Male Contraceptives

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Additional information is available at the end of the chapter

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Abstract

Background: The world's population has been growing exponentially, however, currently the choices for male contraception are limited. This review explores ongoing researches on male contraceptives.

Method: A literature search was conducted on PubMed, Cochrane, and Google Scholar on March 2015.

Results: There are 15 research done on non-hormonal male contraceptives, 2 of which are already widely used and the other 2 are undergoing clinical trials. Hormonal contraceptives are provided in two regiments, testosterone alone, and testosterone with progestins. Currently, no hormonal contraceptives are available for men.

Conclusion: There are a variety of possible methods for male contraception. Non-hormonal methods, such as RISUG and Gandarusa are sent through clinical trials, and may be available in the near future. There are still no hormonal contraceptives for men that are ready for use.

Keywords: male contraception, hormonal contraceptives, non-hormonal contraceptives

1. Introduction

The world's population has been growing exponentially in the recent decades is expected to reach 9 billion in 2050. Considering the current difficulties in managing health and poverty, contraception is becoming increasingly important [1, 2].

Contraception is the intentional prevention of conception or pregnancy by various methods; barrier methods, hormonal contraception, intrauterine devices, sterilization and behavioral methods. Of these methods, only two are available for men, the male condom (barrier), and vasectomy (sterilization). The male condom is an effective method of contraception with the added benefit of prevention of STIs, however relies on discipline and availability of the

condom at the time of intercourse. A vasectomy doesn't depend on the occurrence of intercourse, but has poor reversibility rates and is therefore not ideal for men who still plan on having children [1, 3–5].

Long term, reversible male contraceptives are currently being developed. Male contraceptives are aimed to interfere with normal spermatogenesis, or motility, orientation, and binding to ovum. This paper reviews previous studies on male contraceptives to give a general picture of the possibilities and current available methods.

2. Methods

A literature search was conducted on PubMed in March 2015 with the search terms male AND contraceptives* and male AND infertility* between 2010 and 2015. Titles and abstracts were manually scanned by one researcher and those related to male contraceptives were chosen. When information was found to be lacking, more searches were done with specific terms and no time limit, for example "CDB 4022".

Further searches were done on Google Scholar with Indonesian terms "kontrasepsi pria" and results were once again manually searched for articles related to male contraception. All searches were limited to articles that were available for free.

3. Results

3.1. Spermatogenesis

Spermatogenesis is the formation of sperm from primordial germ cells. At puberty, spermatogenic germ cells (spermatogonia) produce BMP8B which cause the germ cells to differentiate. Spermatogonia are attached to Sertoli cells, which nourish and protect the cells as they undergo spermatogenesis [6].

Spermatogonia undergo several divisions and forms various forms of Spermatogonia A, intermediate spermatogonia and spermatogonia B. Spermatogonia A1 are stem cells and can continue to divide into more spermatogonia, thus spermatogenesis occurs continuously. Spermatogonia B divides into primary spermatocytes, which undergoes meiotic divisions to form round, haploid cells known as spermatids [6].

Spermatids then go through spermiogenesis to form mature sperm. During spermiogenesis, Golgi apparatus forms the acrosome that caps the nucleus. Flagellum is formed on the opposite side of the nucleus. The nucleus itself is condensed, and mitochondria forms a ring at the base of the tail. Once all of these changes have taken place, mature spermatozoa is released into the lumen, a process called spermiation [6].

In humans the process from spermatogonia to spermatozoa takes up to 65 days. About 100 million sperm are produced every day, and each ejaculation contains up to 200 million sperm. Each day, some 100 million sperm are made in each human testicle, and each ejaculation releases 200 million sperm. Unused sperm are either resorbed or passed out of the body in urine [6].

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3.2. Nonhormonal contraceptive

Nonhormonal male contraception targets sperm production, maturation and/or function, without interrupting the hormonal pathway. Many nonhormonal targets in the spermatogenesis and fertilization process has been identified, and contraceptive opportunities have been tested and implemented [7].

3.2.1. Condoms

Condoms prevent pregnancies by blocking the path of semen into the cervix. With correct use, the efficacy is 97%, with the added benefit of prevention against STIs and HIV. However with typical use, failure rates are as high as 12%. The correct use of condom refers to application of condom before vaginal penetration, preferably before any penile-vaginal contact. On application, the tip of the condom must be pressed to release trapped air and consequently provide space for semen [7].

Drawbacks of this method apart from its failure rates are latex allergies, possibility of breakage, and decreased pleasure for some couples [7].

3.2.2. Vasectomy

Vasectomy is a procedure in which the vas deferens are divided and ligated so as to prevent flow of sperm from testis. This is an outpatient procedure, conducted with local anesthesia with minimal side effects. Following vasectomies, pregnancy rates drop to below 1%. However reversibility rates after vasectomy is less than 50%. There is no effect on libido [7].

3.2.3. Reversible inhibition of sperm under guidance (RISUG)

RISUG is a method of contraception directed at destruction of sperm as it passes through the vas deferens. RISUG is applied by injection of steric maleic anhydride (SMA) and dimethyl sulfoxide (DMSO) into the vas deferens. Within the next 72 h, RISUG forms electrically charged precipitates in the lumen, with positive charges dominating [7]. This forms an acidic environment. The precipitate then layers the lumen wall, implanting themselves on the microfolds on the vas deferens' inner walls. Sperm that pass through the RISUG injected vas deferens, suffer ionic and pH stress, causing acrosomal damage, rendering them unable to fertilize oocytes [5, 8]. Studies so far have shown RISUG to be 100% effective. Because of the time needed for action, however, condom use is suggested in the first 10 days after injection [8].

RISUG can be flushed out with intravasal injections of sodium bicarbonate, which will reverse its infertility effects, as has been shown in mice [9]. Reversibility testing in humans has not been performed.

There has been no serious side effect within 10 years after RISUG injections in humans. Scrotal swelling may occur after injection, but resolves on its own. A study that studied RISUG's side effects on the prostate found that there was no increased risk of developing prostatic diseases even after a period of 8 years [9].

Smart RISUG [9] comprises of iron oxide-copper-styrene maleic anhydride-dimethyl sulfoxide (Fe_3O_4–Cu–SMA–DMSO), and has been shown to give better spermicidal action in vitro and in vivo in rats. Copper has been known to displace molecules such as zinc from sperm membrane, decreasing their potential to fertilize. Studies need to be conducted on toxicity of this new drug before application on humans [9].

3.2.4. Ultrasound

Application of low intensity ultrasound to the scrotum can elevate tissue temperatures in the testes [10, 11]. Spermatogenesis cannot occur in body temperature, which is why the human testes is suspended in the scrotal sack with a network of blood vessels to allow for cooling. Studies show that heat stress on the testes lead to apoptosis of germ cells [12]. In the past, local application of heat to the testes, such as immersing in a hot baths, has been used as a method of contraception [1].

Experiments on monkeys have shown that ultrasound exposure to the scrotum was 93% effective in inducing azoospermia in 1–2 weeks with sperm counts rebounding to normal after 7 weeks [11]. Intensity of ultrasound required to cause infertility depended on testes size [10, 11]. Heat treatment during therapy by dipping scrotum in 37C water or saline increased ultrasound potential as seen in rats and monkeys [10]. There are no side effects noted in ultrasound treatments, however there is concern that heat treatment may cause DNA damage in consecutive sperm productions [10, 11].

3.2.5. Vaccines

Contraceptive vaccines are developed under the concept of targeting sperm specific antigens [1, 13]. Vaccination with these sperm antigens (recombinant/synthetic peptide/DNA) has been found to cause reversible contraceptive effects in animals through formation of systemic and local antisperm antibody responses. The sperm antigens which have been examined for contraceptive effect include: FA-1, YLP12, LDH-C4, P10G, A9D, SP56, 80 kDaHSA, Eppin, and Izumo. There has been no contraceptive vaccine tested on men [13, 14].

Eppin is a protein secreted by the epididymis for sperm maturation [1, 14]. It is found on sperm surface and aids in fertilization. The vaccinated subjects produce antibodies against Eppin molecules, thus impairing sperm maturation and its capability to fertilize [13, 14].

An in vivo study of Eppin in monkeys resulted in 78% of the monkeys becoming infertile. Seventy one percent of them regained fertility after 450 days. Adjuvants were required every 3 months to maintain antibody levels. Studies are being conducted to improve safety, efficacy and reversibility before application in humans [14]. So far, no other in vivo studies have been conducted on other contraceptive vaccines.

3.2.6. Indenopyridines

CDB-4022, an indenopyridine is being studied as a potential oral contraceptive for men [15]. This compound was found to affect sertoli and germ cells, causing alterations in sertoli-germ

cell junctions and causing apoptosis of germ cells in rats. It causes irreversible azoospermia in rats, but reversible oligospermia in monkeys. There are no changes to serum LH and Testosterone levels, but increased levels of FSH attributed to reduction of inhibin B caused by destruction of germ cells [15]. There were no toxicities noted. Efficacy and reversibility are missing on literature.

3.2.7. Adjudin

Adjudin is derived from an anticancer drug, lonidamine. Lonidamine was found to be antispermatogenic, thus causing infertility. However, it also caused several side effects such as muscular pain, testicular pain, and liver damage. To attain the anti-fertility functions without the toxicity, Adjudin was developed. Adjudin targets adherence junctions between Sertoli cells and spermatids, causing early spermiation. One hundred percent infertility was achieved 5 weeks after administration of adjudin and fertility returned 11 weeks after treatment. Serum testosterone, FSH and LH remained normal, however, liver and skeletal muscle atrophy occurred in one third of the rats. To overcome this, adjudin was administered with an FSH mutant, which successfully bypassed the liver and muscle effects. Unfortunately, this made adjudin too costly as a contraceptive [16].

A study was conducted by Wang et al. [17] to assess the possibility of adjudin to be as a spermicide. In vitro evaluation showed that adjudin was found to significantly limit sperm motility and viability by targeting sperm mitochondria [17].

3.2.8. Gamendazole

Gamendazole is also derived from ionidamine, and causes infertility by targeting Sertoli cells [18, 19]. A study in rats showed that administration of a single dose of gamendazole resulted in 100% infertility 4 weeks post treatment, however, reversibility was only 57%. At half the dose, only 67% infertility was achieved, albeit with 100% reversibility. There were no changes in LH and testosterone levels, but a slight transient increase in FSH was observed due to depletion of inhibin B. There were no noticeable side effects, however at there was 60% mortality in rats given 200 mg/kg gamendazole, but not at any lower dose. Another option being investigated is administration of daily gamendazole at 1 mg/kg to achieve 100% infertility with 100% reversibility. Human trials are still pending [18–20].

3.2.9. Calcium channel blockers (CCBs)

Calcium is required for sperm motility, capacitation and acrosome reactions. Uptake of calcium is facilitated by calcium channels on sperm membranes. Calcium channel blockers inhibit calcium influx into sperm cell and thus impair fertility. Although there are many CCBs available, none has been tested as contraceptives because of the impracticality of using antihypertensive agents as contraceptives.

Calcium entry into sperm is also facilitated by transmembrane CATSPER channels which exist primarily in the testis. Blockade of CATSPER channels is a plausible mechanism for contraceptives, however as of today, there are still no known antagonists [21].

3.2.10. Retinoic acid inhibitor

Vitamin A is crucial for normal spermatogenesis. It is transported as retinol and synthesized into retinoic acid in the testis. Retinoic acid works through Retinoic Acid Receptors (RAR) on Sertoli cells. Retinoic acid inhibition and retinoic acid receptor blockers inhibit spermatogenesis and are easily reversed [22–26].

WIN 18,446 inhibits testicular retinoic acid biosynthesis through inhibition of aldehyde dehydrogenase 1A2 in vitro in humans. Administration of WIN 18,446 in dogs and monkeys have been found to induce azoospermia. Testicular biopsies show complete arrest of spermatogenesis [22, 25]. In the 1960s, administrations of oral WIN 18,446 in men have shown adequate contraceptive effects. These effects were completely reversible upon cessation of treatment. Reduced testicular volume was observed, but serum testosterone remained unchanged [26].

WIN 18,446 caused no liver or kidney toxicities. However when men taking WIN 18,446 consumed alcohol, they develop a "disulfiram reaction," which consists of nausea, vomiting, palpitations and sweating. This is because inhibition of aldehyde dehydrogenase 1A2 interferes in the metabolism of alcohol [25, 26]. Studies are being conducted to find a compound which inhibits retinoic acid synthesis without affecting alcohol metabolism [26].

3.2.11. Retinoic acid receptor antagonists

BMS-189453 is a synthetic retinoic acid receptor antagonist. It binds to retinoic acid receptors (RARs) but do not activate them. The testis and epididymis, especially sertoli cells are rich in RARs. Introducing a RAR antagonist was found to induce the same effects as Vitamin A deficiency in terms of apoptosis of germ cells and inhibition of spermatogenesis [23, 24].

A research done with low dose BMS-189453 on mice fertility showed 100% efficacy in inducing azoospermia. This is followed by 100% reversibility after 4 weeks of stopping treatment. Toxicity analysis showed no hematology or blood chemistry abnormalities, and tissue pathology was isolated to the testis, where there is failure of spermatogenesis, spermatid alignment, and sloughing of germ cells [24].

3.2.12. Gandarusa

Gandarusa is derived from the plant Justicia gendarussa [27, 28], which has been used by many tribes in eastern Indonesia as a contraceptive medicine. The roots and leaves are boiled in water and the water is then consumed twice a month to elicit contraceptive effects. This plant is also used as herbal medication for pain and inflammation. Gandarusa has since been standardized and is now available in pill form [27].

Gandarusa was found to affect spermatogenesis in rats as well as human. The proposed mechanism of Gandarusa is weakening of the sperm's hyaluronidase activities required for penetration of sperm into ovum, thus preventing fertilization [27]. Animal studies have shown no liver or kidney toxicities [28]. This drug is currently undergoing phase III clinical trials. There is no available data on efficacy of gandarusa as a contraceptive in humans, as well as reversibility rates and effects on libido.

3.2.13. Gossypol

Gossypol is found in cotton plant genus Gossypium [1, 29]. In 1972, a research on the effects of gossypol on 10,000 men were observed. Gossypol was found to be 99.07% effective as a contraceptive. Gossypol has been reported to interfere in hypothalamus-pituitary axis, disrupt spermatogenesis and reduce sperm motility. In 1996, a study on the effects of gossypol in vitro found that Gossypol decreases sperm motility by inhibiting cAMP production. There are no noted side effects. However, reversibility rates are only 80% [29].

3.3. Hormonal contraceptives

The gist of hormonal contraception in men is altering the hormonal pathway so that spermatogenesis does not occur. Gonadotropin releasing hormone (GnRH) from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary. FSH stimulates sertoli cells to begin spermatogenesis, while LH stimulates Leydig cells to produce testosterone. Testosterone then provides negative feedback to hypothalamus and pituitary, suppressing their activity and subsequently its own production [4].

Male hormonal contraception focuses on suppressing hypothalamus and the pituitary action to inhibit spermatogenesis. This has been done by provision of testosterone alone as well as testosterone and progestins [4].

3.3.1. Testosterone alone

Oral preparations of testosterone that are safe for consumption are not readily available. Long-acting injections and implants are being developed as alternatives. Testosterone gel and patches are in development, however, they are costly and require frequent application thus making them unaffordable as a commercial contraceptive [30].

Common side effects of testosterone are acne, oily skin, mood changes, increased hemoglobin, weight gain, decreased testicular volume, gynecomastia, and dyslipidemia. Long term effects of testosterone supplementation on the prostate are still unclear. Other considerations in using testosterone preparations are the possible misuse as anabolic steroids [3].

3.3.1.1. Testosterone enanthate (TE)

TE is a long acting preparation that requires weekly administration through intramuscular injections [31]. In a study by WHO, azoospermia is achieved by an average of 3 months in 70% of men receiving 200 mg TE weekly. Once azoospermia is reached, TE can be effectively used alone as a contraceptive; with 0.8% failure rate. Reversibility is 100% within an average of 4 months after discontinuation. Side effects of TE were reductions in HDL levels and testicular volumes, albeit reversible after cessation of use.

This method has a few drawbacks. First, not all men receiving this therapy will become azoospermic. Second, weekly injections are required. Third, there were worrying side effects regarding to HDL levels and testicular volume. Finally, it requires 3–7 months to achieve azoospermia, therefore requiring another form of contraceptive until azoospermia is achieved.

3.3.1.2. Testosterone undecanoate (TU)

TU is formulated in long acting depot preparations with a half-life of 70 days that can be administered intramuscularly in intervals of 4–8 weeks [3]. A clinical trial in China reported that 95% of test subjects achieved azoospermia, defined as sperm concentration < 1 million per milliliter. Pregnancy rates were at 1.1%. Sperm count was reversed after 15 months of stopping therapy. A European clinical trial by WHO produced similar results. However, trials were stopped due to reports of side effects such as mood swings.

3.3.1.3. 7α-Methyl-19-nortestosterone (MENT)

MENT is a synthetic androgen five times more potent than testosterone [3, 31]. MENT was developed to replace testosterone for contraceptive use because of the large amount of testosterone required to achieve long term infertility. Also because it is resistant to 5α-reductase, there is less prostate stimulation. However, substituting testosterone with MENT led to a decrease in bone density.

MENT has been introduced in implant form as a contraceptive and has been found to cause azoospermia in two thirds of men receiving it. To improve its efficacy researchers combined it with etonogestrel implants and levonorgestrel implants. Results were the same as with MENT alone. In addition, men receiving MENT and etonogestrel experienced loss of libido. Research are continuously being conducted on a form of dosing that will attain a higher rate of azoospermia with minimal side effects.

3.3.2. Combination therapy

Exogenous progestins combined with testosterone provide better suppression of gonadotropins, thus more effective at producing azoospermia at lower doses [3]. There has been several researches combining various progestins with androgens for male contraceptive. Among them are:

- Depot medroxyprogesterone acetate (DMPA) + TE (efficacy 98%) [3].
- Antiandrogenic Progestogen Cyproterone Acetate (CPA) + TE [3].
- Androgenic progestin Norethisterone (NET) + TU (efficacy 92%) [3].
- Oral Levonorgestrel (LNG) + testosterone patches (efficacy < 60%) [3].
- LNG + TE (efficacy 93%) [3].
- Synthetic progestin Desogestrel (DSG) + TE (efficacy 100%) [3].
- MENT implant + Jadelle implant (efficacy < 60%) [31].

Data on reversibility, effect on libido of these tested regiments were not found on the literature.

4. Discussion

In the past, male contraceptives have been acknowledged. There are few commonly applied methods of male contraception such as local application of heat, consumption of herbal medicines, coitus interruptus, vasectomy, and male condoms. Each of these methods has had drawbacks that cause them to only be used by a minority of the population. Heat application and herbal medicines lack evidence of overall efficacy. Coitus interruptus has a 12% failure rate even when practiced correctly. Condoms depend a lot on correct use, and are rendered useless in the case of breakage. Vasectomy has less than 50% reversal rates. There is still no long term, reversible contraceptive available for men.

Method	Efficacy	Mechanism	Effect on libido	Reversibility	Side effects	Additional information
Condom	97%	Forms barrier to prevent sperm from entering female reproductive tract (FRT)	No effect	100%	Possible latex allergy in 3% of men, decreased sexual pleasure	Highly effective in preventing STI
Vasectomy	99%	Occlusion of vas deferens to prevent sperm from being ejaculated in semen	No effect	50%	Scrotal pain	
Ultrasound	93%	Produces thermal effect on testes	No effect	100% after 7 weeks	No side effects	Intensity and duration of ultrasound depends on size of testes There are risks of DNA damage in heat treated testes
Indenopyridines	–	CDB-4022 appears to target the Sertoli cell, disrupting germ cell-sertoli time	–	–	Increased FSH	
Adjudin	100%	Adjudin affects fertility by disrupting Sertoli-germ cell junctions, and once this occurs, germ cells slough the seminiferous epithelium prematurely	No changes in testosterone, LH, or FSH	100%	Muscle atrophy and liver inflammation	Adjudin + FSH mutant bypasses liver and muscle atrophy, but is costly
RISUG	100%	Injection of RISUG into vas deferens to destroy sperm ability to fertilize	No effect	100% in monkeys and langurs	No side effects. Reversible scrotal edema may occur after injection	Phase III clinical trial (safety and efficacy on humans established)

Method	Efficacy	Mechanism	Effect on libido	Reversibility	Side effects	Additional information
Calcium Channel Blocker	–	Blocks Ca++ influx into sperm and affects sperm membrane cholesterol, thereby compromising fertility	–	–	–	CCBs have never been tested as contraceptives
Gamendazole	100% after 4 weeks	Affects sertoli cells	No effect	57% after 11 weeks	No side effects	Causes death in rats at doses 200 mg/kg
WIN 18,446	100%	Suppresses spermatogenesis by inhibiting testicular retinoic acid biosynthesis	No effect	100%	"Disulfiram" effect upon consumption of alcohol	Nausea, vomiting, palpitation when drinking alcohol
BMS 189453	100%	Causes marked testicular degeneration	No effect	100%	No side effects	
Gossypol	99.07%	Decreases sperm motility by inhibiting cAMP production	Not mentioned	80%	No side effects	Research conducted in Chinese men
Gandarusa	–	–	–	–	–	Undergoing clinical trials

Cited from: Blithe [30].

Table 1. Non-hormonal contraceptives.

Method	Efficacy	Mechanism	Effect on libido	Reversibility	Side effects	Additional information
Testosterone Enanthate	70%	Suppresses gonadotropin production	No effect	100%	Reduced testicular volume and HDL level	
Testosterone undecanoate	95%	Suppresses gonadotropin production	No effect	100%	Mood swings	
Testosterone gel		Suppresses gonadotropin production through increase of testicular testosterone	No effect	100%	–	Expensive
Testosterone + Progestogen	Variable	Suppresses gonadotropin production	–	100%	–	

Cited from: Blithe [30].

Table 2. Hormonal contraceptives.

Considering numerous hormonal contraceptive methods available for women, hormonal pathways have been studied to develop an effective and safe male contraceptive. Disappointingly, no hormonal regiments have yet been approved for contraceptive use.

Non hormonal contraceptives have shown more promise. RISUG and Gandarusa are undergoing relatively successful clinical trials in terms of efficacy and safety [7]. RISUG requires only a single injection, which has maintained infertility for up to 10 years now. Reversibility also requires only a single injection, but has yet to be tested on humans. Gandarusa is available in pill form, giving men the choice to be an oral contraceptives. The success of these agents, however, depends largely on the men's willingness to take responsibility for family planning.

A review on male contraceptives shares the same conclusion that despite the expression of interest and tremendous advances in research however, a modern male hormonal contraceptive method has remained an elusive goal. Testosterone (T) alone, or in combination with a progestin currently provides the most promising lead to male hormonal contraception. The principle relies on enhanced negative feedback of exogenous T to suppress gonadotropins, thereby blocking the endocrine stimulus for the process of spermatogenesis. A serious drawback is the inconsistent suppression among men of different ethnic backgrounds. This has increased the quest for development to include other nonhormonal methods. In reality many obstacles still have to be overcome before an acceptable method is available [32].

To conclude, there are a variety of possible methods for male contraception. Non-hormonal methods RISUG and Gandarusa are undergoing clinical trials, and may be available in the near future. There are still no hormonal contraceptive ready to use for men (**Tables 1** and **2**).

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References

[1] Matthew V, Bantwal G. Male contraception. Indian Journal of Endocrinology and Metabolism. 2012;**16**(6):9

[2] Nya-Ngatchou JJ, Amory JK. New approaches to male non-hormonal contraception. Contraception. 2013;**87**:4

[3] Yapar EA, Inal O. Pharmaceutical approaches and advancements in male contraception. Tropical Journal of Pharmaceutical Research. 2012;**11**(6):10

[4] Roth MY. Male hormonal contraception. Virtual Mentor. 2012;**14**(2):126

[5] Chaudhury K, Bhattacharyya AK, Guha SK. Studies on the membrane integrity of human sperm treated with a new injectable male contraceptive. Human Reproduction. 2004;**19**(8):5

[6] Gilbert SF. Developmental Biology. 6th ed. Sunderland: Sinauer Associates; Spermatogenesis; 2000 Available from: http://www.ncbi.nlm.nih.gov/books/NBK10095/

[7] Guha SK. Biophysical mechanism-mediated time-dependent effect on sperm of human and monkey vas implanted polyelectrolyte contraceptive. Asian Journal of Andrology. 2007;**9**(2):7

[8] Sharma U, Chaudhury K, Jagannathan NR, Guha SK. A proton NMR study of the effect of a new intravasal injectable male contraceptive RISUG on seminal plasma metabolites. Reproduction. 2001;**122**:6

[9] Jha RK, Jha PK, Guha SK. Smart RISUG: A potential new contraceptive and its magnetic field-mediated sperm interaction. International Journal of Nanomedicine. 2009;**4**:10

[10] Tsuruta JK, Dayton PA, Gallippi CM, O'Rand MG, Streicker MA, Gessner RC, Gregory TS, Silva EJR, Hamil KG, Moser GJ, Soka DC. Therapeutic ultrasound as a potential male contraceptive: Power, frequency and temperature required to deplete rat testes of meiotic cells and epididymides of sperm determined using a commercially available system. Reproductive Biology and Endocrinology. 2012;**10**:15

[11] VandeVoort CA, Tollner TL. The efficacy of ultrasound treatment as a reversible male contraceptive in the rhesus monkey. Reproductive Biology and Endocrinology. 2012;**10**:8

[12] Hansen PJ. Effects of heat stress on mammalian reproduction. Philosophical Transactions of the Royal Society B: Biological Sciences. 2009;**364**(1534):3341-3350

[13] Naz RK. Antisperm contraceptive vaccines: Where we are and where we are going? American Journal of Reproductive Immunology. 2011;**66**(1):11

[14] Karande A. Eppin: A candidate male contraceptive vaccine? Journal of Biosciences. 2004;**29**(4):373

[15] Koduri S, Hild SA, Pessaint L, Reel JR, Attardi BJ. Mechanism of action of l-CDB-4022, a potential nonhormonal male contraceptive, in the seminiferous epithelium of the rat testis. Endocrinology. 2008;**149**(4):11

[16] Mok KW, Mruk DD, Lie PPY, Lui WY, Cheng CY. Adjudin, a potential male contraceptive, exerts its effects locally in the seminiferous epithelium of mammalian testes. Reproduction. 2011;**141**:10

[17] Wang H, Chen XX, Wang LR, Mao YD, Zhou ZM, Sha JH. AF-2364 is a prospective spermicide candidate. Asian Journal of Andrology. 2010;**12**:14

[18] Tash JS, Attardi B, Hild SA, Chakrasali R, Jakkaraj SR, Georg GI. A novel potent indazole carboxylic acid derivative blocks spermatogenesis and is contraceptive in rats after a single oral dose. Biology of Reproduction. 2008;**78**:12

[19] Tash JS, Chakrasali R, Jakkaraj SR, Hughes J, Smith SK, Hornbaker K, et al. Gamendazole, an orally active indazole carboxylic acid male contraceptive agent, targets HSP90AB1 (HSP90BETA) and EEF1A1 (eEF1A), and stimulates Il1a transcription in rat Sertoli cells. Biology of Reproduction. 2008;**78**(6):1139-1152

[20] Cheng CY, Mruka D, Silverstirini B, Bonanomib M, Wong CH, Siua MKY, Lee NPY, Luia WY, Moa MY. AF-2364 [1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide] is a potential male contraceptive: A review of recent data. Contraception. 2005;**72**:11

[21] Nazari M, Bamdad T, Mirsahi M, Sarikhani S, Mowla SJ. Investigation in vitro expression of CatSper sub fragment followed by production of polyclonal antibody: Potential candidate for the next generation of non hormonal contraceptive. Cell Journal. 2012;**14**(3):10

[22] Hogarth CA, Evanoff R, Snyder E, Kent T, Mitchell D, Small C, Amory JK, Griswold MD. Suppression of Stra* expression in the mouse gonad by WIN 18,446. Biology of Reproduction. 2011;**84**:9

[23] Schulze GE, Clay RJ, Mezza LE, Bregman CL, Buroker RA, Frantz JD. BMS-189453, a novel retinoid receptor antagonist, is a potent testicular toxin. Toxicological Sciences. 2001;**59**:12

[24] Chung SW, Wang X, Roberts SS, Griffey SM, Reczek PR, Wolgemuth DJ. Oral administration of a retinoic acid receptor antagonist reversibly inhibits spermatogenesis in mice. Endocrinology. 2011;**152**(6):11

[25] Amory JK, Muller CH, Shimsoni JA, Isoherranen N, Paik J, Moreb JS, Amory DW, Evanoff R, Goldstein AS, Griswold MD. Suppression of spermatogenesis by bisdichloroacetyldiamines is mediated by inhibition of testicular retinoid acid biosynthesis. Journal of Andrology. 2011;**32**(1):17

[26] Hogarth CA, Amory JK, Griswold MD. Inhibiting vitamin A metabolism as an approach to male contraception. Trends in Endocrinology and Metabolism. 2011;**22**(4):14

[27] Handayani L. Pil Kontrasepsi Laki-laki dengan Bahan Dasar Gandarusa (Justicia gendarussa Burm.F). Majalah Kedokteran. Indonesia. 2007;**57**(8):6

[28] Prajogo BEW, Ifadotunnikmah F, Febriyanti AP, Jusak N. Efek Fase Air Daun Gandarusa (Justicia gendarussa Burm.f.) pada Fungsi Hati dan Fungsi Ginjal Kelinci Jantan (Uji Toksisitas Fase Air Daun Gandarusa Sebagai Bahan Kontrasepsi Pria). Veterinaria Medika. 2008;**1**(3):4

[29] Zivos PM, Zarmakoupis-Zavos PN. The inhibitory effects of gossypol on human sperm motility characteristics: Possible modes of reversibility of those effects. The Tohoku Journal of Experimental Medicine. 1996;**179**:9

[30] Blithe D. Male contraception: What is on the horizon? Contraception. 2008;**78**:5

[31] Nieschlag E, Kumar E, Sitruk-Wareb R. 7α-Methyl-19-nortestosterone (MENTR): The Population Council's contribution to research on male contraception and treatment of hypogonadism. Contraception. 2013;**87**:8

[32] Oduwole OO, Huhtaniemi IT. Feasibility of male hormonal contraception: Lessons from clinical trials and animal experiments. Current Molecular Pharmacology. 2014;**7**(2):109-118

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