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Research Article



Male Contraceptives: Present and Future Approaches

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Abstract

There is general agreement that men, like women, must take full control of their fertility, an important global health issue. However, the contraceptives for preventing pregnancy that primarily involve male physiology have not changed in the last century. These options are still limited to the non-surgical methods of the use of a condom, abstinence, and a timely withdrawal (coitus interrupts) or the surgical approach of vas occlusion (vasectomy) that prevents sperm from being released during ejaculation. When not defective and used correctly, condoms are effective in preventing unwanted pregnancies as well as providing protection against sexually transmitted diseases. However, condoms, abstinence and timely withdrawal approaches have relatively higher typical-use failure rates whereas vasectomy is largely irreversible and not suitable for younger men. Thus, providing a safe, effective, reversible and affordable contraceptive for men has remained an elusive goal. In this article, we intend to discuss many details of currently available contraceptives for men, the current status of the research and development of non-surgical male contraceptives and also to describe experimental details of three intra-vas approaches that are undergoing advanced clinical trials and may soon be available for men to regulate their fertility. Finally, we will introduce the “sperm switch” approach. This is the latest invention that will allow men to decide if and when to ejaculate spermatozoa during coitus. The availability of several safe, effective, reversible and affordable contraceptives will allow men to take full control of their fertility.

Keywords: Male Contraception; Male contraceptives; Condoms; Gandarusa Pill; Intra-vas devices; RISUG; Smart RISUG; Vasalgel; Vasectomy; Sperm Switch

Introduction

The world population, currently estimated to be over seven billion, is expected to double in the next four decades [1]. The projected population growth will cause severe competition for existing resources, not to mention the overcrowding of our planet and its adverse effects on ecological health. Accumulated data from surveys suggest that a majority of today's young men in many countries are willing to have fewer children than their parents did [2]. However, the contraceptive options available to men have not changed in several decades. Thus, the contraceptive needs of tens of millions of men/couples go unmet every single day and results in millions of unwanted pregnancies.

Ever since the approval of the birth control pill for women by the Food and Drug Administration (FDA) in 1960, scientists have been hoping for a male equivalent. It has, however, been a difficult road, in part because of the complicated science of the male reproductive system. It is easier to control a monthly event of ovulation in women than to regulate the production of millions of fertile spermatozoa every single day in men. In spite of the general agreement that men, like women, must take full responsibility for their fertility, the contraceptive options available to men are relatively fewer compared to the options available to women.

The contraceptive options currently available to men have not changed in the past century. They are still limited to the traditional approaches of abstinence and timely withdrawal (coitus interruptus), non-surgical approach of the use of condoms or a surgical procedure (*i.e.*, vasectomy). If not defective and used correctly, condoms can provide safe protection against unwanted pregnancies as well as low and high risk papilloma virus [3, 4]. However, condoms and the two traditional approaches mentioned above have relatively higher typical use failure rates whereas vasectomy is largely irreversible and not suitable for younger men. Thus, providing safe, effective, reversible and

affordable contraceptives for men has remained an elusive goal.

When the question of new contraceptives for men is discussed, many wonder how many men will be interested to use them. Accumulated data suggest that approximately 33% of men use currently available contraceptives [5] which are not very effective. Thus, it is reasonable to argue that the availability of safe, effective, reversible and user friendly male contraceptive will encourage many more men to use them to take full control of their fertility.

Male contraceptives are methods of preventing pregnancy that primarily involve male physiology. Thus, contraception for men can be achieved by: (I) suppressing/preventing sperm production in the testes [6-8]; (II) preventing spermatozoa from reaching the site of sperm-egg interaction leading to fertilization [9-11]; and (III) interfering with sperm functions necessary for normal fertilization [12-14]. The male contraceptives currently available are based on approaches that prevent sperm from reaching the site of fertilization using either device-free traditional methods (*i.e.* abstinence and withdrawal) or barrier approaches (*i.e.*, use of condoms and vasectomy). These approaches have been available for several decades and have not improved in the past century. In this article, we will discuss many details of currently available male contraceptives and the new hormonal and non-hormonal approaches that are at various stages of research and development and may lead to new contraceptives for men. We will also discuss many details of three vas-based approaches that have undergone advanced clinical trials and are either available or will soon be available for use by men in multiple countries. Finally, we will discuss the "sperm switch" approach that will implant a switch on the spermatic duct. This switch will allow men to decide if and when sperm cells are ejaculated during coitus.

The Male Reproductive System

A brief discussion of the male reproduction system and how it operates to fertilize an egg that results in pregnancy will provide useful information to many readers about male fertility and how to regulate it. In a sexually mature male, the two testicles, or the testes, produce and store millions of spermatozoa every day of their adult life [6-8]. Along each testicle is an epididymis and *vas deferens (vas)* that make up the network of the male reproductive system. The epididymis is a set of two coiled tubules, one from each testicle, where spermatozoa undergo many biological and morphological changes, collectively referred to as epididymal sperm maturation [9-11]. The convoluted epididymal tubules are connected to *vas*, a pair of muscular tubules that transport sperm-containing fluid to the urethra and semen out of the body through the penis [15]. The testes, along with epididymides, hang in a specialized pouch-like structure, the scrotum, outside the pelvis. The pouch has five features that keep the testes a few degrees cooler than the core body temperature [16]. Warming the testes by even 1°C can cause a significant drop in sperm production and their motility, two factors that are important for the control of male fertility [16-18].

In addition to the testes, epididymides and *vas*, there are two accessory glands, namely the seminal vesicles and prostate gland that provide fluids to lubricate the duct system. The seminal vesicles are sac-like structures attached to the *vas* whereas the prostate gland surrounds the ejaculatory duct at the base of the urethra. The prostate is a part of every man's reproductive system. It requires the male sex hormone, testosterone, to function properly, helping to regulate bladder control and normal sexual function. The urethra, the tube that transports semen out of the body through the penis, is a spongy organ that can expand and contract depending on man's state of sexual arousal [15].

Spermatozoa are formed throughout the post pubertal male reproductive life from spermatogonial sperm cells in the testes by a highly orchestrated process referred to as spermatogenesis [6-8]. The sperm cells released from the testes (testicular spermatozoa) are morphologically differentiated cells; however, they are neither motile nor capable of fertilizing an egg. They acquire progressive motility and become fertilization competent cells during passage through the epididymis [9-11]. The epithelial cells, lining the epididymal duct, form a luminal fluid environment by actively secreting and absorbing small molecules (sugars, electrolytes, etc.) and macromolecules (proteins, glycoproteins, etc.). Thus, the epididymal duct secretions mixed with the testicular contents, provide a specific environment in which the functionally immature sperm cells undergo morphological and biochemical modifications. The net result of these alterations is the production of self-propelled spermatozoa capable of undergoing additional modifications in the female genital tract [19,20].

When millions of spermatozoa are ejaculated into the female reproductive tract at coitus, they have forward motility; however, they cannot bind to the ovulated egg and fertilize it. This property develops during their residence in the female genital tract. The ejaculated spermatozoa undergo biochemical and functional changes collectively referred to as capacitation [19], a multifaceted process that produces hyperactive spermatozoa capable of binding to the egg's extracellular coat [19,20], the zona pellucida (ZP). Finally, the bound spermatozoa undergo signal transduction cascade; the net result is the exocytosis of acrosomal contents at the site of sperm-egg binding. The hydrolytic action of the acrosomal enzymes along with the hyper activated sperm motility, are important factors that allow the acrosome-reacted spermatozoon to penetrate the ZP and fertilize the egg [21,22]. Many sperm cells can bind to the zona-intact egg; however, usually

a single sperm penetrates the ZP and fuses with the egg.

The fusion of the sperm and egg, also referred to as fertilization, results in the formation of a zygote and pregnancy [23]. Though the male reproductive system provides numerous target events for the development of male contraceptives, many details that regulate the development of millions of spermatozoa in the testes, maturation in the epididymis, capacitation in the female reproductive tract, and the sperm-egg fusion are still far from clearly understood, making it difficult to target a particular event for the development of a male contraceptive. Furthermore, there are serious concerns whether men will actually use new contraceptives and uncertainties over whether women who are not in stable relationships will trust men who claim to be on a contraceptive. These concerns have resulted in mediocre investments from the pharmaceutical companies in the research and development that will lead to safe and affordable contraceptives for men.

Will men use new contraceptives to regulate their fertility? Accumulated data provide evidence suggesting that approximately 33% of men use currently available contraceptive approaches [5]. A recent survey found that a majority of young men in many developing countries want fewer children than their parents did [2]. However, the contraceptive options available to them have not changed in the past century and are still limited to non-surgical traditional approaches of abstinence and timely withdrawal, and the use of a condom to prevent release of ejaculated spermatozoa into the female genital tract or a surgical procedure of the occlusion of the vas deferens (vasectomy). The non-surgical approaches have relatively higher typical use failure rates whereas vasectomy is largely irreversible and not recommended for younger men [24-26]. Thus, providing a safe, affordable and reversible contraceptive for men has remained an elusive goal.

Progress in male contraceptive technology is crucial for controlling population growth. This will require a serious commitment and resources from governments of all nations as well as resources from both small and large pharmaceutical companies to invest generously in the research and development of male contraceptive technology. Since any failure in male contraceptives has a personal consequence for women, serious concerns and uncertainties remain whether women who are not in a stable relationship will trust a man who claims to be using a male contraceptive. These concerns have resulted in mediocre investments by many pharmaceutical companies in the research and development of male contraceptives.

In addition to effectiveness, safety, reversibility and cost-effectiveness of any potential contraceptive drug are also a major consideration. These hurdles, and the fact that the development of any new drug is a relatively slow and painstaking process that can take a decade or more from the time the potential drug is identified, to the completion of all clinical trials and its approval for human use, have kept many drug companies on the sidelines. Despite numerous obstacles, investigators and clinicians around the globe are making significant progress. World-wide collaborations have begun in the development of hormonal and non-hormonal contraceptives for men. The new approaches will allow men to control their fertility and participate in family planning.

Male Contraceptives: Current and Future Approach

The purpose of male contraceptives is to prevent sperm-egg interactions and fertilization that results in the formation of an embryo and pregnancy. This can be achieved by: (I) suppressing/preventing sperm production in the testes; (II) blocking the sperm maturation in the epididymides; (III) preventing spermatozoa from reaching the site of fertilization; (IV) preventing the capacitation of spermatozoa in the female

reproductive tract; and (V) interfering/preventing sperm-egg interaction and fertilization. The contraceptive choices currently available to men are all based on approaches that prevent sperm from reaching the egg, using either device-free traditional approaches (*i.e.*, abstinence and withdrawal), or barrier approaches (condoms and vasectomy). No new male contraceptives have been introduced in the last century. We will first briefly describe currently available male contraceptives before discussing potentially new approaches that may become available in the future. Some of the future approaches are undergoing advanced clinical trials and are likely to be approved soon for human use. The contraceptive approaches that are currently available to men can be divided into two groups.

Approaches in **Group 1**: Traditional that are cost free and theoretically effective in preventing pregnancies. These approaches are (I) abstinence and (II) withdrawal (coitus interruptus). Many details of these two approaches have been described in an early publication [27]. Both these approaches have a relatively higher failure rate (~ 25%) that limits their use.

Group 2: Barrier methods prevent spermatozoa from being released in the female genital tract during intercourse (condoms and vasectomy) and are used by a significant number of sexually active couples to prevent pregnancy. Many details of these approaches have been described previously [27]. Though condoms provide safe protection against unwanted pregnancies as well as sexually transmitted infections, they have higher failure rates (~ 25%). In contrast, though vasectomy is effective in preventing unwanted pregnancies, the approach is largely irreversible [24-26] and not suitable for younger men. Men who have completed their families and are not concerned about getting transmitted diseases from their partner can take full control of their fertility by undergoing this much improved minor surgical procedure.

Future Contraceptive Approaches for Men

In this section, we will briefly explain potentially new hormonal and non-hormonal based approaches for men that are undergoing research and development. We will discuss a male contraceptive pill available to men in Indonesia and also many details of three intra-vas approaches and “sperm-switch” approach; some intra-vas approaches have undergone advanced clinical trials and are either available or will soon be available to men in multiple countries. Based on current knowledge of spermatogenesis, investigators are working on hormonal [28, 29] and non-hormonal approaches to prevent sperm formation and develop new and readily available contraceptives for men.

Non-hormonal contraceptive approaches include many natural [30-33] and synthetic compounds [34,35] that have the ability to either inhibit/suppress spermatogenesis or interfere with the sperm functions necessary for normal fertilization. Many details of the non-hormonal contraceptives have been discussed in the original articles and a review article [27]. The compounds described in the original articles can one day provide orally effective contraceptives for men. However, work on these compounds is still in the early stages of research; many years of basic and clinical work is needed before the natural and synthetic compounds can be approved for use as safe and effective agents to control male fertility. Other non-hormonal approaches that have been studied are: (I) immuno-contraception [36,37]; and (II) suppressing spermatogenesis by raising the temperature of the testes [16-18]. Interested readers may want to read the original articles for many more details. We will, however, discuss the Indonesian male pill which is said to be 99% effective in preventing pregnancy.

Contraceptive pill for men

Ever since the approval of the birth control pill for women by the FDA in 1960, scientists have been hoping for a male equivalent. Investigators in multiple

countries have been working to identify agents which can either block Ca^{2+} channels on sperm membranes [38,39] or interfere with the whiplash (hyperactive) sperm motility and prevent them from penetrating the egg coat, the ZP, and fertilizing the egg [40,41]. These agents, though promising, are still at the basic science stage. Many more years of basic and clinical research is needed before these agents can be used in the form of a pill to control male fertility. We now know that at least one country (Indonesia) has approved the use of a contraceptive pill that will allow men to take full control of their fertility.

Tribesmen on a remote island of Papua, Indonesia, have long known that if they chewed leaves of the plant "Gandarusa" (*Justicia gendararussa*) 30-40 minutes before coitus, their wives did not get pregnant. Researchers in Indonesia began analyzing Gandarusa leaves in 1988, and began animal and human trials in the 1990's. The biologically active compound from the plant was identified and patented in 2007. There are no published reports on the compound or how it functions. However, according to government reports, the purified agent, when used by men in the form of a pill, prevents pregnancy by inhibiting the activity of multiple enzymes that prevent sperm from penetrating the egg's extracellular coat to fertilize it.

Researchers in Indonesia have tested the male pill called "Gandarusa Pill" on several groups of male volunteers. Spermatozoa from the men taking the pill remain healthy but are unable to fertilize an egg. The spermatozoa from these men regained the ability to fertilize an egg after they stopped taking the pill for 72 hours. The pill has undergone multiple clinical trials with satisfactory results. There are minor side effects in less than 2% of the men taking the pill and include abdominal discomfort and headaches. Interestingly, many men taking the pill report increased stamina, appetite and libido.

The distribution of the pill was approved by the Indonesian government in 2013 to see how the pill was received by the Indonesian population. The pill became available to Indonesian men by prescription at the end of 2014. We are optimistic that the worldwide collaborations will make the pill available in other countries. Interested readers may search "Indonesian male pill" on the worldwide web for additional details.

Surgical and non-surgical intra-vas

Approaches to Regulate Male Fertility
Vasectomy, a surgical male contraceptive, is the only effective and readily available approach throughout the world to control male fertility. The approach involves ligation of vas or surgically removing a segment of vas deferens, the muscular tubes that transport spermatozoa to the penis [42]. The surgery is routine and has no known side-effects on male organs and no adverse effect on libido. Although the vasectomy can be reversed in some cases by microsurgery, the pregnancy rates following reversal surgery are low and largely depend on the skills of the surgeon and the amount of time elapsed since the surgery [24-26]. It is reasonable to conclude that the approach is largely irreversible and may not be suitable for younger men who want children in the future.

Vasectomy is highly effective once spermatozoa are flushed out from the distal vas deferens. Thus the patient and the partner must use other contraception until almost all spermatozoa are cleared from the reproductive tract of the patient. The procedure causes no changes in the levels of male hormones, semen volume, sexual function, or any risk of cardiovascular or other diseases. Antibodies to the sperm antigens have been found in most men who have undergone the procedure; however, the antibodies have no known health effect on men except they may contribute to reduced fertility even after the reverse vasectomy is successful [27,38].

A modification to traditional vasectomy was introduced in China in 1974 [42,43] which eliminates the use of scalpel in

the surgery and was named no-scalpel vasectomy. The protocol eliminates skin incision in the scrotum and reduces immediate side effects such as bleeding and infection. The procedure, like the traditional vasectomy, is performed under local anesthesia. The surgeon uses a curved sharp hemostat to puncture the skin of scrotum, and exposes the vas deferens. The exposed vas tubes are occluded and placed back in the scrotum. During no-scalpel vasectomy, there is very little or no bleeding or other complications compared to the traditional vasectomy. The patient remains awake during the procedure, and is allowed to leave after a brief rest and relaxation. Also, patient can resume sexual activity sooner, compared to the traditional vasectomy. The patient still have to use other contraceptives until the reproductive tract is cleared of all spermatozoa. The procedure, being less painful, has a higher acceptance rate; however, no-scalpel vasectomy does not assure reversibility.

No needle, no scalpel vasectomy is yet another modification to the no-scalpel vasectomy. The protocol uses a jet injection to spray an anesthetic solution through the skin and around the vas tubes prior to the procedure. Following the anesthesia, the procedure employs two instruments: a ring forceps to encircle and secure the vas without penetrating the skin of scrotum. A sharp-tipped dissecting forceps is then used to puncture the skin of scrotum to make a small opening in the skin and vas sheath; the vas tubes are lifted and occluded. Unlike traditional vasectomy, no stitches are needed to close the small opening of the scrotum. The modified approach, though safer, does not improve the chances of reversibility.

How does traditional vasectomy/no-scalpel vasectomy/no needle, no-scalpel vasectomy work? During these procedures, vas tubes are cut or blocked by ligation that prevents the transport of spermatozoa through these tubes. Without ejaculation of spermatozoa during coitus, a man can no longer make the female partner pregnant. After the vasectomy procedure, men's sexual

organs (*i.e.*, penis and testes) do not change in size and shape. Men still have erections, and during coitus, the volume of semen ejaculated is not different except it has very few or no motile spermatozoa.

In addition to vasectomy, researchers and clinicians in multiple countries are engaged in developing other vas-based approaches or intra-vas devices (IVDs) to regulate male fertility. The advantage of the new intra-vas approaches is that these procedures are reversible and ideal for men who think that they are finished expanding their family but may change their mind in case they remarry. These approaches will also be suitable for men who want to space their children or young students who want to complete their education for a decent job before adding the responsibility of children. At least two intra-vas approaches with different mechanisms have undergone advanced clinical trials in multiple countries with satisfactory results and proven reversibility. To the best of our knowledge, the new approaches have either been approved or will soon be approved for use by men. The approaches are: Reversible inhibition of sperm under guidance (RISUG); and Intra-vas device (IVD).

RISUG approach is similar to no-scalpel vasectomy [43] except that the procedure uses a non-toxic chemical, maleic anhydride, dissolved in dimethyl sulfoxide (DMSO). The maleic anhydride solution is injected into the lumen of vas tubes; enough of the solution, containing a bioactive chemical, is injected into vas tubes to coat the inner walls of the tubes. Within minutes of injection, the chemical polymerizes and coats/anchors the inner walls of the vas tubes, partially or fully closing them. Because of the high molecular weight, the polymer does not get absorbed and stays in place for extended periods of time.

The procedure takes less than 15 minutes. Within few minutes, the chemical polymerizes and forms a gel that allows fluid to pass through it; however, the gel prevents the transport of intact spermatozoa through the vas tubes. This causes less back pressure

on epididymides than vasectomy [44,45]. The method can be reversed by injecting DMSO, a chemical used in many medical treatments or a solution of sodium bicarbonate [46] in the lumen of the vas tubes. The solvent dissolves the polymer and flushes it out of the vas tubes. Thus the procedure is similar to no-scalpel vasectomy except that it is fully reversible. The RISUG approach has another advantage over the no-scalpel vasectomy since the procedure is effective immediately after the chemical is injected into the vas lumen. By contrast, vasectomy may take nearly three months before the patient becomes infertile.

The chemicals used in the RISUG procedure are inexpensive and easy to administer. The protocol, approved and supported by the Government of India, has undergone multiple clinical trials in India [44,45]. Some of the men are said to have been using the RISUG method for nearly two decades. The procedure has undergone advanced clinical trials at multiple centers in India and is likely approved or will soon be approved.

RISUG's effect on spermatozoa is not fully understood. Experimental evidence suggests that the bioactive polymer disturbs the negative charge of the sperm membrane when the cells come in contact with the gel, causing complete disintegration of the sperm plasma membrane and exocytosis of the acrosomal contents [47]. Dr. Guha's team has been working with the chemicals for nearly three decades. The only side effect of the RISUG approach reported during this time is a slight swelling of the scrotum in some volunteers.

Smart RISUG is yet another version of the male contraception and contains iron oxide and copper particles to the original compound. The addition of iron and copper gives it magnetic properties and the name "Smart RISUG". After the solution is injected into the vas lumen, its exact location inside the vas tube can be measured and visualized by x-ray and magnetic imaging. The location of the polymer can be externally controlled using pulse magnetic field. The rodents used

to develop the Smart RISUG have not had any adverse symptoms [48].

RISUG, the vas-based male contraceptive has gathered interest beyond India. Parsemus Foundation, a nonprofit organization in the USA, has bought international rights to the RISUG technology. The polymer male contraceptive is renamed as Vasalgel, a non-hormonal long-acting reversible male contraceptive. Vasalgel is a high molecular weight hydrogel polymer. It consists of styrene maleic acid dissolved in DMSO and is distinct from styrene maleic anhydride used in RISUG studies. Since Vasalgel uses similar chemicals as in the RISUG approach, it enjoys all the benefits listed above for the RISUG approach. Both approaches will be fully reversible long-lasting male contraceptives.

Vasalgel is injected into the lumen of vas deferens (in the ball sack). The gel fills the anterior of the lumen, forming a soft, semi-permeable gel barrier that nestles into the tiny folds in the walls of the vas deferens. Once there, the gel blocks sperm from leaving the vas. The gel has been found to be an effective long-acting male contraceptive in rabbit model [49]. Injection of the polymer into the rabbit vas tubes produced rapid onset of azoospermia that was durable throughout the 12 month period. The effect of Vasalgel on the structure of the injected vas tubes appears to be minor and supports the potential for a return to full function following its removal from the vas tubes. In part two of the study in rabbits, the gel was successfully flushed out. Sperm flow through the vas returned almost immediately after the reversal procedure (unpublished study).

After successfully completing studies with rabbits, the researchers of the foundation have moved on to baboons. Three male baboons injected with the Vasalgel were given unrestricted sexual access to 10-15 female baboons each for several months. No female baboons were impregnated in the six month study. In a follow-up study, sixteen male monkeys were returned to their groups following Vasalgel treatment. There were no babies from the Vasalgel treated monkeys.

The next step for Vasalgel is to be tried on men. Clinical trials with volunteers will start soon. According to the bulletin from the foundation, the selection of the clinical trial participants will be done by the doctor in charge of the trial. The physician will have a say in deciding age, health etc. of the participants. The foundation hopes to see the Vasalgel available to all men by 2018. According to the foundation's bulletin, an injection of Vasalgel will be less expensive than the cost of a flat-screen television. Readers interested to get updates on Vasalgel's progress in the USA, can see Parsemus Foundation.org and/or Vasalgel.

Intra-vas Device (IVD) is another approach that blocks the transport of spermatozoa through vas deferens. The approach uses a set of tiny preformed implants that are inserted into each of the two vas tubes to prevent the flow of sperm through them. Initially, two sets of IVD's were introduced; one in the USA [50] and one in China [51-53]. Although the USA approach demonstrated encouraging results in blocking the flow of sperm through vas tubes, and potential reversibility following their removal in non-human primates, results with men were less favorable [50]. Only 90% of the men with the tiny devices displayed complete absence of spermatozoa in their ejaculates; the remaining 10% of the men had low sperm counts. Because of the partial effectiveness in blocking the flow of sperm through the vas tubes, the procedure is not being pursued further.

The initial Chinese IVD used urethane or polypropylene tube/shell filled with medical grade nylon mesh (sieve) to capture spermatozoa [51]. By allowing semen to pass through the vas, the device eliminates any back pressure on the epididymis. When inserted correctly, the device is 100% effective in preventing pregnancy. In later experiments, the use of polypropylene or polytef IVDs was discontinued because they were not ideal to be in place for long periods of time. The new generation of IVD is made of polyurethane, an implant ideal for long periods of time. When the new device was

used in animals, it gave satisfactory results; also the fertility was restored when the device was removed. The new generation of IVD has undergone multi-center clinical trials in China with satisfactory results [52]. The pregnancy rates in the IVD group were not higher than the no-scalpel vasectomy group. Thus it is reasonable to conclude that the new generation of the Chinese IVD provides good contraception for men with fewer complications. This approach is advantageous due to its simple surgical procedure that provides a high degree of contraception with proven reversibility [53]. If all goes well, the approach is expected to be approved for use in Chinese men in early 2018.

Finally, we will describe a new approach in progress that involves installing a switch on spermatic duct. The switch can be turned on/off to control the flow of sperm. The male contraceptive switch, crafted by Clemens Bimex, a German carpenter, is a valve that can start/stop the flow of sperm through the vas deferens. The one- inch valve weighs < 0.1 ounce and is surgically implanted under the skin of the scrotum during a 30 min operation. When closed, the valve prevents the flow of sperm from entering semen and the man is rendered sterile, although he can still ejaculate as normal. If the man at any point in his life decides that he wants to father a child, he simply turns the switch on by pressing it through the skin of his scrotum and becomes fertile.

After the switch is installed, it takes 3-6 months for men to get rid of sperm in the duct. Thus additional protection would be needed if the switch is installed as a contraceptive. Switching it back the other way, however, should give immediate results as the reproductive system does not stop producing sperm. The man can wear the switch "Bimek SLV" for his lifetime and regulate it himself with just a flip of the switch.

The valve has to undergo extensive safety and clinical trials before it is approved and made available to the public. When

approved, the valve will be implanted during an outpatient surgery under local anesthesia. The patient will be allowed to leave the doctor's office after a brief rest and should be well enough to return to work the next day. The estimates are that if everything goes well (safety and clinical trials), after the switch is approved by the Ethics Committee, the valve may become available to the public by the end of 2018 or early 2019. Readers interested in following the progress of sperm switch, or lack of it, can do so by searching "sperm switch" on the Worldwide Web.

In summary, this review has discussed various hormonal and non-hormonal approaches that are at various stages of research and development to regulate fertility in men. The new intra-vas approaches come as more and more men try to take full control of their fertility. We are cautiously optimistic that men will soon have multiple choices to regulate their fertility.

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