Male Contraceptives:

An Integrative Learning Experience

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ABSTRACT:

With rising populations and large numbers of unwanted pregnancies in the world, birth control is an increasingly important issue. While female contraceptives have been available for decades in a plethora of forms, contraceptive options available to men have been limited to condoms, withdrawal, and vasectomy. This paper examines why novel male contraceptives need to be developed, discusses the few contraceptive methods currently available for men, and examines some of the potential male contraceptives under development. It also discusses the largest barrier in the way of male contraceptive development and makes some suggestions on how more funding might be procured.

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INTRODUCTION

Traditionally, birth control has been viewed as the woman's responsibility. Social and gender roles dictate that the mother is most responsible for the children. Unwanted pregnancies also disproportionately affect the mother, who must face the decision to adopt, abort, or raise the child and also experience abortion or single motherhood. Male partners may be involved in these decisions but they have the luxury of their body not necessarily being affected by the outcome.

With rising populations and large numbers of unwanted pregnancies in the world, however, birth control is an increasingly important issue and surveys say men are willing to get more involved in contraception. But while a plethora of female contraceptive methods are available on the market, there remain few options for men to control their fertility. This paper examines why novel male contraceptives need to be developed, what contraceptive methods are currently available for men, and what methods are under development. It also discusses the largest barrier in the way of male contraceptive development and makes some suggestions on how more funding might be procured.

WHY WE NEED IT

World Population

The current world population is estimated to be 7.6 billion as of 2017 and the UN estimates that by 2100 the population will reach 11.2 billion (United Nations Department of Economic and Social Affairs, 2017). This growing population puts a great burden on the world's

natural resources, which will only serve to make life on earth more difficult. If the population continues to grow at current rates, we will eventually reach a point where there is not enough food to feed everyone. Researchers claim growing competition for land, water, and energy, as well as overexploitation of resources will affect our ability to produce food while compounding the threat posed by the effects of climate change (Godfray et al., 2010).

High rates of population growth are in part attributable to inadequate use of and lack of access to contraception (Henshaw, Singh, & Haas, 1999). Improving contraceptives and people's access to them could therefore help slow population growth to a level that is more sustainable. A multitude of female contraceptive options have been on the market for years but the other 50% of the world's population, that is almost all men, have very limited options when it comes to preventing pregnancy. Providing novel contraceptive options that are safe and effective for men could help improve family planning and reduce humanity's growing burden on the planet.

Unwanted Pregnancies

Despite numerous contraceptive options available for women, nearly half of all pregnancies worldwide are unplanned. Pregnancy in general carries natural health risks but numerous studies have indicated that unwanted pregnancies are especially associated with various negative health, economic, social, and psychological outcomes for both women and children (Sedgh, Singh, & Hussain, 2014).

Not only do these unintended pregnancies pose health risks to the mother, they also burden public health funding. In the United States, 68% of the 1.5 million unplanned births that occurred in 2010 were paid for by public insurance programs, primarily Medicaid, compared to 38% of planned births (Sonfield & Kost, 2016). Government expenditures on the births,

abortions, and miscarriages resulting from unintended pregnancies nationwide totaled $21 billion in 2010 (Sonfield & Kost, 2016).

Increasing the availability of effective contraceptives could help reduce the incidence of unwanted pregnancy and it's subsequent risks and costs.

Social Reasoning & Acceptability

We also need to develop male birth control to keep up with the times, as gender roles and social values change. Surveys by the UN Population Control Division suggest that a majority of young men in many countries are willing to have fewer children than their parents did (Tulsiani & Abou-Haila, 2014). Male birth control could help make that possible.

Studies show many men would be willing to use a reversible contraceptive, believing a "male pill" to be a good idea (Glasier et al., 2000). This apparent acceptability of male contraceptives is emphasized by fertility patterns. In 1970 only 15% of men who were fathering children were over the age of 35, compared to 25% today (O'Rand, Silva, & Hamil, 2016). This increase in time before a man chooses to become a father demonstrates the need for reliable yet reversible contraceptive options to ensure men are able to control if and when they become fathers.

Women seem to be in favor of the idea as well. A survey of 1894 women attending family planning clinics in Scotland, China, and South Africa found that over 65% of women thought the responsibility for contraception falls too much on women while all but 2% would trust their partner to use male contraception (Glasier et al., 2000). Making male contraceptives available can reduce the contraceptive burden placed on females, serve as double insurance in case one method of contraception fails, and empower men to control their own fertility.

EXISTING MALE BIRTH CONTROL

Though the reasons discussed above are pressing, there are very few birth control methods available for male use in the United States today. In fact, the Male Contraceptive Initiative only lists three existing methods on their website: condoms, withdrawal, and vasectomies.

Condoms

A condom is a sheath that covers the penis during intercourse, serving as a barrier that prevents sperm from entering the vagina. Originally made from animal intestines, sheath-like condoms were developed around 400 years ago (Page, Amory, & Bremner, 2008). Today, condoms are typically made out of latex or polyurethane.

Condoms are one of the most commonly used forms of birth control and are the most common method used at first intercourse (Mosher, Martinez, Chandra, Abma, & Willson, 2004). Over the 20 years from 1982 to 2002, the percentage of women who had ever had a partner who used the male condom increased from 52% to 90% (Mosher et al., 2004) while the proportion of contraceptive-using US women relying on the condom rose from 15% to 20% between 1988 and 1995 (Piccinino & Mosher, 1998).

With perfect use, only 2% of couples would experience a pregnancy after one year but the condom's real-world pregnancy rate is closer to 18% ("Existing Methods - Male Contraceptives," n.d.). This makes them significantly less effective at preventing pregnancy than most other birth control methods available to women. Their marginal contraceptive efficacy is perhaps the largest drawback to condoms. Much of this is due to poor long-term compliance:

more than half of users report inconsistent use with every act of intercourse which is compounded by the fact that many men dislike condoms, feeling they diminish sexual pleasure (Grady, Klepinger, Billy, & Tanfer, 1993; Page et al., 2008). Condoms do, however, have the added benefit of having proven effective in preventing the spread of sexually transmitted diseases, including HIV. While this is an advantage over most other forms of birth control, their perception as being undesirable and their low real-world efficacy make condoms less than ideal.

Withdrawal

Withdrawal, also known as “pulling out”, is a behavioral form of birth control where the man removes his penis from the vagina before ejaculating. The percentage of women who had ever had a partner who used withdrawal increased from 25% in 1982 to 56% in 2002 (Mosher et al., 2004). Among couples who practice it perfectly, it is estimated that only 4% will experience a pregnancy after one year but real-world pregnancy rates among couples who use withdrawal as their primary birth control method are high at 22% (“Existing Methods - Male Contraceptives,” n.d.). Many do not consider withdrawal as a legitimate form of birth control because of its relative intangibility and unreliable efficacy.

Withdrawal does have some advantages in that there is no cost, no chemical substance, no risk of side effects common with hormonal birth control, and it is still compatible with religious beliefs that might otherwise prohibit the use of contraception (Hinders, n.d.). The disadvantages are that withdrawal requires expert self-control and is difficult to perform correctly, it does not protect against sexually transmitted diseases, and compared to other forms of birth control it has a high rate of failure.

Vasectomy

Vasectomies are surgical procedures that sever or close the vans deferens tubes through which sperm travel from both testes. This prevents sperm from mixing with the semen ejaculated from the penis. A vasectomy is considered permanent and is extremely effective as a method of birth control. One year after the procedure, a couple's chance of experiencing a pregnancy is between one and two out of one thousand ("Existing Methods - Male Contraceptives," n.d.).

Vasectomy has almost no side effects and, compared with female sterilization, is a less risky procedure, has a quicker recovery period, and costs the health system less per patient (Shattuck, Perry, Packer, & Quee, 2016). Despite these benefits, however, only 2.4% of men around the world use vasectomies as a contraceptive method (Shattuck et al., 2016). Many people are unaware of the option for male sterilization or have erroneous assumptions about the procedure. Gender and cultural contexts may also inhibit the perceived acceptability of vasectomy or male involvement in family planning in general.

Common perceptions that inhibit the uptake of vasectomy include the idea that vasectomy is an act against God, hurts a man's pride or causes him to lose his masculinity, causes others to look down on him or view him as "under the control of" his wife, would lead to male infidelity, or inhibit his libido and his ability to perform sexually (Adongo et al., 2014; Shattuck et al., 2016). Cultural and religious beliefs may contribute to these perceptions but they also inhibit vasectomies through other means. For example, a doctor in the Philippines was unable to advertise his free vasectomy service on local billboards because the term vasectomy was seen as "a dirty word" in the local, predominately Catholic culture (Stack & Weinfield, 2013).

Despite being a safe and simple procedure, complications can sometimes arise. Common long-term complications from vasectomy are scrotal pain, with about 1% reporting it noticeably affects quality of life, and spontaneous recanalization of the vas deferens, which occurs in 0.03-1.2% percent of patients after spermatozoa had previously cleared the semen (Adongo et al., 2014). The relative rarity of complications, combined its high efficacy makes vasectomy a great option for those willing to seek a permanent contraceptive, however the fact that the procedure is permanent and may go against some cultural beliefs means it is not right for everyone.

PROSPECTIVE MALE CONTRACEPTIVES

With an increasing world population, large numbers of unwanted pregnancies, and changing social values, the reasons for developing viable male contraceptives are numerous. The contraceptive options currently available to men are not satisfactorily effective or appropriate for everyone. This has prompted researchers to develop novel methods of male contraception.

The research on potential male contraceptives has been ongoing for decades, despite the fact that no new method has been made commercially available since vasectomies were developed in the late 1800s. This section will discuss some of the most promising prospective male contraceptives, examining both hormonal and nonhormonal methods.

HORMONAL METHODS

Hormonal Mechanisms

Male hormonal contraception typically suppress the function of the hypothalamic-pituitary-testicular feedback loop to inhibit spermatogenesis. Normally, men secrete gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Both LH and FSH enter the testes where LH stimulates the interstitial cells, called Leydig cells, to make and release testosterone while FSH stimulates the Sertoli cells, which facilitate spermatogenesis. Testosterone synthesized in the testes also enters the bloodstream and regulates its own production via a negative feedback loop which acts on the hypothalamus and pituitary gland by inhibiting the release of GnRH, LH, and FSH.

Male hormonal contraception capitalizes on testosterone's negative feedback loop by utilizing exogenous testosterone to suppress the secretion of LH and FSH and deprive the testes of the signals required for spermatogenesis (M. Y. Roth & Amory, 2010). The subsequent decrease of testosterone production in the testes, however, may require an add-back androgen therapy to maintain physiological levels of testosterone as well as androgen-dependent physiological functions (Antonietta, Giulia, Marta, & Cristina, 2014). Other researchers contend, however, that exogenous administration of testosterone supports the androgen effects on sexual function and other organs without supporting spermatogenesis (Wang & Swerdloff, 2010). Results may depend on the type of testosterone used and the method of administration, which is why further research is so important.

In order to be effective, hormonal contraceptives must reduce sperm count to a level unlikely to produce pregnancy. A normal sperm concentration is defined as greater than 15

million sperm per milliliter of ejaculate (Roth & Amory, 2016; World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1996). While a lack of any measurable sperm in the ejaculate, also known as azoospermia, would make fertilization impossible, blocking sperm production entirely is difficult to achieve. For that reason, studies have focused on achieving various levels of severe oligozoospermia, or reduced sperm counts. Early work by the WHO, for example, has shown that a sperm concentration below 1 million/mL is associated with a pregnancy rate of 1% per year of use, which puts failure rates at a level similar to those seen with perfect use of female oral hormonal contraceptives (Roth & Amory, 2016; World Health Organization Task Force on Methods for the Regulation of Male Fertility, 1996).

While such hormonal methods are reversible, one disadvantage is the long amount of time it may take for sperm counts to return to normal. While most men have normal sperm counts within six months of discontinuing hormonal contraceptive regimens, some can take up to a year for their sperm levels to return to baseline (M. Y. Roth & Amory, 2010).

Combining Testosterone with Progestins

In some men, the administration of testosterone alone fails to completely suppress sperm production, which has lead to a number of studies combining testosterone with progestins to increase efficacy. There are race-related differences in the response to testosterone-only male hormonal contraceptives as well, with some claiming that only in East Asian men can testosterone alone suppress spermatogenesis to a level compatible with contraceptive protection (Nieschlag, 2010). Studies have shown that while Asian men exhibit rates of azoospermia in the 90-100% range on testosterone-alone regimens, similar regimens produce azoospermia rates closer to 60% in Caucasians (M. Y. Roth & Amory, 2010). The

reasons for these differences are still unknown but their discovery has sparked further research on combination contraceptives.

Combination regimens of both testosterone and progestins were first tested for male hormonal contraception in the 1970s and their efficacy has only improved over time. One six-month study published in 1996 found that adding a dose of oral levonorgestrel to weekly administration of testosterone enanthate (TE) improved rates of azoospermia in Caucasian men to 67% compared to 33% in the control group (Bebb et al., 1996). Subjects who received the combination, however, also experienced more weight gain and further decreases in high-density lipoprotein (HDL) cholesterol, side effects which subsequent studies have tried to mitigate through reduction of levonorgestrel dosage (Bebb et al., 1996; Page et al., 2008). One more recent study tested the combination of etonogestrel implants with testosterone decanoate (TD) injections and found the combination achieved rates of azoospermia in the 80-90% range with a low incidence of side effects (Brady et al., 2005; Page et al., 2008).

Many different progestins have been tested in combination with testosterone, including levonorgestrel, etonogestrel, norethindrone, and medroxyprogesterone. All have been found to result in azoospermia rates of almost 90% which makes many researchers believe one of these combinations is most likely to result in a clinically useful contraceptive (Page et al., 2008).

Side Effects

Male hormonal contraceptives can have small but significant effects on nonreproductive systems. These are important to understand in order to ensure the safety of long-term use if male contraceptives are ever to become commonplace. Overall, no serious adverse events have been associated with male hormonal contraceptives though common adverse effects include acne, suppression of high-density lipoprotein (HDL) cholesterol, weight gain, reversible

reduction in testicular volume, and increase in hematocrit, the proportion of red blood cells found in the blood (Page et al., 2008; M. Y. Roth & Amory, 2010).

In a recent study of intramuscular injections of norethisterone enanthate combined with testosterone undecanoate, researchers found a 98.4% efficacy rate in preventing pregnancy but it was accompanied by a high side effect rate, which had 45.9% of the men experiencing acne, and just under 20% reporting mood disorders (pmhdev, 2016). The study was terminated early due to the conclusion that "the risks to the study participants outweighed the potential benefits" due to concerning reports of mood changes, depression, pain at the injection site, and increased libido (Behre et al., 2016).

The intensity and incidence of side effects seems to be modulated by whatever progestin is used in combination regimens too. While the combination of progestins with testosterone increases the efficacy of spermatogenesis suppression, the effects on HDL and weight are magnified by the progestin dose (Anawalt et al., 2000, 2005; Page et al., 2008).

It is possible that just as protective effects result from female hormonal contraceptives, male hormonal contraceptives could have various health benefits as well. Exogenous androgens increase lean body mass and decrease fat mass in healthy young men while hypogonadal men experience similar improvements in body composition from androgen replacement, in addition to increased bone mineral density (Page et al., 2008). It is possible that such benefits could be experienced by men using hormonal contraceptives over the long term. Better body composition could reduce the risk of metabolic syndrome or cardiovascular disease while increases in bone mineral density could decrease fracture risk, especially as men age. While hormonal contraceptives appear to be generally safe, additional studies are needed to investigate the long-term effects to ensure men can safely use them for extended periods of time.

NONHORMONAL METHODS

Nonhormonal male contraception can be defined as a form of male contraception that does not involve the administration of hormones or compounds that block hormone secretion or hormone action (Roth & Amory, 2016). Nonhormonal contraception may be more appealing to men, as it avoids any negative connotations associated with the use of anabolic steroids, does not interfere with hormones associated with masculinity, and it may be more easily dosed orally than hormonal methods that may require injection or transdermal administration (Roth & Amory, 2016). Several approaches to nonhormonal male contraception have been studied over the years. This section will review some of the most promising methods to date.

Reversible Inhibition of Sperm Under Guidance (RISUG)

RISUG, short for “Reversible Inhibition of Sperm Under Guidance”, is a promising reversible alternative to vasectomy that involves the injection of steric maleic anhydride (SMA) combined with dimethyl sulfoxide (DMSO) into the vas deferens to create a partial obstruction that damages sperm as they pass, resulting in infertility. The US patent reports that the manner by which this method works is still not fully understood though a few methods have been reported regarding RISUG’s mode of action in more recent research (Lohiya, Alam, Hussain, Khan, & Ansari, 2014).

As sperm pass through vas deferens affected by RISUG, their plasma and acrosomal membranes, midpieces and tails are severely destroyed (Cheng & Mruk, 2010). Research suggests that the sperm acrosome is disrupted by the electrical charge and pH lowering effects of the injection (Guha, 2005; Lohiya et al., 2014) while varying concentrations of styrene in particular and SMA in general determine whether the vas deferens is completely or only partially

blocked by the injection (Lohiya et al., 2014). Phase III clinical trials have shown variation in the time it takes for subjects to become azoospermic after RISUG administration, ranging from one to four months (Lohiya et al., 2014).

The goal is for RISUG to be a fully reversible yet long lasting male contraceptive and so far the research is promising. Vasalgel, one example of RISUG, has shown rapid restoration of sperm flow in rabbit studies after an injection of sodium bicarbonate (baking soda) solution was used to dissolve the initial injection of SMA and DMSO (Waller, Bolick, Lissner, Premanandan, & Gamerman, 2017). RISUG seems to be effective for at least eight years and does not affect sperm count, libido, or erectile function (Anna, 2011). The longest duration of infertility in a RISUG subject was more than 10 years (Lohiya et al., 2014). Hailed as a new alternative to vasectomy, RISUG seems to have even fewer side effects because sperm can still exit the body unimpeded, preventing the pressure or granulomas that can result from permanent sterilization (Anna, 2011). It is also cost-effective as it could cost as little as $10 in poor countries while providing fertility control for years (Altstedter, 2017).

Whether RISUG results in any toxicity has not been reported extensively, though genotoxicity, mutagenicity, and carcinogenicity studies have been conducted at many centers in India (Lohiya et al., 2014). For example, one rat study published in 2013, concluded RISUG was unlikely to produce any DNA damage as it was not associated with genotoxicity in leukocytes or the testes of pre- or post-reversal rats (Ansari, Alam, Hussain, Khan, & Lohiya, 2013). More research is required to confirm effective quality control, but so far the procedure seems relatively safe.

Spermatic Duct Valve

Developed by the German inventor Clemens Bimek, the Bimek Spermatic Duct Valve, or Bimek SLV, is a small device surgically attached to each of the vas deferens. Each device contains a valve with a switch that can be felt through the skin of the scrotum, allowing men to turn the flow of their sperm on and off. The device is made of a medical implant material called PEEK Optima and is meant to be inserted via a 30 minute outpatient surgery.

Advertised as a 100% vegan product that's the size of a gummy bear and may be used for life, the Bimek SLV attracted a lot of media attention in January 2016, but not much has been heard since. The inventor claims to have installed one on himself, but much more testing, funding, and clinical trials will be required to prove the device is safe and effective.

Wolgang Buhmann, the spokesman for the Professional Association of German Urologists, remains skeptical, worrying that implanting the valve could cause scarring where it meets the vas deferens, preventing the flow of sperm even when the valve is open (Liotta, 2016). He also claims the valve could become clogged over time if left in the closed position, effectively making contraception irreversible (Liotta, 2016).

Even if it works perfectly as intended, the device can take some time to prevent fertility. Bimek's FAQ site claims there will still be sperm cells present in the semen for up to three months or about thirty ejaculations after installation (Bimek SLV Team, n.d.). This is similar to the wait necessary for a vasectomy to be fully effective.

While updates on the Bimek SLV's development since early 2016 are hard to find, if it were to be proven safe, effective, and reversible, it would make a promising example of alternative nonhormonal contraceptive methods for men.

Anti-Eppin Agent

Epididymal protease inhibitor, also known as Eppin, is a protein which in humans is encoded by a single copy gene on chromosome 20 by the same name whose expression is androgen dependent (O'Rand et al., 2016). Eppin is present in, and binds to each protein within a protein complex on the surface of human sperm that contains lactotransferrin, clusterin, and semenogelin (Mitra, Richardson, & O'Rand, 2010). The protein exhibits strong antibacterial activity and modulates the proteolytic activity of prostate specific antigen (PSA), which usually breaks down the protein Semenogelin-1. Both of these functions serve to protect spermatozoa from bacterial and proteolytic attack during transit in the female reproductive tract (O'Rand et al., 2016). Eppin also inhibits sperm motility when it binds semenogelin on the sperm surface, by controlling the sperm's internal pH and calcium levels (Silva, Hamil, Richardson, & O'Rand, 2012). This acts as an additional layer of protection by preventing premature hyperactivation and capacitation while sperm are in the female reproductive tract (O'Rand et al., 2016).

Eppin made its debut as a target for male contraception in 2004, when a study on macaques demonstrated that Eppin immunization produced reversible infertility (M. G. O'Rand et al., 2004). Such immunization works by binding antibodies to the surface of Eppin, preventing its binding with semenogelin as well as the inhibition of PSA's proteolysis of semenogelin. Binding anti-Eppin antibodies or semenogelin to eppin's semenogelin binding site results in a rapid decrease in sperm intracellular pH, a decrease in sperm intracellular calcium levels, and the cessation of sperm motility (Spinasanta, 2015). Studies have shown anti-eppin antibodies significantly decrease the progressive motility of human spermatozoa as measured by decreased total distance traveled, decreased straight-line distance, and decreased velocity (Michael G. O'Rand, Widgren, Beyler, & Richardson, 2008).

Eppin makes an attractive target for male contraception because it is specific to the male reproductive system and has an essential function on ejaculate spermatozoa; furthermore, that function can be reversibly blocked with easy access to the target on the sperm surface (O'Rand et al., 2016). The development of an anti-Eppin immunocontraceptive, however, is not considered a viable commercial option. This is due to many reasons, including efficacy, safety, and economics, but researchers are still utilizing what they've learned about Eppin to pursue other possibilities. Some for example, are developing a series of small organic compounds that mimic the effect of anti-Eppin antibodies binding to the sperm surface and thus inhibiting motility (O'Rand et al., 2016). While anti-Eppin agents themselves may not be commercially viable as contraceptives, the research conducted on them has been integral to the development of other contraceptive possibilities. More research is needed to see what will come of them but the utilization of protein bindings or vaccines for contraception is promising.

Other Contraceptive Vaccines

Antisperm contraceptive vaccines are an exciting proposition that has sparked various labs to delineate, clone, and sequence multiple sperm antigens and genes in the hopes of producing an immunocontraceptive. Vaccines currently being investigated target gamete production, function, and outcome, with those inhibiting gamete function as the preferred target (Naz, 2011). The viability of a sperm antigen in contraceptive vaccine development depends on many factors, including sperm/testes-specificity, role in fertility, surface expression, and immunogenicity (Naz, 2011). Potential targets for immunization include genes and proteins such as LDH-C4, P10G, FA-1, YLP12, A9D, SP56, contraceptive vaccinogen (CV), testis-specific antigen (TSA)-1, epididymal protein inhibitor (Eppin), and Izumo (Naz, 2011).

After nearly three decades of research, however, there are no immunocontraceptives on the market for human use, largely because contraceptive vaccines have been shown to be ineffective. Such vaccines are unable to induce long-term infertility in all subjects, probably due to differences in individual immune responses (Cheng & Mruk, 2010). As a result, the current and future focus of most immunocontraceptive research is on enhancing the immunogenicity, bioefficacy, and reducing inter-individual variability in immune response (Naz, 2011). Recent findings suggest that multi-epitope vaccines can enhance efficacy and obliterate the concern regarding inter-individual variability (Naz, 2011). While these findings are optimistic, more research is needed to truly develop a viable immunocontraceptive option.

Adjudin

Adjudin is a lonidamine derivative that functions as a contraceptive by disrupting the adhesion of germ cells, especially spermatids, to the Sertoli cells within the testes, causing release of immature spermatids and resulting in infertility (Mok, Mruk, Lie, Lui, & Cheng, 2011; Roth & Amory, 2016). Rat studies have shown adjudin can induce 100% infertility within 5 weeks (Roth & Amory, 2016). This is especially promising in combination with the finding that such infertility seems to be reversible because adjudin does not destroy spermatogonial stem cells (Cheng & Mruk, 2010).

Concerns, however, have arisen from the fact that adverse effects such as muscle atrophy and liver inflammation have been observed in rats receiving adjudin orally (Cheng & Mruk, 2010; Mruk, Wong, Silvestrini, & Cheng, 2006). Administering adjudin directly to the testes via conjugation to a recombinant follicle-stimulating hormone (FSH) mutant, which acts as a carrier, has demonstrated increased efficacy and selectivity compared to oral administration but is prohibitively expensive due to the costs associated with producing the FSH mutant and

attaching adjudin to it (Cheng & Mruk, 2010; Mruk et al., 2006). Such costs seem to have stalled progress on development of adjudin as a contraceptive and it has not yet been tested in human studies (Roth & Amory, 2016).

Other compounds besides adjudin seem to act similarly in the seminiferous epithelium to disrupt germ cell adhesion and induce infertility in rodents. Gamendazole is another analog of lonidamine that has been shown to induce reversible infertility with no apparent side effects and without disrupting the hormonal hypothalamic-pituitary-testicular axis but results of toxicity are as of yet unknown and deaths have occurred (Cheng & Mruk, 2010; Mok et al., 2011). CDB-4022 is an idenopyridine shown to have anti-spermatogenic effects in rodents and monkeys though the reversibility of treatment is variable from species to species (Mok et al., 2011). Both these and adjudin are potentials for further development of a nonhormonal male contraceptive but much more research will be required to fully develop any of them for human use.

Gendarussa

Justicia gendarussa, also known as willow-leaved justicia, gendarussa, or gandarusa, is a plant native to India and Indonesia. An indigenous tribe in Indonesia's Papua province uses it as a contraceptive by boiling the leaves in water and drinking it thirty minutes before intercourse, a practice important to their culture because the men are not allowed to get their wives pregnant until after they have fully paid off their dowries (Coconuts Jakarta, 2014). Indonesian researchers began looking into the properties of gendarussa in the 1980s and conducted animal and human trials through the 1990s. Professor Bambang Prajogo Eko Wardojo of Airlangga University claims gendarussa can disrupt three enzymes in spermatozoa

which prevents sperm penetration during in vitro fertilization without affecting the quality or quantity of sperm produced (The Jakarta Post, 2014).

The plant's contraceptive effects seem to be both effective and reversible. One phase III trial conducted in 2012 demonstrated a contraceptive efficacy rate of 99.96% with normal fertility returning in as little as three days after administration stopped (Coconuts Jakarta, 2014; Lewis, 2014). Gendarussa also appears to have no known side effects except an increased libido in some subjects.

Indopharma, a state-run pharmaceutical company, has been given a purified version of the plant extract for the final phases of production and distribution licensing (Lewis 2014; Hodge 2015). Best estimates say gendarussa could be ready for market by 2020, though it will likely be classified as an herbal medicine and could take several more years before it is found on pharmacy shelves, especially outside of Indonesia (Lewis, 2014). Though phase III trials have already been underway in Indonesia, it would have to repeat phase I and II trials to get approval from the US Food and Drug Administration (Lupkin, 2016).

Clean Sheets Pill

The clean sheets pill is based on phenoxybenzamine, an antihypertensive drug known to produce infertility due to ejaculatory failure as a side effect. It was suggested that phenoxybenzamine's contraceptive effect was due to a selective blockade of α-adrenoreceptors in longitudinal but not in circular muscular contractions of the vas deferens (Aitken et al., 2008). It has been shown that small doses of the drug do not change the hormonal balance of the body or affect blood pressure but manage to reversibly block ejaculation within two to three days of administration beginning (Homonnai, Shilon, & Paz, 1984).

The “clean sheets” pill works similarly, inhibiting release of semen by relaxing the longitudinal muscles of the Wolffian duct system while still permitting the circular muscles to contract (Clinkenbeard, 2012). The Wolffian duct system includes the epididymis and vas deferens, which are the tubes that carry sperm from the testicles, as well as the seminal vesicles that produce some of the fluid found in semen. When the circular muscles contract and clamp down on the longitudinal muscles, these tubes are closed, preventing the passage of both sperm and semen which will instead remain in the tubes and be naturally recycled by the body (“Birth Control for Men: ‘Clean Sheets’ Pill,” 2016; Clinkenbeard, 2012). Men could still experience orgasm as the required muscles are left unaffected but because ejaculation of all fluids is prevented, the clean sheets pill could also potentially reduce or eliminate transmission of all semen-borne STDs, including HIV (Clinkenbeard, 2012).

There are two possible modes of administration: a pill taken two to three hours before intercourse would provide temporary protection and wear off within 16 to 24 hours or an implant under the skin could continuously release small amounts of the drug and provide round-the-clock protection (“Birth Control for Men: ‘Clean Sheets’ Pill,” 2016; Clinkenbeard, 2012). The use of the drug specifically as a contraceptive has only been tested in animals so far and more research is needed in both animals and humans before the clean sheets pill could be made commercially available.

The Parsemus Foundation did an attitudes study in the US to assess acceptability of the pill and found 20% of low- and moderate-income young men were in favor of using it while 80% said it would depend on knowing more about safety and side effects (Parsemus Foundation, n.d.). Overall, 60% of men were interested in learning more about the clean sheets pill (“Birth Control for Men: ‘Clean Sheets’ Pill,” 2016), indicating that the market for it would be promising once development is complete.

THE GREATEST OBSTACLE: FUNDING

While many of the methods discussed above sound promising, there remain several obstacles in the way of developing safe, effective, and marketable male contraceptives, the most pressing of which being lack of funding for further research and development. The pharmaceutical industry has largely discontinued research in male contraception for various reasons. Whether due to concern about limited financial returns, potential increased regulatory hurdles around safety, religious opposition, general bias that family planning is a female issue, or high-profile lawsuits seen with unexpected side effects in female contraceptives, the lack of industry interest has severely hampered the introduction of novel male contraceptives to the market (Roth, Page, & Bremner, 2015).

As a result of the dearth of pharmaceutical funding, non-profit, governmental, and other organizations are both utilizing grants and exploring alternative funding models. The Parsemus Foundation, for example, solicits tax-deductible donations from the public and even accepts payment in Bitcoin. In 2016 they suggested supporters each donate “an hour’s wages” to raise the $127,000 they needed to manufacture a gel for its first clinical trial (Anthes, 2017). The Male Contraception Initiative, a non-profit, has run crowdfunding campaigns for researchers while Contraline, a biotechnology company working on contraceptive options similar to RISUG, has focused on attracting investors for seed money (Anthes, 2017).

While unconventional funding methods can help, they often aren’t enough to move research forward quickly. The Parsemus Foundation’s donation campaign closed with $85,000 of the $127,000 it needed and while that is far better than nothing, they will need a way to procure the rest before trials can begin in 2018 (Anthes, 2017).

Many researchers are approaching pharmaceutical companies about partnerships, but they often need evidence that their contraceptive candidate is safe, effective, and potentially profitable before the pharmaceutical companies will agree. This leads to a catch-22 situation that further stalls research and development. Incentives for pharmaceutical industry involvement and the development of male contraceptives in general would go a long way toward breaking this cycle. Also, while safety regulations are important, having a clearer regulatory process could help ease the industry's concerns around development and approval. Male contraceptives are an entirely new product category for which the FDA has yet to lay out clear guidelines (Anthes, 2017). Clarifying the process required could make companies more willing to invest in contraceptive development. Whatever the method, reliable funding must be procured if successful male contraceptives are ever to become a reality.

CONCLUSION

While female contraceptives have been available for decades in a plethora of forms, contraceptive options available to men have been limited to condoms, withdrawal, and vasectomy. Several potential novel male contraceptive methods, both hormonal and nonhormonal, have shown promise, but more funding, research, and development will be necessary to ensure safety and efficacy before these products can be brought to market. More incentives and clearer regulatory guidelines may be required to incentivize investment in male contraceptive development but as world population continues to increase, gender roles gradually change, and unwanted pregnancies continue to occur with alarming frequency, it is high time an effective, reversible male contraceptive was made available.

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