers

CatSper, a calcium ion channel exclusive to sperm flagella, is vital for sperm proper motility (Carlson *et al*., 2009; Sun *et al*., 2017). It contributes to the hyperactivity of the flagella, potentiating movement toward the female ovum, capacitation, and acrosome response (Sun *et al*., 2017). In mice knock-out models, it has been shown that all four CatSper channels are essential for male fertility (Carlson *et al*., 2009; Qi *et al*., 2007; Quill *et al*., 2003). Numerous viable sperm below is a list of CatSper blocker targets. Additionally being studied as potential targets are the sperm-specific potassium channels Slo3 and KSper.

RU1968: is a SLO3 and CatSper inhibitor. CatSper was inhibited 15 times more effectively than SLO3 in studies involving human, mouse, and sea urchin sperm (Rennhack *et al*., 2018) during interspecies research. There were no negative side effects observed in human sperm. It has been established that RU1968 inhibits the progesterone-induced pro-motility response in the female reproductive system, even if the precise mode of action is yet unknown (Rehfeld, 2020; Rennhack *et al*., 2018).

HC-056456: a CatSper inhibitor that has been demonstrated to selectively and reversibly subside ion transport via the CatSper channel of patch-clamped sperm (Carlson *et al*., 2009). Human sperm that has been given HC-056456 loses flagellar hyperactivity (Carlson *et al*., 2009). In vivo mouse studies showed a decreased rate of fertilization when remedird sperm were fertilized inside the uterus. This was uniquely the first preliminary in vivo investigation to evaluate CatSper inhibitors as a suggestive male contraceptive in a mammalian animal model(Curci *et al*., 2021).

SLO3 channel blocker: Sperm-specific potassium channel SLO3 adjusts calcium entrance via the CatSper channel (Chávez *et al*., 2014). SLO3 works during capacitation by hyperpolarizing the cell to allow CatSper to enter the calcium channel. It could also affect sperm indirectly by

altering their pH. Mice lacking in SLO3 are infertile (Chávez *et al*., 2014). Quinine and quinidine are being studied as potential SLO3 inhibitors, however; there have been no human studies as of yet (Wrighton *et al*., 2015).

Lupeol and pristimerin: Plant triterpenoids called pristimerin and lupeol are suggested to prevent sperm hyperactivation by blocking the CatSper channel. Pristimerin is an isolate of Tripterygium Wilfordii, while Lupeol is an isolate of dandelions, aloe vera, and mangos. It is deemed that their mode of action is based on adhering to CatSper and impeding the activation of the protein by both progesterone and/or pregnenolone (Mannowetz *et al*., 2017). More investigation is still required to evaluate whether these drugs have any potential as male contraceptives because more research has called into question their ability to prevent sperm hyperactivation (Rehfeld, 2020).

E. Small-molecule inhibitors

Small chemical inhibitors of the spermatogenesis pathway are a new area of research. These substances work by obstructing the actions of their intended protein targets, which are usually enzymes. The following list contains illustrations of novel inhibitors that impact the male reproductive system.

JQ1: is a single inhibitory biomolecule. It works by blocking the BRDT protein, which is a testicular bromodomain. JQ1 In epigenetics, bromodomain proteins facilitate transcription factor recruitment, chromatin remodeling, and histone acetylation. It reduces spermatozoa counts, sperm motility, and seminiferous tubule volume with no impact on blood hormone levels, according to animal models of infertility. In male mice that were adminstered JQ1 for six weeks were unable to reproduce when they were kept in the same housing as female mice (Bryant and Berger, 2012). It has reversible off-target effects on non-testicular bromodomain proteins, despite this (Wisniewski and Georg, 2020). Further research will be necessary to improve testicular specificity.

EP055: Eppin is a tiny chemical that inhibits epididymal protease and can be blocked by EP055 (O'Rand *et al*., 2018). Sertoli cells produce Eppin into the testes, where it interacts with the surface of sperm. Semenogelin from the seminal vesicle binds it throughout ejaculation to regulate sperm motility. Eppin then synchronizes the enzymatic action of PSA to degrade semenogelin and encourage continuing motility (O'Rand *et al*., 2011).

Calcineurin blockers: Among the immunosuppressive drugs that use calcineurin inhibitors are FK506 (tacrolimus) and cyclosporine A (Miyata *et al*., 2015). They have been shown to negatively affect male fertility, which has led to research on how effective they are as non-hormonal reversible-male contraceptives. The sperm-dependent calcineurin subunits PPP3CC and PPP3R2 are possible goals for suppression because mice lacking these genes exhibit decreased sperm motility and infertility (Liu *et al*., 2020; Miyata *et al*., 2015). The procedure is assumed to be the stiffness of the sperm midpiece. After 4-5 days, mice in good health that have been given Cyclosporine A or FK506 show abnormalities in the morphology and motility of their sperm. When the medication is stopped, these adverse effects will go away after seven days (Miyata *et al*., 2015). Testis-specific calcineurin inhibitors may be a useful form of reversible male contraception. Targeting additional molecules required for the sperm calcineurin pathway might also be an option. Mice that exhibit decreased sperm motility and infertility as a result of SPATA33 suppression also exhibit mitochondrial localization of calcineurin (Miyata *et al*., 2021).

F. Vasal peristalsis blockers

Another proposed mechanism for male contraceptives is blocking sperm peristalsis through the male reproductive system. An example of a drug that could potentially find such application is Phenoxybenzamine which is an alpha-1-adrenergic antagonist that inhibits the longitudinal muscles of the vas deferens and inhibits peristalsis (Miyata *et al*., 2021). It has been shown to make rats permanently infertile and to stop ejaculation in a small subset of adult males (Homonnai *et al*., 1984; Paz *et al*., 1984).

Studies have also been conducted on two other alpha-1-adrenergic antagonists: tamsulosin and prazosin. Although tamsulosin has unfavorable side effects like orthostatic hypotension and dizziness, it has been shown in the past to lower sperm concentration. This contrasts with prazosin's controversially effective use as a contraceptive (Hellstrom and Sikka, 2009; Hellstrom *et al*., 1998; Kjærgaard *et al*., 1988; Wang *et al*., 2012). To determine whether alpha-1-adrenergic antagonists have the potential to be used as male contraceptives, substantial clinical research has not yet been conducted on them. The most recent alternative to P2X1-purinoreceptor antagonists has been suggested. Lack of P2X1-purinoreceptors reduces the amount of sperm in the semen and hinders peristalsis. The adenosine triphosphate (ATP) ligand-gated cation channels are located along the vas deferens on the smooth muscle cell membrane (Kauffenstein *et al*., 2014; Mulryan *et al*., 2000).

IV. CURRENTLY AVAILABLE MALE NON-HORMONAL CONTRACEPTIVE METHODS

A. Condoms

When male condoms are used perfectly, the rate of unplanned pregnancies is 2-3 %; when they are used sporadically, the rate is 12% (Majra, 2010; Trussell, 2004). Presently, there have been several public health initiatives to incite regular and adequate condom usage in an effort to prevent STIs and unintended births. An analysis of 5865 American teens and adults between the ages of 14 and 94 revealed that about 21.5% of men said they had used a condom at least once in the ten previous instances they had

vaginal sex (Reece *et al*., 2010). A second cross-sectional national poll of people in the 18–44 age range found that 24.8% of respondents said they had used a condom during their most recent sexual encounter (Nasrullah *et al*., 2017). Also, it has been demonstrated that the use of condoms interferes with intimacy or is linked to relationship mistrust (Golub *et al*., 2012; Smith *et al*., 2009). There are condoms made with spermicidal chemicals as well, although there is little data to support their better effectiveness in preventing unintended pregnancies (Gao *et al*., 2022).

B. Vasectomy

In the US, 500,000 vasectomies are carried out annually, and 5–10% of married males have undergone the treatment (Johnson and Sandlow, 2017; Trussell, 2004). In the first year after a vasectomy, the unwanted pregnancy rate ranges from 0.02% to 0.1% (Barone *et al*., 2004; Trussell, 2004). This sterilizing technique is comparatively quick and dependable, with complication rates as low as 1% to 2% (Service *et al*., 2023). One of the primary barriers to the broad use of vasectomy is its permanency, which comes with a high cost and unpredictable success rate for vasectomy reversal. Vasectomy difficulties are primarily impacted by the number of procedures performed; one study found that physicians performing over 50 procedures annually encounter one-third the complications compared to those performing fewer than 10 procedures (Kendrick *et al*., 1987). The most common adverse effects include hematoma (2%), sperm granuloma (40%), infection (3-4 %), and chronic post-vasectomy pain (1–14%) (Yang *et al*., 2021). Many patients prioritize the reversibility of the procedure since it is linked to the procedure's success, along with the technique of the vasectomy and the degree of obstruction. Male patients who underwent a reversal reported patency rates of >95% and a pregnancy rate of 75% less than three years after their initial treatment, with both rates decreasing as blockage duration increased(Belker *et al*., 1991).

V. Conclusion

There has been some progress in the development of male contraceptives, both hormonal and non-hormonal. Hormones like progesterone or testosterone are used in hormonal male contraceptives to inhibit the synthesis of sperm in the testes. Testing of a hormone injection for men, which has shown promise in clinical trials, is one of the most recent advancements in this field. Recent advancements in this field include the testing of a skin-applying gel that has produced promising outcomes in animal studies. Instead of reducing sperm production, non-hormonal male contraceptives focus on the sperm's motility or ability to fertilize eggs. Male contraceptives are developing; however, they are still in the testing stage and have not yet acquired regulatory approval for widespread usage. But the growth of these options might give those looking for contraception—individuals as well as couples—more options.

VI. Conclusion

This study could provide important epidemiologic data on BV for future risk behaviours and population-based studies. BV is one of the major causes of vaginal discharge and itching among childbearing age women and this could be a problem for health among this age in our community. BV is still highly detected among the married women in this study. A higher number of births, low level of education, vaginal discharges, higher vaginal pH, genital ulcer, intrauterine device use as a contraceptive were a main risk factors for such bacteria. There is an urgent regular need for screening for BV among symptomatic women with abnormal vaginal discharges. Therefore, the early detection of risk factors associated with bacterial vaginal growth is critical to enhance the health condition of married women, in order to prevent the risk of BV among them.

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