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Review Article

Intra-Vas Approaches to Control Male Fertility

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Abstract

The world population continues to grow at an alarming rate. If the growth continues at the current rate, the population of our planet, currently estimated to be over seven billion, is expected to double in next forty years. The projected population growth will cause severe competition for existing resources, in addition to overcrowding and its adverse effects on the ecological health of our planet. In spite of the general agreement that men, like women, must take full responsibility of their fertility, an important global health issue, the contraceptive methods for preventing pregnancy that primarily involve male physiology have not changed in the past century. These methods are still limited to the use of condoms, abstinence, a timely withdrawal/pulling out (*coitus interrupts*) or the surgical method of vas occlusion (vasectomy) that prevents sperm from being released during ejaculation. When not defective and used correctly, condoms can protect from unwanted pregnancies as well as sexually transmitted diseases. However, condoms, abstinence and withdrawal approaches have relatively high typical-use failure rates whereas vasectomy is largely irreversible and not suitable for younger men. Thus, providing a safe, effective, and affordable contraceptive for men has remained an elusive goal. In this article, we will discuss many details of three intra-vas approaches that have undergone advanced clinical trials and are close to being approved for use by men to control their fertility. In addition, our intention is to introduce "sperm switch" approach, the latest invention designed to allow men to decide if and when to ejaculate sperm cells during coitus. The availability of several safe, reliable, affordable and reversible contraceptives will allow men to take full responsibility of their fertility and participate in family planning.

Keywords: Condoms; Male contraceptives; Male fertility control; Indonesian pill; Intra-vas devices; RISUG; Vasalgel; Vasectomy; Sperm switch

Introduction

The contraceptive options currently available to men have not changed in the past century and are still limited to traditional approaches of abstinence and timely withdrawal (*coitus interrupts*), non-surgical approach of the use of condoms or a surgical procedure, vasectomy. Condoms can provide safe protection against unwanted pregnancies as well as low and high-risk papillomavirus [1,2] if they are not defective and used properly. However, condoms, and the two traditional approaches mentioned above have relatively higher typical-use failure rates where as vasectomy is largely irreversible and not suitable for younger men [3,4]. Thus, providing a safe, reliable, affordable and reversible contraceptive for men has remained an unfulfilled goal. Accumulated data from recent surveys show that the majority of today's young men in many countries are willing to take full control of their fertility [5]. However, the contraceptive needs of tens of millions of men/couples go unmet every single day and results in millions of unwanted pregnancies and thousands of abortions [6]. 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 post-pubertal men. Thus, the contraceptive options available to men are relatively limited compared to the options available to women.

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 [7-9]; ii) preventing sperm from reaching the site of fertilization; and iii) interfering with the sperm functions necessary for normal fertilization [10,11]. The contraceptives currently available for men 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 briefly discuss 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 contraceptive approaches that have undergone advanced clinical trials and will soon be available for use by men in multiple countries. Finally, our intention is to introduce "sperm switch" approach in progress that involves implanting a switch on the spermatic duct. This switch can be turned on/off to control the flow of sperm. The newly invented switch will allow men to decide if and when sperm cells are ejaculated during coitus.

The Male Reproductive System

How does the male reproductive system operate to fertilize

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an egg which results in the formation of zygote and pregnancy [12]? This discussion is aimed to provide useful information to many readers about male fertility and how it can be regulated. In a sexually mature man, the two testicles or the testes produce and store millions of spermatozoa every day of their adult life [7-9]. Along each testicle is epididymis and vas deferens (vas) that makes up the male reproductive network. The epididymis is a set of two coiled tubules, one from each testicle, where testicular spermatozoa undergo multiple morphological and biochemical changes, collectively referred to as epididymal sperm maturation [13-16]. The convoluted epididymal tubules are connected to vas, a pair of muscular tubules that transports sperm-containing fluid to the urethra and semen out of the body through penis [17]. The testicles and epididymides hang in a specialized pouch-like structure outside the pelvis, the scrotum. The pouch has five features that keep the testes a few degrees cooler than the core body temperature [18]. These features have been discussed in an earlier article [19] and will not be repeated here. Warming the testes by even a 1°C can cause a significant drop in sperm production and their motility, two factors that are important for the control of male fertility [19-21].

The relationship between temperature and sperm production and their motility has been exploited to develop temperature regulated fertility control in men. Many details of the published studies have been described in an earlier article [17]. Interestingly, the scrotum changes in size to keep the temperature of the testes cooler than the body temperature. When the body is warm, the scrotum becomes larger and hangs away from the body cavity. However, when body temperature gets cooler, scrotum shrinks and becomes tighter to hold the body heat. The temperature sensitive changes in the scrotum keep the sperm production at a constant level.

In addition to the testes, epididymides and vas deferens, there are two accessory glands, namely seminal vesicle and prostate gland. These glands provide fluids that lubricate the duct system. The seminal vesicles are sac-like structures attached to the vas whereas prostate gland surrounds the ejaculatory duct at the base of urethra. The prostate gland is a part of every man's reproductive system. It requires the male sex hormone, testosterone, to function properly, helping to properly regulate bladder control and normal sexual function. The urethra, the tube that transports semen out of the body through penis, is a spongy organ that can expand and contract depending on the man's state of sexual arousal [19].

The reproductive system works together to produce millions of spermatozoa every single day throughout post-pubertal male reproductive life. Many details of sperm formation and development in the testes have been described in previous reports [7-9,22,23]. Although spermatozoa released from the testes are morphologically differentiated cells, they are neither motile nor capable of fertilizing an egg. They acquire progressive motility and become fertilization competent cells during passage through the epididymis [13-15]. The epithelial cells, lining the epididymal duct, form a luminal fluid environment by actively secreting and absorbing small molecules (electrolytes, sugars etc.) and macromolecules (proteins, glycoproteins etc.). Thus, the epididymal duct secretions mixed with testicular fluid, provide a specific environment in which the functionally immature spermatozoa undergo many biochemical modifications. The net result is the production of self-propelled spermatozoa capable of undergoing additional modifications in the female genital tract.

Millions of spermatozoa are deposited into the female reproductive tract at coitus. The ejaculated spermatozoa have forward motility; however, they cannot interact with the ovulated egg and fertilize it. This property develops in the female reproductive tract. During residence in the female tract, spermatozoa undergo biochemical and physiological modifications collectively referred to as capacitation, a multifaceted process that produce hyper activated spermatozoa capable of binding to the egg's extracellular coat, the zona pellucida [24-26]. Finally, the bound spermatozoa undergo signal transduction cascade; the net result is the fusion of sperm Plasma Membrane (PM) and the outer acrosomal membrane at multiple sites and the release of acrosomal contents (i.e., glycohydrolases, proteinases, esterases, sulfatases etc.) at the site of bound spermatozoon. The hydrolytic action of the acrosomal enzymes along with the hyper activated sperm motility, are important factors that allow the acrosomal-reacted spermatozoa to penetrate the zona pellucida and fuse with the egg [27].

The fusion of the sperm and egg, also referred to as fertilization, results in the formation of zygote and pregnancy [12]. Thus, it appears that the male reproductive system provides numerous target sites for the development of male contraceptives. It should, however, be noted that many details of the events that regulate the development of spermatozoa in the testes, their maturation in the epididymides, capacitation in the female genital tract and the events that regulate the union of the opposite gametes, are still far from being clearly understood, making it difficult to target any particular event for development of contraceptives for men. Moreover, there has been mediocre investment by pharmaceutical companies in the research and development of male contraceptives for two major concerns. First, will men use the new contraceptives? Second, how many women who are not in a stable relationship will trust a man who claims to be using a male contraceptive? These are serious concerns that have kept many pharmaceutical companies on the side lines.

As stated above, male contraceptives are methods of preventing pregnancy that primarily involve the male physiology. Since the introduction of oral contraceptive pill for women over five decades ago, there have been numerous collaborations between investigators and pharmaceutical companies to improve the effectiveness and delivery of contraceptives to women who wish to safely regulate their reproductive physiology and participate in birth control. However, for men, the contraceptive options available to them have not changed in several decades and are still limited to non-surgical traditional approaches of abstinence and timely withdrawal, and the use of a condom to prevent release of spermatozoa into the female 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 [3,4]. Thus, providing a safe, affordable and reversible contraceptive for men has remained an elusive goal.

When the question of male fertility control (male contraception) is discussed, many wonder how many men will use them to regulate their fertility. Accumulated data show that approximately 33% of men use currently available contraceptive approaches [17]. A recent survey found that a majority of young men in many developing

countries want fewer children than their parents did [5]. However, the contraceptive options available to them are not very satisfactory. No new approaches have been introduced in the past century to control male fertility. Thus, it is reasonable to argue that the development of a safe, reversible, and user-friendly contraceptive for men remains an important component of future successes in slowing the growth of world population.

It is no secret that success in slowing the growth of world population can only be achieved if both men and women take full responsibility of their fertility. Although a majority of today's young men in many countries prefer fewer children [5], the contraceptive options available to them are less satisfactory than for women in both developing and developed countries.

It is obvious from the discussion above that the male contraceptives currently available are not enough to meet the urgent need of growing world population. The future contraceptives for men will be expected to come in various forms to meet the wide range of contraceptive needs of a man's social, economic, religious and medical situation. Since men and women remain at a high risk of contracting sexually transmitted diseases, a male contraceptive that can provide simultaneous protection from pregnancy and infections is desirable and will be of particular interest to a vast majority of men and women throughout the world. However, we are still many years away from providing such an ideal male contraceptive.

New Male Contraceptives

Accumulated data suggest that approximately 33% of man use currently available contraceptives [17] which are not very satisfactory. Thus, it is reasonable to argue that the development of a safe, effective, and user-friendly male contraceptive will encourage many more men to use them. The potentially new contraceptives for men are important for future successes in controlling the growth of world population.

Despite a 10% drop in teen (ages between 15-19) pregnancy rate in 2013, current estimates are that a significant number of teens will still get pregnant in the USA than in neighboring Canada or many European countries [17]. Despite the drastic drop in the USA teen pregnancy rate in 2013 [28,29], it is still 5.5 times higher than in Western Europe, where the teen pregnancy rate is in single digits. These are significant differences that can be reduced further by proper education to teens and providing with safe, reliable and affordable contraceptives to teenage girls and boys.

Progress in male contraceptive technology is a crucial part of controlling the population growth around the globe. This will require a serious commitment and resources from governments of all nations and resources from both small and large pharmaceutical companies to invest generously in the research and development of male contraceptive field that will meet the needs of a growing number of men. 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 (information from website: Malecontraceptives.org.). These concerns have prevented many pharmaceutical companies from generously participating in the research and development of new male contraceptives. Many drug companies are also reluctant to invest in male contraceptive products intended for healthy men who may use them for several decades, raising the possibility of their unintended side effects on their health, including the loss of libido. The pharmaceutical companies may need incentives from governments to assure their full participation in the research and development of male contraceptives. This type of partnership between various groups will hasten the process of providing men with new and improved contraceptives.

In addition to safety, effectiveness and reversibility, cost-effectiveness of any new contraceptive for men is another major consideration. Combined, these obstacles and the fact that development of any new drug is a relatively long and painstaking process that can take a decade or more from the time a potential drug is identified, to the completion of all clinical trials and its approval for human use, have kept may drug companies on the sidelines. Despite these 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 who wish to control their fertility to do so by using new and improved contraceptives that will be safe, effective, reversible and affordable.

Scientific Basis of Current and Future Contraceptives for Men

The purpose of the male contraceptive is to either prevent sperm from reaching the egg or prevent sperm-egg interaction that leads to the formation of zygote and pregnancy [12,24]. This can be achieved by: i) preventing/suppressing sperm production in the testes [6-8]; ii) blocking their maturation in the epididymides [13-16]; iii) interfering with the sperm capacitation in the female genital tract [26]; iv) preventing sperm from reaching the in vivo site of fertilization; and v) interfering with sperm function(s) necessary for normal fertilization [10,11]. 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 (abstinence and withdrawal), or barrier approaches (condoms and vasectomy). No new male contraceptives have been introduced in the past century. Our intention is to briefly discuss potentially new approaches that are undergoing research and may become available in the future. Finally, we will discuss many details of intra-vas approaches that have undergone advanced clinical trials and are either approved or will soon be approved for human use. Based on the current knowledge of spermatogenesis [7-9], investigators are working on hormonal-based [30,31] and non-hormonal approaches to prevent spermatogenesis and develop new and readily available contraceptive to control male fertility.

Two hormonal-based approaches that have been tried on men include using a combination of progestin and androgen or a high dose of testosterone [30,31]. The progestin is supplemented with androgen because if administered alone, it can cause the loss of libido due to its effect on testosterone deprivation. Though the hormonal approach is within our reach, investigators have to overcome two major hurdles before the approach can become reality. The first hurdle is that the approach shows ethnic differences between Chinese men (> 90% responsive) compared to Caucasian men (< 60% of Europeans, American and Australian men are responsive) [31]. The second hurdle is the cost effectiveness of the approach. These

are serious hurdles which make it difficult to predict the future of hormonal-based contraceptives for men.

Non-hormonal approaches include many natural [32-36] and synthetic [37,38] compounds that have ability to either inhibit/suppress spermatogenesis or interfere with the sperm function(s) necessary for normal fertilization. Suffice it to say that the natural and synthetic compounds described in the article can one day provide orally effective contraceptives for men. However, 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 fertility in men. Other non-hormonal approaches that have been tried are: 1) The relationship between temperature and spermatogenesis [20,21]; 2) immuno-contraception [39-41]. Interested readers may want to see these articles for many more details. We will, however, describe and discuss the Indonesian male pill which appears to inhibit multiple enzymes on the sperm head and prevent the male gamete from penetrating the zona pellucida and fertilize the egg. The pill is said to be 99% effective in preventing pregnancies without altering hormones in the man or his partner.

On a remote island of Papau, Indonesia, tribesmen have long known that if they chewed the leaves of plant, "Gandarusa" (*Justicia Gendarussa*) 30-40 minutes before coitus, their wives did not get pregnant. Researchers in Indonesia began analyzing Gandarusa in 1988, and began animal and human trials in the 1990s. 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 the Indonesian government sources, the purified drug, when used by men in form of a pill, prevents pregnancy.

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. The minor side effects on the men taking the pill include abdominal discomfort and headaches in less than 2% of the men. 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 worldwide collaborations will make the pill available throughout the world. Additional details about the male contraceptive pill can be found by searching, "Indonesian male pill" on the worldwide web.

Surgical and Non-Surgical Intra-Vas Approaches to Control Male Fertility

As stated above, vasectomy (male sterilization) is the only intra-vas approach available to control male fertility. The procedure, used by millions of men for family planning, involves occlusion or removal of a segment of vas, the tube that transports semen during ejaculation. The surgery is routine and has no known side-effects on male organs or libido. Although the vasectomy can be reversed in some cases by microsurgery by a highly trained physician, the pregnancy rates following reversal are low and largely depend on the skill of the surgeon and the amount of time elapsed since the vasectomy [3,4,7]. Thus, it is reasonable to conclude that the procedure is largely irreversible and may not be suitable for younger men who want children in the future.

A modification to the traditional vasectomy was introduced in China in 1974 [42]. The modification 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 sharp and curved hemostat to puncture the skin of scrotum and expose the vas tubes. The tubes are either tied or occluded, and placed back in the scrotum. The procedure, being less painful, has a higher acceptance rate; however, the no-scalpel vasectomy does not assure reversibility.

Investigators are working on multiple intra-vas approaches. The advantage of the new approaches is that there is no surgery involved, and the procedures are reversible. These approaches will be ideal for men who think that they are finished expanding their family but may change their minds in case of remarriage. Because the new approaches will be fully reversible, they will be suitable for men who want to space their children and also for young students who can reverse the approach after completion of their education. At least two intra-vas approaches with different mechanisms have undergone advanced clinical trials in multiple countries with satisfactory results and proven reversibility. These new approaches have either been approved or will soon be approved for use by men in multiple countries. The approaches are:

1. Reversible Inhibition of Sperm Under Guidance (RISUG) approach is similar to no-scalpel vasectomy except that the procedure uses a non-toxic chemical, maleic anhydride, dissolved in dimethyl sulfoxide (DMSO). The solution is injected into the lumen of the vas tubes through which semen containing millions of fertile spermatozoa move before ejaculation. Enough of the chemical is injected into the lumen to cover the inner walls of the vas deferens. Within minutes of injection, the chemical polymerizes and coats/anchors the inner walls of the vas tubes, partially or fully closing them. The poly-electrolytic nature of the chemical kills spermatozoa when they come in contact with the polymer [43-47]. Because of the high molecular weight, the polymer does not get absorbed and stays in place for extended periods of time. The polymer forms a gel that allows semen to pass through the vas; however, it prevents the transport of intact spermatozoa through the vas tubes. The method can be reversed by the injection of DMSO, the solvent used in many medical treatments or a solution of sodium bicarbonate [44]. The injected solvent solubilizes the polymer and flushes it out of the vas tubes. The RISUG approach has an advantage over no-scalpel vasectomy, since it is effective immediately after the chemical is injected. By contrast, vasectomy/no-scalpel vasectomy may take nearly three months before the patient becomes infertile.

2. Intra-Vas Device (IVD) is another new approach different from vasectomy. Early generations of IVD used a set of pre-formed implants in the vas tubes to prevent the flow of sperm through them [48-50]. Two sets of IVD's were introduced; one in the USA and one in China. In the USA design, two preformed silicone plugs were inserted in each vas. The tiny plugs (< 1 inch long) were inserted in the same vas with a small space between them. The plugs were secured to the vas tube with sutures. The entire procedure is said to take less than 20 minutes. The use of two plugs on each vas tube is to catch the sperm that escape from the first plug. Although, the approach

demonstrated encouraging results in blocking spermatozoa through the vas, and potential reversibility following their removal in non-human primates, results with men were less favorable [51]. Only 90% of the men with the inserted devices displayed complete absence of sperm in the ejaculates; the remaining 10% of the men had low sperm counts. Because of its partial effectiveness in blocking the flow of sperm through the vas, the procedure is not being pursued further [51].

The initial Chinese design of IVD used urethane or polypropylene tube/shell [52] filled with medical grade nylon mesh (sieve) to capture spermatozoa. By allowing fluid to pass through the vas, the devise eliminates any back pressure on the epididymis. When inserted correctly, the IVD has provided 100% contraception in Phase II clinical trials [52]. In future 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 investigators developed new generation of IVD with polyurethane. The new IVD has undergone multi-center clinical trials [53]. The pregnancy rates in the IVD group were not higher than that of the no-scalpel vasectomy group. Thus, it is reasonable to conclude that the new generation of IVD will provide good contraceptive efficacy with few complications. The contraception with IVD is advantageous due to its low cost and simple surgical protocol [53]. If all goes well, the approach is expected to be approved for use in Chinese men in 2016.

RISUG, the intra-vas injectable male contraceptive described above, is gathering interest beyond India. Parsemus, a not for profit organization in the USA, has bought international rights to the RISUG technology. The polymer male contraceptive is renamed as Vasalgel, a multi-year male contraceptive. Since the Vasalgel approach uses the same chemical as in RISUG approach, it enjoys all the benefits listed above for the RISUG approach. Both approaches will be fully reversible long-acting male contraceptive. Vasalgel is a polymer hydrogel which is injected into the lumen of vas deferens. The gel fills the anterior of the lumen, forming a soft, semi-permeable gel barrier that nestles into the tiny folds of the anterior walls of vas deferens. The gel allows fluids from the semen to pass through it; however, sperm cells are too big to get through the gel barrier.

It should be noted that the Vasalgel and RISUG approaches are based on the same concept of using maleic anhydride gel injected into vas deferens, the formulations are not the same. While RISUG was developed in India, the Vasalgel is being developed in the USA to conform to the latest FDA international codes of production and safety. Researchers of the Vasalgel have completed safety and efficacy studies with rabbits. The treated animals have shown no sperm from the second semen samples onward; sperm started flowing through the vas in rabbits that had the polymer flushed.

After successfully completing studies with rabbits, the researchers 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 six months. The Parsemus foundation is planning to start human trials on Vasalgel soon. The foundation hopes to see the Vasalgel available for all men in 2016-2017. In their words, an injection of Vasalgel will be less expensive than the cost of a flat-screen television. There are no published reports. The information included here was obtained by an internet search of Vasalgel.

Finally, there is a new approach in progress that involves installing a switch on the spermatic duct. The switch can be turned ON/OFF to control the flow of sperm and male fertility. The contraceptive switch, crafted by Clemens Bimek, a German carpenter, is a valve that can stop/start the flow of sperm. This invention, when approved, could change men's reproductive future. The valve, about an inch long and weighing less than 0.1 ounce, is surgically implanted under the skin of scrotum during a 30 minute operation. When closed, the valve prevents flow of sperm from entering semen and the man is rendered sterile, although he can still ejaculates as a normal. If the man at any point decides that he wants to father children, he simply opens the switch by pressing it through the skin of his scrotum.

The valve is mounted on spermatic duct. When closed, the valve disrupts the flow of sperm and the user becomes sterile. The man can wear the switch,"Bimek SLV' for his life-time and regulate the flow of sperm himself with just a flip of the switch. The valve is implanted during an outpatient surgery under local anesthesia. The patient is allowed to leave the office after a brief rest; he should be well enough to return to work next day.

The sperm switch is designed to divert flow of sperm away from penis. Three to six months after the switch is closed, the man becomes sterile. Unlike vasectomy or intra-vas devices, there is no need to have the switch removed. The man can simply flick the switch back to open and the fertility will return. The sperm switch is the latest invention and is designed to allow men to take full control of their fertility.

The valve in the sperm switch has to undergo extensive clinical trials before it is made available to public. The estimates are that if the clinical trials are successful, the sperm switch may become available to public by the years 2018-2019. Readers interested in following the progress of this approach or lack of it, can do so by searching, "sperm switch" on the worldwide web.

In summary, we have discussed various hormonal and non-hormonal approaches that are at various stages of research and development to regulate fertility in men. We are cautiously optimistic that intra-vas approaches will provide safe, affordable and reversible contraception in multiple countries by the end of this year. The availability of these contraceptives will allow many men to take full control of their fertility.

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References

1. Steiner MJ, Cates W Jr. Condoms and sexually-transmitted infections. N Engl J Med. 2006; 354: 2642-2643.

2. Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK. Condom use and the risk of genital human papillomavirus infection in young women. N Engl J Med. 2006; 354: 2645-2654.

3. Silber SJ. Vasectomy and vasectomy reversal. Fertil Steril. 1978; 29: 125-140.

4. Sharlip ID. What is the best pregnancy rate that may be expected from vasectomy reversal? J Urol. 1993; 149: 1469-1471.

5. Heinemann K, Saad F, Wiesemes M, White S, Heinemann L. Attitudes toward male fertility control: results of a multinational survey on four continents. Hum Reprod. 2005; 20: 549-556.

6. Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect. 1998; 30: 24-29, 46.

7. Kierszenbaum AL. Mammalian spermatogenesis *in vivo* and *in vitro*: a partnership of spermatogenic and somatic cell lineages. Endocr Rev. 1994; 15: 116-134.

8. Abou-Haila A, Tulsiani DRP. Mammalian sperm acrosome: formation, contents, and function. Arch Biochem Biophys. 2000; 379: 173-182.

9. Dym M. Spermatogonial stem cells of the testis. Proc Natl Acad Sci U S A. 1994; 91: 11287-11289.

10. Mandal A, Naaby-Hansen S, Wolkowicz MJ, Klotz K, Shetty J, Retief JD. FSP95, a testis-specific 95-kilodalton fibrous sheath antigen that undergoes tyrosine phosphorylation in capacitated human spermatozoa. Biol Reprod. 1999; 61: 1184-1197.

11. Li YF, He W, Jha KN, Klotz K, Kim WF, Mandal A. et al. FSCB, a novel protein kinase A-phosphorylated calcium binding protein is a CABYR-binding partner involved in late steps of fibrous sheath biogenesis. J Biol Chem. 2007; 282: 34104-34119.

12. Yanagimachi Y. Mammalian fertilization. In: Knobil E, Neill JD, editors. The Physiology of Reproduction. New York: Raven Press. 1994; 189-317.

13. Orgebin-Crist M-C. Morphological basis of human reproduction function. In: Kretzer DM, Spera G, editors. New York: Acta Medica. 1987; 115-74.

14. Toshimori K. Biology of spermatozoa maturation: an overview with an introduction to this issue. Microsc Res Tech. 2003; 61: 1-6.

15. Dacheux JL, Gatti JL, Dacheux F. Contribution of epididymal secretory proteins for spermatozoa maturation. Microsc Res Tech. 2003; 61: 7-17.

16. Tulsiani DRP. Glycan-modifying enzymes in luminal fluid of the mammalian epididymis: an overview of their potential role in sperm maturation. Mol Cell Endocrinol. 2006; 250: 58-65.

17. Tulsiani DRP, Abou-Haila A. Importance of male fertility control in family planning. Endocr Metab Immune Disord Drug Targets. 2014; 14: 134-144.

18. Morgentaler A, Stahl BC, Yin Y. Testis and temperature: an historical, clinical, and research perspective. J Androl. 1999; 20: 189-195.

19. Tulsiani DRP, Abou-Haila A. Male contraception: an overview of the potential target events. Endocr Metab Immune Disord Drug Targets. 2008; 8: 122-131.

20. Mieusset R, Bujan L, Mansat A, Pontonnier F, Grandjean H. Hyperthermia and human spermatogenesis: enhancement of the inhibitory effect obtained by artificial cryptorchidism. Int J Androl. 1987; 10: 571-580.

21. Mieusset R, Bujan L. The potential of mild testicular heating as a safe, effective and reversible contraceptive method for men. Int J Androl. 1994; 17: 186-191.

22. Tulsiani DRP, Abou-Haila A, Loeser CR, Pereira BM. The biological and functional significance of the sperm acrosome and acrosomal enzymes in mammalian fertilization. Exp Cell Res. 1998; 240: 151-164.

23. De Krester Dm, Kerr JB. In: Cytology of testis; Knobil E, Neil JD Eds; The Physiology of Reproduction. Raven Press, New York. 1994; 1177-1290.

24. Tulsiani DRP, Yoshida-Komiya H, Araki Y. Mammalian fertilization: a carbohydrate-mediated event. Biol Reprod. 1997; 57: 487-494.

25. Tulsiani DRP, Abou-Haila A. Molecular events that regulate mammalian fertilization. Minerva Ginecol. 2011; 63: 103-118.

26. Abou-Haila A, Tulsiani DRP. Signal transduction pathways that regulate sperm capacitation and the acrosome reaction. Arch Biochem Biophys. 2009; 485: 72-81.

27. Tulsiani DRP, Abou-Haila A. Mammalian fertilization: Scientific basis and recent progress. Applied Clin Res Trials & Clin Regul Affairs. 2015; 2: 50-59.

28. The Tennessean. 2013; 5A.

29. USA Today for the Tennessean. 2014; 3B.

30. Anawalt BD, Bebb RA, Bremmer WJ, Matsumoto AM. A lower dosage levonogesterol and testosterone combination effectively suppresses spermatogenesis and circulating gonadotropin levels with fewer metabolic effects than higher dosage combination. J Androl. 1999; 20: 407-415.

31. Wu FC. Hormonal approaches to male contraception: approaching reality. Mol Cell Endocrinol. 2006; 250: 2-7.

32. Zhen QS, Ye X, Wei ZJ. Recent progress in research on *Tripterygium*: a male antifertility plant. Contraception. 1995; 51: 121-129.

33. Lue Y, Sinha Hikim AP, Wang C, Leung A, Baravarian S, Reutrakul V. Triptolide: a potential male contraceptive. J Androl. 1998; 19: 479-486.

34. Qian SZ, Hu YZ, Wang SM, Luo Y, Tang AS, Shu SY. Effects of Tripterygium hypoglaucum (Lévl.) Hutch on male fertility. Adv Contracept. 1988; 4: 307-310.

35. Lohiya NK, Manivanan B, Mishra PK, Pathak N, Sriram B, Bhande SS. et al. Chloroform extract of Carcia papaya seeds induces long-term reversible azoospermia in langur monkey. Asian J Androl. 2002; 4: 17-26.

36. Kamal R, Gupta RS, Lohiya NK. Plants for male fertility regulation. Phytother Res. 2003; 17: 579-590.

37. Cheng CY, Mruk D, Silvestrini B, Bonanomi M, Wong CH, Siu MK. AF-2364 [1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide] is a potential male contraceptive: a review of recent data. Contraception. 2005; 72: 251-261.

38. Aarnoud C van der Spoel, Mylvaganam Jeyakumar, Terry D Butters, Harry M Charlton, Harry D Moore, Raymond A Dwek. et al. Reversible infertility in male mice after oral administration of alkylated imino sugars; a non-hormonal approach to male contraception. Proc Natl Acad Sci USA. 2002; 99: 17173-17178.

39. O'Rand MG. Antigens of spermatozoa and their environment. In: Dhinsa, D.S. & Schumaker, G.F.B., Editors. Immunological aspects of infertility and fertility regulation. New York, N.Y., Elsevier-North Holland. 1980; 155-171.

40. O'Rand MG, Widgren EE, Wang Z, Richardson RT. Eppin: an epididymal protease inhibitor and a target for male contraception. Soc Reprod Fertil Suppl. 2007; 63: 445-453.

41. O'Rand MG, Widgren EE, Wang Z, Richardson RT. Eppin: an effective target for male contraception. Mol Cell Endocrinol. 2006; 250: 157-162.

42. Li SQ, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol. 1991; 145: 341-344.

43. Guha Sk. US Patent 5488075. 1996.

44. Koul V, Srivastav A, Guha SK. Reversibility with sodium bicarbonate of styrene maleic anhydride, an intravasal injectable contraceptive, in male rats. Contraception. 1998; 58: 227-231.

45. Chaudhury K, Bhattacharyya AK, Guha SK. Studies on the membrane integrity of human sperm treated with a new injectable male contraceptive. Hum Reprod. 2004; 19: 1826-1830.

46. Guha SK, Singh G, Anand S, Ansari S, Kumar S, Koul V. Phase I clinical trial of an injectable contraceptive for the male. Contraception. 1993; 48: 367-375.

47. Guha SK, Singh G, Ansari S, Kumar S, Srivastava A, Koul V. Phase II clinical trial of a vas deferens injectable contraceptive for the male. Contraception. 1997; 56: 245-250.

48. Chen ZW, Gu YQ, Liang XW, Wu ZG, Yin EJ, Li-Hong. Safety and efficacy of percutaneous injection of polyurethane elastomer (MPU) plugs for vas occlusion in man. Int J Androl. 1992; 15: 468-472.

49. Zhao SC, Zhang SP, Yu RC. Intravasal injection of formed-in-place silicone rubber as a method of vas occlusion. Int J Androl. 1992; 15: 460-464.

50. Soebadi DM, Gardjito W, Mensink HJ. Intravasal injection of formed-in-place medical grade silicone rubber for vas occlusion. Int J Androl. 1995; 18: 45-52.

51. Zaneveld LJ, Burns JW, Beyler S, Depel W, Shapiro S. Development of a potentially reversible vas deferens occlusion device and evaluation in primates. Fertil Steril. 1988; 49: 527-533.

52. Song L, Gu Y, Lu W, Liang X, Chen Z. A phase II randomized controlled trial of a novel male contraception, an intra-vas device. Int J Androl. 2006; 29: 489-495.

53. Lu WH, Liang XW, Gu Y, Wu WX, Bo LW, Zheng TG. et al. A randomized controlled multi-center contraceptive efficacy clinical trial of the intra-vas device, a non-occlusive surgical male sterilization. Asian J Androl. 2014; 16: 1-5.

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