Published in final edited form as:

Semin Reprod Med. 2016 May ; 34(3): 183–190. doi:10.1055/s-0036-1571435.

Beyond the Condom: Frontiers in Male Contraception

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Abstract

Nearly half of all pregnancies worldwide are unplanned, despite numerous contraceptive options available. No new contraceptive method has been developed for men since the invention of condom. Nevertheless, more than 25% of contraception worldwide relies on male methods. Therefore, novel effective methods of male contraception are of interest. Herein we review the physiologic basis for both male hormonal and nonhormonal methods of contraception. We review the history of male hormonal contraception development, current hormonal agents in development, as well as the potential risks and benefits of male hormonal contraception options for men. Nonhormonal methods reviewed will include both pharmacological and mechanical approaches in development, with specific focus on methods which inhibit the testicular retinoic acid synthesis and action. Multiple hormonal and nonhormonal methods of male contraception are in the drug development pathway, with the hope that a reversible, reliable, safe method of male contraception will be available to couples in the not too distant future.

Keywords

testosterone; retinoic acid; contraception; spermatogenesis

Do We Need a Male Contraceptive?

Unintended pregnancies have dramatic negative effects on women's health worldwide, with widespread social, economic, and health impacts.¹ The World Health Organization (WHO) and United Nations 2015 Millenium Goals have recognized maternal health as a key factor to improving development, yet unplanned pregnancies due to inadequate or lack of access to family planning continues to expose women to negative health outcomes and an increased risk of death.^{2,3} Unintended pregnancies in the United States alone are estimated to cost the nation more than 15 billion dollars,⁴ highlighting the need in both developing and developed countries for improved access and availability to contraception and family planning services.

Traditionally, family planning has focused on providing contraception to women, and numerous reversible contraceptive options are available including pills, patches, injections,

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Disclosure Statement

No conflicts of interest to disclose.

intrauterine devices, and implants.⁵ Yet despite the fact that more than 25% of couples worldwide use a male method of contraception, primarily condoms and vasectomy, no new reversible contraceptive option for men has been developed for over 400 years.⁶ In addition, condoms are notoriously unreliable as a contraceptive, with up to an 18% failure rate in the first year of use.⁷ International surveys have highlighted theoretical interest in novel reversible male hormonal contraceptives with significant interest from communities of varied races, religions, and ethnicities.^{8–10}

Herein we review the physiologic basis for both male hormonal and nonhormonal methods of contraception. We review the history of male hormonal contraception development, current hormonal agents in development, as well as the potential risks and benefits of male hormonal contraception options for men. Nonhormonal methods reviewed will include both pharmacological and mechanical approaches in development, with specific focus on methods which inhibit the testicular retinoic acid pathway.

Mechanism of Male Hormonal Contraception

Male hormonal contraceptive approaches capitalize on the normal hypothalamic–pituitary–gonadal feedback loop that regulates steroidogenesis and spermatogenesis in men (Fig. 1). Pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus triggers pulsatile release of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. In normal healthy men, LH binds to the androgen receptor on Leydig cells in the testes to stimulate steroidogenesis, primarily testosterone synthesis. FSH binds to Sertoli cells in the seminiferous tubules, which further stimulates spermatogenesis.^{11,12} Testosterone diffuses out of the testes into the systemic circulation, providing negative feedback at both the level of the hypothalamus and pituitary.¹³

Male hormonal contraceptives work by suppressing gonadotropin release from the pituitary. This leads to an acute decline in type B spermatogonia production.¹⁴ Spermatogonia that have passed this point of differentiation will complete the maturation process into elongated spermatids, therefore requiring several weeks of androgen therapy, with or without the use of progestins, for adequate contraception.¹⁵

A normal sperm concentration is defined as greater than 15 million sperm per milliliter (million/mL) of ejaculate.¹⁶ While azoospermia, or a lack of any measurable sperm in the ejaculate, would make fertilization of the ova impossible, achieving this complete block in sperm production has been impossible in all subjects in clinical trials. Moreover, depending on how semen is analyzed to look for sperm, complete azoospermia is likely impossible to achieve.¹⁷ Based on early seminal work by the WHO,¹⁸ fertility rates have been evaluated for various levels of severe oligozoospermia and have demonstrated that a sperm concentration of below 1 million/mL is associated with a pregnancy rate of 1% per year of use.¹⁹ At this level of severe oligozoospermia, failure rates using a male hormonal contraceptive as a sole method of contraception are similar to those seen with “perfect use” of female oral hormonal contraceptives.^{18,20}

Finally, a key goal for development of a novel male contraceptive is complete reversibility with cessation of contraceptive use. Time to return of fertility varies with types of androgens and progestins used for male hormonal contraception.²¹ Given the enormous variability in sperm concentrations within an individual, guidelines for male contraceptive development recommend return to a normal seminal fluid analysis as defined by the WHO criteria.¹⁹ More than 2,000 normal, eugonadal men have enrolled in clinical trials of male hormonal contraceptives with near universal return of testicular function both for steroidogenesis and spermatogenesis.^{21,22} Only one small trial has enrolled men with subnormal semen parameters at baseline, all of whom returned to baseline semen parameters after completion of the 34-week treatment phase of the clinic trial.²³

Development of Male Hormonal Contraceptive Regimens

Reduction in human sperm concentrations has been a recognized side effect of testosterone therapy since it was first developed for therapeutic use.²⁴ Active clinical trials to develop a male hormonal contraceptive based on the effects of testosterone therapy on sperm concentrations began in the 1970s and led to two landmark studies sponsored by the WHO in the 1980s and 1990s. These large, multicenter international clinical trials for contraceptive efficacy using testosterone enanthate alone for weekly injections proved that testosterone therapy can lead to suppression of spermatogenesis in the majority of men enrolled and can serve as an effective contraceptive when used alone to prevent fertility.^{18,25,26} However, only 65% of men enrolled in the first study suppressed sperm concentrations to an undetectable level; therefore, the second trial allowed couples to enter the efficacy phase with a sperm concentration <3 million/mL. These early trials proved that suppression of spermatogenesis with testosterone could be an effective, reversible, safe method of contraception for men, but highlighted that 4 months of treatment was needed to achieve adequate sperm suppression and that some subjects (~15–25%) did not achieve adequate suppression of sperm production during treatment, suggesting that further work is needed before this method of contraception can be used clinically.

Subsequent trials showed that addition of a progesterone agent could both hasten the onset of sperm suppression and improve the number of subjects who achieve adequate suppression of spermatogenesis.^{27,28} Various combinations of testosterone, in topical, injectable, and implantable formulations, and progesterone agents have been evaluated, including cyproterone acetate,²⁹ levonorgestrel,^{30–33} etonogestrel,^{34–36} desogestrel,^{37,38} norethisterone enanthate,^{39,40} and medroxyprogesterone acetate.^{41,42} While the exact mechanism of progesterone's role in male contraception is unknown, these agents appear to work at both the levels of the pituitary and testes to maximally suppress gonadotropins and, possibly, to directly decrease spermatogenesis.^{21,43} Several trials have added agents to directly suppress GnRH release from the hypothalamus or to prevent testosterone metabolism by 5 α -reductase, but neither improved upon the levels of sperm suppression seen with an androgen and progesterone agent combined.^{44–46}

Novel Agents in Male Hormonal Contraceptive Development

Despite promising results from multiple clinical trials, no regimen has progressed to the approval phase for a novel male hormonal contraceptive. One challenge has been the complexity of regimens requiring both an androgen and progesterone, often administered by different routes and at different times. Novel agents in development have focused on improving the ease of administration or use of a regimen if it were to become commercially available. Three agents are currently being studied in clinical trials.

Nestorone and Testosterone Combination Therapy

Nestorone is a 19-norprogesterone-derived progestin with no androgenic, estrogenic, or glucocorticoid activity.⁴⁷ Nestorone and testosterone can both be applied as a daily transdermal gel, and showed effective suppression of gonadotropins when used for 20 days.⁴⁸ When studied in a 6-month trial with sperm suppression as the primary outcome, 89% of men achieved suppression of sperm concentration down to 1 million/mL and the majority of subjects were very satisfied with the regimen, and would be likely to use it if it were commercially available.^{49,50} Ongoing studies are working to simplify the regimen into a single combination gel to improve compliance and long-term use of this potential male hormonal contraceptive.

Dimethandrolone Undecanoate

Dimethandrolone undecanoate (DMAU) is a potent synthetic 19-norandrogen that is hydrolyzed to dimethandrolone (DMA) in vivo. DMA acts at both androgen and progesterone receptors,⁵¹ making DMAU a potential single-agent contraceptive. Animal studies in rodents and rabbits have shown both reversible suppression of gonadotropins and sperm with orally administered DMAU and no significant side effects on metabolic outcomes or bone.^{52,53} Phase I testing in humans demonstrated short-term safety and tolerability with reversible suppression of gonadotropins⁵⁴ and phase Ib testing is currently ongoing for the oral formulation (National Clinical Trials database 01382069). DMAU can be administered either orally or by intramuscular injection, potentially balancing the options of both patient preference in choosing an oral regimen and improved compliance and efficacy as seen with injectable regimens.^{9,10,55} Therefore, DMAU is being developed as both an oral and injectable contraceptive.

7-Alpha-Methyl-19-Nortestosterone

7-Alpha-methyl-19-nortestosterone (MENT) is a potent synthetic androgen, but has no activity at the progesterone receptor. Developed as an implant for long-term hormonal contraception, MENT is not metabolized by 5 α -reductase and has much higher binding avidity at the androgen receptor than testosterone.^{56,57} MENT may have additional benefits for men's health by potentially decreasing androgen activity in the prostate, yet supporting bone health as MENT is aromatizable.^{58,59} While a dose-finding study of MENT implants showed sustained release of MENT over 1 year with adequate gonadotropin and sperm suppression,⁶⁰ subsequent trials have not reproduced similar results due to variation in drug release from the implants.⁶¹ Ongoing implant development work will focus on improving

drug release rates to achieve adequate serum MENT concentrations before a planned randomized controlled trial can begin.

Side Effects and Safety Concerns in Male Hormonal Contraceptives

As men do not suffer the negative health consequences of an unintended pregnancy, the safety of a male contraceptive is paramount to regulatory approval to ensure the benefits outweigh the risks of treatment. Although no clinical trials to date have exceeded 2.5 years of use, limiting our understanding of long-term risks and benefits, clinical studies conducted over the past several decades point to areas requiring further study.

While testosterone therapy in hypogonadal men significantly improves several metabolic parameters including increased lean body mass and bone mineral density, decreased fat mass, and improved sexual function,⁶² eugonadal men receiving physiologic doses of testosterone are unlikely to see similar benefits. Several recent studies have highlighted the importance of estradiol for maintaining bone mineral density and sexual function in men, highlighting the need for continued study on the possible metabolic effects of the synthetic androgens in development.⁶³

In general, the most common side effect noted in male hormonal contraceptive studies has been acne, but these studies have all been limited by a lack of a placebo group. Only one male hormonal contraceptive trial included a placebo group for an accurate comparison of side effects.³⁶ Other common side effects have varied based on the progesterone used, but have included change in body weight, changes in cholesterol profile with a decreased HDL, LDL and total cholesterol, and mood changes.²¹ No contraceptive study conducted to date has found an increase in cardiovascular or thromboembolic events, but these studies were not designed to specifically study this outcome. This is an issue of importance, as the Food and Drug Administration (FDA) is concerned regarding these risks in hypogonadal men receiving testosterone therapy.

Most recently, the WHO and CONRAD sponsored a large, multicenter male hormonal contraceptive trial using a long-acting injectable combination therapy with testosterone undecanoate and norethisterone enanthate.⁴⁰ While prior studies had shown this to be a highly effective and acceptable regimen,^{39,64,65} the study was stopped early due to side effect concerns (<http://www.conrad.org/news-pressreleases-63.html>). Additional explanation regarding the concerns which lead to study discontinuation will hopefully be forthcoming.

Nonhormonal Contraception—General Considerations

Several approaches to “nonhormonal” male contraception have been studied. 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. Nonhormonal contraception may be more appealing to men, as it avoids any negative connotations associated with the use of anabolic steroids, such as sports disqualification, and it may be more easily dosed orally than steroid preparations that require injection or transdermal administration. Herein, we describe several promising pharmaceutical approaches to male nonhormonal contraception that have been shown to reversibly suppress

spermatogenesis in animal models and one promising barrier to physical approach that has been tested in both animals and humans.

Adjudin

Adjudin is a lonidamine derivative that functions as a contraceptive by disrupting the adhesion of spermatids to the Sertoli cells, causing premature spermiation and infertility^{66–68} (Fig. 1). Weekly administration of two doses of 50 mg/kg of adjudin induced 100% infertility 5 weeks after treatment in adult rats. Because liver inflammation occurred in a 29-day study of adjudin administration in rats, researchers conjugated adjudin to a FSH β mutant specifically targeting it to Sertoli cells, thereby significantly reducing the dose necessary for contraception.⁶⁹ Unfortunately, the cost of this approach and the development of anti-FSH autoantibodies have stalled progress on the use of this compound, which has not been tested in human studies to date.

H2-Gamendazole

H2-Gamendazole is another lonidamine derivative that works by impairing the function of the apical ectoplasmic specialization⁷⁰ (Fig. 1). In one notable study, fertile male rats received a single oral dose of gamendazole at 6 mg/kg.⁷¹ This dose produced 100% infertility after a single oral administration; however, the drug had only 57% reversibility at this dose, raising the concern of irreversibility with longer periods of administration. The mating behavior of the treated rats returned to normal and the F1 offspring of the animals that regained fertility did not seem to be affected. In terms of toxicology, three out of five rats died after receiving a dose of 200 mg/kg of H2-gamendazole; however, no observable abnormalities including liver inflammation, necrosis, or hemorrhage were detected at dosages lower than 200 mg/kg. As a result, researchers are preparing an Investigational New Drug (IND) application to the FDA to proceed to human testing, but no clinical trials in humans have occurred to date.

Retinoic Acid Inhibition

It has been known since 1925 that vitamin A (retinol) is required for normal sperm production in mammals.⁷² Vitamin A and its metabolite, retinoic acid, are required at puberty for the initiation of spermatogenesis and maintenance of spermatogenesis.^{73,74} Within the seminiferous tubules, both germ and Sertoli cells synthesize retinoic acid from retinal via aldehyde dehydrogenases.⁷⁵ Retinoic acid binds one of several retinoic acid receptors, α , β , or γ which regulate gene expression. Male retinoic acid receptor knockout animals are sterile due to various problems in spermatogenesis.^{76–78} These observations suggest that blockade of retinoic acid binding to its receptors, or inhibition of retinoic acid synthesis from vitamin A, has the potential to inhibit spermatogenesis and may be a viable approach to male nonhormonal contraceptive development.

BMS-189453

BMS-189453 is an orally active retinoic acid receptor antagonist, which blocks the binding of retinoic acid to all three retinoic acid receptors (Fig. 1). BMS-189453 was originally formulated by Bristol-Myers-Squibb (New York City, NY) as part of the retinoid research

program in the late 1990s. In the first publication to describe testicular effects of this compound, 1 month daily oral doses of BMS-189453 produced marked testicular degeneration in rats, but also led to increases in leukocyte counts, alkaline phosphatase, and alanine aminotransferase levels.⁷⁹ Significant overt signs of toxicity and deaths occurred at oral doses in excess of 240 mg/kg, whereas body weight and food consumption decreases occurred at 60 and 240 mg/kg. This original study, however, did not explore the fertility status of the animals nor did it look at reversibility of testicular changes after the study period.

Therefore, another group conducted an important followup study in mice specifically examining whether a lower dose of BMS-189453 might function as a reversible contraceptive without the systemic toxicities seen at higher doses.⁸⁰ In this study, two groups of mice were administered BMS-189453 orally at 5 mg/kg for 2 weeks and 2.5 mg/kg for 4 weeks. All of the mice were completely sterile by 4 weeks with either dose, and the infertility persisted for 2 weeks at the highest dose after cessation of treatment. Importantly, spermatogenesis was completely restored by 20 weeks in all males. This group has recently focused on the development of specific retinoic acid- α antagonists^{81,82}; however, these compounds did not suppress sperm production, possibly due to poor oral or tissue bioavailability.

WIN 18,446

More than 50 years ago, the oral administration of WIN 18,446 was shown to reversibly inhibit spermatogenesis in many species including man after 12 weeks of administration.^{83–85} Testicular biopsies from men in these studies treated with WIN 18,446 revealed a complete arrest of spermatogenesis, with only spermatogonia remaining in the seminiferous tubules.⁸⁴ It was apparent that these compounds had no effect on the endocrine function of the testes, but their mechanism of action was undetermined. Nevertheless, at least 60 men were administered WIN 18,446 for up to 1 year with sperm concentrations below 1 million/mL of ejaculate,⁸³ and no significant adverse events. Unfortunately, further development was abandoned in the 1960s, as subjects taking WIN 18,446 experienced disulfiram reactions with nausea, vomiting, and sweating, when they drank alcohol.⁸⁵

WIN 18,446 suppresses spermatogenesis by inhibiting testicular retinoic acid biosynthesis.^{86,87} In vitro, WIN 18,446 inhibits the function of aldehyde dehydrogenase 1a2, which functions in testicular retinoic acid biosynthesis. WIN 18,446 induced reversible azoospermia in rabbits after approximately 12 weeks of oral administration. The reduction in spermatogenesis was preceded by a significant decrease in the retinoic acid concentration within the testes, suggesting that WIN 18,446 functions as a male contraceptive by inhibiting the testicular biosynthesis of retinoic acid. Preclinical work continues on developing novel, specific inhibitors of testicular retinoic acid biosynthesis that can reversibly inhibit spermatogenesis without significant side effects, such as disulfiram reactions.

RISUG

Since the early 1980s, efforts have been underway in India to develop a reversible plug for the vas deferens, called RISUG for “reversible inhibition of sperm under guidance.” Under ultrasound guidance, sterile styrene maleic anhydride is instilled into the vas bilaterally effectively occluding it and preventing the passage of sperm. Several small clinical trials in men have been performed using this technique,^{88,89} which appears to afford excellent contraceptive efficacy over periods of up to 1 year. The procedure has been shown to be reversible in animal models, but reversibility data and large-scale clinical trial experience in humans are lacking.⁹⁰ Similar vas occlusion devices, such the medical-grade silicone⁹¹ or polyurethane⁹² plugs studied in China, have had problems with both time to sperm suppression and time to recovery of sperm counts after reversal, somewhat dampening enthusiasm for this approach. Recently, a U.S. foundation, the Parsemus Foundation (<http://www.parsemusfoundation.org/vasalgel-home/>) has attempted to reinvigorate research into this intriguing approach to male contraceptive development, but no clinical trial data from their efforts are currently available.

Conclusion

Contraception is the most important tool available to humanity to prevent unintended population growth and abortion. In addition, increased use of contraception has the potential to stabilize world population and improve global health and economics. As more than 25% of couples worldwide rely on a male method of contraception, namely condoms, with a high failure rate, new effective, reversible, male-focused contraceptive technologies are likely to be widely used. Hormonal-based regimens are currently in clinic trials, with extensive prior data establishing safety and efficacy in men. Nonhormonal methods in development, especially retinoic acid antagonists and/or lonidamine derivatives, appear promising and are approaching the clinical testing phase to determine their safety and efficacy in men for the prevention of unintended pregnancy. While commercial development is still many years down the drug development pathway, acceptance of novel, reversible, male contraceptive methods could revolutionize the way that contraceptive delivery occurs around the world.

Acknowledgments

This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, a division of the National Institute of Health through cooperative agreement K23 HD073164-02 (MYR) and U01 HD060408 (JKA).

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Normal Male Reproductive Function

Hormonal Methods of Contraception

Non-Hormonal Methods of Contraception

Fig. 1.

Mechanisms of male contraception. Left panel illustrates normal hypothalamic–pituitary–gonadal feedback loop with positive stimulation (green arrows) of the testes from gonadotropins stimulating spermatogenesis and testosterone production, and negative feedback (red arrows) from testosterone at the hypothalamus and pituitary. Middle panel illustrates disruption of the normal feedback loop due to persistent negative feedback from exogenous androgens (red arrows), with or without addition of progesterone. Right panel illustrates the mechanism of action of nonhormonal contraceptives that either disrupt retinoic acid synthesis or action (WIN 18,446 and BMS 189,453) or disrupt the normal binding of spermatids to Sertoli cells (adjuvin and H2-gamendazole), without any alteration in normal hypothalamic–pituitary–gonadal function. Normal hormonal feedback loop remains intact with nonhormonal methods of contraception.