Review Article

Reversible male contraceptives: Current progress

Phawat Luangtangvarodom, Manint Usawachintachit

Division of Urology, Department of Surgery, Faculty of Medicine, Chulalongkorn University,
King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Keywords:
Reversible,
male contraception

Introduction

The current world population is 7.5 billion and growing. It is expected to be over 9.7 billion by 2050[1]. Contraception is important in controlling population. While several contraceptive methods are available, there is room for improved methods. Most are being utilized by women and few are being developed for males[2]. This review summarized the current evidence of male contraception based on contemporary clinical trials in human and animal models. We intentionally omitted a discussion of protective measures such as condoms as surgical vasectomy is already accepted in clinical practice.

Methodology

We reviewed the available evidence using a search engine from PubMed and Scopus. Unwanted pregnancy is an ideal control arm for studies regarding the effectiveness of various contraceptive methods. However, due to study designs and ethical issues in human research, either sperm concentration or serum gonadotropin is mostly used as a surrogate outcome instead of pregnancy rates. The ideal target for male contraception is "azoospermia," in which no sperm is found in a routine semen analysis; however, in practice, a sperm concentration of less than 1 million/ml is acceptable according to a recommendation by the American Society of Andrology[3].

Corresponding author: Manint Usawachintachit
Address: Division of Urology, Department of Surgery, Faculty of Medicine, Chulalongkorn University,
King Chulalongkorn Memorial Hospital, Bangkok, Thailand
E-mail: Manint.u@chula.ac.th
Received: Febuary 14, 2019
Revision received: October 8, 2019
Accepted after revision: October 22, 2019

1. Hormonal Contraceptives

Hormone contraceptives for males are derived from the physiology of the hypothalamic-pituitary-gonadal axis (HPG axis) where the hypothalamus secretes gonadotropins releasing hormones (GnRH) that stimulate FSH from the anterior pituitary gland, which in turn stimulates spermatogenesis. GnRH also stimulates the secretion of luteinizing hormone which promotes androgen production. Thereby, androgens, whether endogenous or exogenous, act as negative feedback stimulators to both the hypothalamus and the anterior pituitary gland, suppressing spermatogenesis and androgen production. Thus, androgens are being studied to suppress spermatogenesis in the hope of inducing infertility[4].

Injected Testosterone

Since unesterified testosterone has low oral bioavailability and rapid clearance from serum[5], injected forms of esterified testosterone are more commonly utilized in clinical practice. They include testosterone ethanoate (TE) and testosterone undecanoate (TU). Intramuscular TE 200 mg weekly was investigated in 271 healthy fertile males in a clinical trial conducted by the World Health Organization (WHO). Azoospermia was found in 65% of participants which resulted in a pregnancy rate of 0.8 per 100 person-years. Following injection withdrawal of TU, sperm concentration rose above 20 million/ml after a mean duration of 3.6 months[6]. A subsequent study, utilizing the same regimen in 399 healthy fertile males, demonstrated a pregnancy rate of 1.4 per 100 person-years[7]. However, a small sub set of non-responders, defined by a persistently high sperm concentration above 3 million/ml, were found in both studies.

Compared to TE, TU has a longer half-life and requires drug administration less often, only at every 6-8 weeks[8]. This distinct advantage might help increase patient satisfaction, since a weekly injection schedule of TE was a cause of withdrawal in some patients[7]. A study of 1,045 Chinese males with intramuscular TU 500 mg monthly for 30 months demonstrated that only 4.8% of subjects had a sperm concentration above 1 million/ml. The pregnancy rate was 1.1 per 100 subjects throughout a 24-month period of drug administration[9].

Although showing some success in male contraception, the adverse effects of high dose testosterone must be considered. The most concerning are weight gain and decline in serum HDL, which may lead to an increased risk of metabolic syndrome[6,10]. Compounds such as progestins and 5-alpha reductase inhibitors have been combined with testosterone in order to reduce the adverse effects and improve contraceptive efficacy.

One randomized controlled trial demonstrated that a combination of intramuscular TE 100 mg weekly and oral levonorgestrel (LNG) 500 mcg daily suppressed sperm concentration better than intramuscular TE 100 mg weekly alone (94% vs 61% of patients achieved a sperm concentration below 3 million/ml). The most likely explanation is that the additional gonadotropin inhibitory effect resulted from LNG[11]. Nevertheless, side effects were encountered more often in the combination group, including decreased HDL (22% vs 1.8%) and weight gain (5.3 kg vs 2.3 kg)[12]. Another study reduced the oral LNG dose to 31 and 62 mcg per day in combination with intramuscular TE 100 mg weekly. Sperm concentration was suppressed below 3 million/ml in 90% and 95% in the 31 and 62 mcg groups, respectively, and there was no significant weight gain in the 31 mcg group while there was a 2.5 kg weight gain in the 62 mcg group. HDL, however, decreased significantly in both groups: 12% and 15% respectively[13].

Levonorgestrel, in the form of implantable rods combined with intramuscular TU, has also been studied and has a slightly higher efficacy rate[14]. Other progestins have been evaluated. A double-blinded multicenter trialusing etonogestrel implant combined with intramuscular TU every 10-12 weeks resulted in sperm concentration <1 million/ml

in 89% of participants[15]. Another study in 2016 used intramuscular norethisterone 200 mg combined with TU every 8 weeks and demonstrated that 96% of participants had sperm concentrations<1 million/ml. However, this study was terminated due to a high incidence of adverse events, including mood changes, depression, and increased libido[16]. Depotme droxyprogesterone acetate (DMPA) in combination with TU has been studied. All 30 participants had sperm concentrations below 3 million/ml during the treatment period[17].

Apart from progestins, 5-alpha reductase inhibitors (5ARI) were studied. Oral dutasteride 0.5 mg daily was added to a combination of intramuscular TE 100 mg weekly plus oral LNG 125 mcg daily. When compared to TE+LNG alone, however, sperm concentration and serum gonadotropin levels were not different between the 2 groups[18,19].

Other forms of testosterone

Because of a low oral bioavailability of testosterone, most studies have been driven into intramuscular injection. Nevertheless, a study using a combination of oral testosterone in sesame oil was able to achieve therapeutic levels of serum testosterone. When oral dutasteride was added, serum testosterone levels increased due to the oral testosterone in the oil alone[20]. Its efficacy was shown by significantly suppressed levels of FSH and LH[21].

Another potential route is transdermal administration, which has been a contraception method of choice in women for years. This route of administration is simple and does not require any injection and, thus, requires fewer healthcare visits. Results of studies using transdermal testosterone vary. One study using a testosterone transdermal patch with implanted LNG, showed poor efficacy in suppressing spermatogenesis; with less than 60% of participants achieving sperm concentration <3 million/ml compared with 100% in a group using intramuscular TE with implanted LNG[22]. Another study used transdermaldi hydro testosterone with or without implanted LNG. It revealed that no participant achieved a sperm concentration of <3 million/ml[23]. In contrast, another study using a combination of transdermal testosterone and nestorone gel showed a promising result with 89% of participants achieving a sperm concentration <1 million/ml[24].

One possible disadvantage of the transdermal route is a need to avoid physical contact with females and children while the medication is on the skin. There was also a report of significant skin discomfort among dihydrotestosterone gel users[23].

2. Non-Hormonal Contraceptives

Adjudin

Adjudin is a lonidamine analogue which can disrupt adhesion between spermatids and Sertoli cells causing the premature detachment of spermatids and then infertility[25]. An animal study in 2001, using oral administration of adjudin, revealed no pregnancy in all the rats, although the males were allowed to mate with the females freely. All the rats in the control group had viable offspring[26]. Full reversibility was observed at 11 weeks after treatment withdrawal[27]. However, high doses of adjudin are nephrotoxic and may causes liver inflammation, which is a major obstacle to the use of adjudin in humans[25,28]. Several drug delivery technologies were proposed to improve intratesticular bioavailability of adjudin and to reduce its effective dose[29].

H2-Gamendazole& CDB-4022

H2-Gamendazole and CDB-4022 are also lonidamine analogues and able to induce infertility in the same way as adjudin. From a study of H2-Gamendazole in rats, a single dose of 3 mg/kg induced infertility in 67%, while a single dose of 6 mg/kg induced infertility in 100%. However, full reversibility was only observed in the 3 mg/kg group. Unspecified mortality was also observed at 200 mg/kg dose where 3 out of 5 mice died, but there was no evidence of inflammation, necrosis, hemorrhage, or tumors in doses

lower than 200 mg/kg[30]. For CDB-4022, infertility was fully achieved in rats and monkeys without any observed toxicity. CDB-4022-induced infertility was irreversible in rats, but was reversible in monkeys with unknown mechanisms[31,32].

BMS-189453

Retinoic acid is involved in various steps of spermatogenesis, including spermatogonia differentiation and meiosis[33]. Thus, using a retinoic receptor antagonist may be a potential male contraceptive. BMS-189453 is a pan-antagonist of retinoic acid receptors that was initially developed for use in dermatology. It was later found to negatively affect spermatogenesis[34]. A study in mice using oral 2.5 mg/kg of BMS-189453 for 4 weeks resulted in a disruption of spermatogenesis from testicular histopathology, a significant reduction in sperm concentration and motility, and ultimately failure to cause pregnancy. Spermatogenesis was completely restored after medication withdrawal, and no toxicity was found[35]. Subsequent studies from the same group reduced the dose to 1 mg/kg and demonstrated similar results[36].

3. Physical Occlusion of Vas Deferens

RISUG

The concept of "Reversible Inhibition of Sperm Under Guidance," also known as RISUG, has been proposed as a male contraceptive method since the 1980s. It involves an injection of styrene maleic anhydride (SMA), dissolved in dimethyl sulphoxide (DMSO), into the vas deferens on both sides through a small incision of scrotal skin. The mechanism of action of these compounds has not been discovered. However, some possible mechanisms include total occlusion of the vas deferens, a pH-lowering effect which reduces sperm motility, a change in sperm membrane electric charge balance, and even oxidative stress damage of sperm. Original studies of RISUG in rats and monkeys successfully induced infertility[37]. The phase I clinical trial was conducted in 1993 and showed an optimal dose of 60 mg of SMA to be effective and safe[38]. The phase II clinical trial was conducted in 12 healthy fertile subjects and revealed persistent azoospermia for at least 425 days with no long-term adverse effects[39]. A phase III trial is currently ongoing. Complete reversibility of RISUG was demonstrated in monkeys at 60-90 days after reversal with normal motility and viability; however, evidence of reversibility of RISUG in humans is still lacking[40].

Male contraceptives in Thailand

In Thailand, a clinical trial of male contraception was conducted at the Faculty of Medicine, Chulalongkorn University in 1996. This study administered intramuscular TE 200 mg weekly to 17 healthy Thai men and measured sperm concentration, FSH and LH level. All participants eventually developed azoospermia at a median duration of 85 days. FSH and LH were also suppressed below detectable levels. Adverse effects were found in 2 participants. One had abnormal liver function tests and the other had hypertension and weight gain, causing them to withdraw from the study[41].

Conclusion

There are several different concepts of male contraceptives currently in development. All are aiming towards a contraceptive that is effective with the least adverse effects and complete reversibility. Testosterones, either alone or in combination with other agents, are effective in spermatogenesis suppression. However, there are concerns about the drug delivery route and side effects regarding a possible increased risk of metabolic syndrome. Several agents, inhibiting various steps of spermatogenesis, show promising results in animal models, including primates in one agent, but have yet to progress to human clinical trials. Regarding vas occluding agents, which are effective in animal models and phase I and II clinical trials, we are currently awaiting the results of the phase III clinical trial.

References

1. World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. United Nations, Department of Economic and Social Affairs PD; 2017.
2. Hardee K, Croce-Galis M, Gay J. Are men well served by family planning programs? Reprod Health 2017;14:14. doi:10.1186/s12978-017-0278-5
3. Aaltonen P, Amory JK, Anderson RA, Behre HM, Bialy G, Blithe D, et al. 10th Summit Meeting consensus: recommendations for regulatory approval for hormonal male contraception. J Androl 2007;28:362-363.
4. Turek PJ. Male Reproductive Physiology. In: Wein AJ, Kavoussi LR, W. PA, C. PA, editors. Campbell-Walsh Urology. Volume I. 10th ed. Philadelphia: Elsevier, Inc.; 2016. p. 516-519.
5. Kanakis GA, Goulis DG. Male contraception: a clinically-oriented review. Hormones 2015;14: 598-614.
6. World Health Organization Task Force on Methods for the Regulation of Male F. Contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet 1990;336:955-959.
7. World Health Organization Task Force on Methods for the Regulation of Male F. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 1996;65:821-829.
8. Zhang GY, Gu YQ, Wang XH, Cui YG, Bremner WJ. A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. J Androl 1998;19:761-768.
9. Gu Y, Liang X, Wu W, Liu M, Song S, Cheng L, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. J Clin Endocrinol Metab 2009; 94:1910-1915.
10. Singh AB, Hsia S, Alaupovic P, Sinha-Hikim I, Woodhouse L, Buchanan TA, et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab 2002;87:136-143.
11. Meyer WJ, 3rd, Walker PA, Emory LE, Smith ER. Physical, metabolic, and hormonal effects on men of long-term therapy with medroxyprogesterone acetate. Fertil Steril 1985;43:102-109.
12. Bebb RA, Anawalt BD, Christensen RB, Paulsen CA, Bremner WJ, Matsumoto AM. Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: a promising male contraceptive approach. J Clin Endocrinol Metab 1996;81:757-762.
13. Anawalt BD, Amory JK, Herbst KL, Coviello AD, Page ST, Bremner WJ, et al. Intramuscular testosterone enanthate plus very low dosage oral levonorgestrel suppresses spermatogenesis without causing weight gain in normal young men: a randomized clinical trial. J Androl 2005; 26:405-413.
14. Gui YL, He CH, Amory JK, Bremner WJ, Zheng EX, Yang J, et al. Male hormonal contraception: suppression of spermatogenesis by injectable testosterone undecanoate alone or with levonorgestrel implants in chinese men. J Androl 2004;25:720-727.
15. Mommers E, Kersemaekers WM, Elliesen J, Kepers M, Apter D, Behre HM, et al. Male hormonal contraception: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 2008; 93:2572-2580.
16. Behre HM, Zitzmann M, Anderson RA, Handelsman DJ, Lestari SW, McLachlan RI, et al. Efficacy and Safety of an Injectable Combination Hormonal Contraceptive for Men. J Clin Endocrinol Metab 2016;101:4779-4788.
17. Gu Y-q, Tong J-s, Ma D-z, Wang X-h, Yuan D, Tang W-h, et al. Male Hormonal Contraception: Effects of Injections of Testosterone Undecanoate

and Depot Medroxyprogesterone Acetate at Eight-Week Intervals in Chinese Men. J Clin Endocrinol Metab 2004;89:2254-2262.

18. Matthiesson KL, Amory JK, Berger R, Ugoni A, McLachlan RI, Bremner WJ. Novel Male Hormonal Contraceptive Combinations: The Hormonal and Spermatogenic Effects of Testosterone and Levonorgestrel Combined with a 5α-Reductase Inhibitor or Gonadotropin-Releasing Hormone Antagonist. J Clin Endocrinol Metab 2005;90:91-97.
19. Matthiesson KL, Stanton PG, O'Donnell L, Meachem SJ, Amory JK, Berger R, et al. Effects of Testosterone and Levonorgestrel Combined with a 5α-Reductase Inhibitor or Gonadotropin-Releasing Hormone Antagonist on Spermatogenesis and Intratesticular Steroid Levels in Normal Men. J Clin Endocrinol Metab 2005;90:5647-5655.
20. Amory JK, Bremner WJ. Oral Testosterone in Oil Plus Dutasteride in Men: A Pharmacokinetic Study. J Clin Endocrinol Metab 2005;90:2610-2617.
21. Amory JK, Kalhorn TF, Page ST. Pharmacokinetics and pharmacodynamics of oral testosterone enanthate plus dutasteride for 4 weeks in normal men: implications for male hormonal contraception. J Androl 2008;29:260-271.
22. Gonzalo ITG, Swerdloff RS, Nelson AL, Clevenger B, Garcia R, Berman N, et al. Levonorgestrel Implants (Norplant II) for Male Contraception Clinical Trials: Combination with Transdermal and Injectable Testosterone. J Clin Endocrinol Metab 2002;87:3562-3572.
23. Pöllänen P, Nikkanen V, Huhtaniemi I. Combination of subcutaneous levonorgestrel implants and transdermal dihydrotestosterone gel for male hormonal contraception. International J Androl 2001;24:369-380.
24. Ilani N, Roth MY, Amory JK, Swerdloff RS, Dart C, Page ST, et al. A new combination of testosterone and nestorone transdermal gels for male hormonal contraception. J Clin Endocrinol Metab 2012;97:3476-3486.
25. Mok KW, Mruk DD, Lie PP, Lui WY, Cheng CY. Adjudin, a potential male contraceptive, exerts its effects locally in the seminiferous epithelium of mammalian testes. Reproduction 2011;141:571-580.
26. Cheng CY, Silvestrini B, Grima J, Mo MY, Zhu LJ, Johansson E, et al. Two new male contraceptives exert their effects by depleting germ cells prematurely from the testis. Biol Reprod 2001;65:449-461.
27. Cheng CY, Mruk D, Silvestrini B, Bonanomi M, Wong CH, Siu MK, et al. 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.
28. Zdrojewicz Z, Konieczny R, Papier P, Szten F. Brdt Bromodomains Inhibitors and Other Modern Means of Male Contraception. Adv Clin Exp Med 2015;24:705-714.
29. Chen H, Mruk DD, Xia W, Bonanomi M, Silvestrini B, Cheng CY. Effective Delivery of Male Contraceptives Behind the Blood-Testis Barrier (BTB) - Lesson from Adjudin. Curr Med Chem 2016;23:701-713.
30. Tash JS, Attardi B, Hild SA, Chakrasali R, Jakkaraj SR, Georg GI. A Novel Potent Indazole Carboxylic Acid Derivative Blocks Spermatogenesis and Is Contraceptive in Rats after a Single Oral Dose1. Biol Reprod 2008; 78:1127-1138.
31. Ann Hild S, Reel JR, Larner JM, Blye RP. Disruption of Spermatogenesis and Sertoli Cell Structure and Function by the Indenopyridine CDB-4022 in Rats1. Biol Reprod 2001;65: 1771-1779.
32. Hild SA, Marshall GR, Attardi BJ, Hess RA, Schlatt S, Simorangkir DR, et al. Development of l-CDB-4022 as a nonsteroidal male oral

contraceptive: induction and recovery from severe oligospermia in the adult male cynomolgus monkey (Macaca fascicularis). Endocrinology 2007;148:1784-1796.

33. Teletin M, Vernet N, Ghyselinck NB, Mark M. Chapter Seven - Roles of Retinoic Acid in Germ Cell Differentiation. In: Forrest D, Tsai S, editors. Current Topics in Developmental Biology. 125: Academic Press; 2017. p. 191-225.
34. Schulze GE, Clay RJ, Mezza LE, Bregman CL, Buroker RA, Frantz JD. BMS-189453, a novel retinoid receptor antagonist, is a potent testicular toxin. Toxicol Sci 2001;59:297-308.
35. Chung SSW, Wang X, Roberts SS, Griffey SM, Reczek PR, Wolgemuth DJ. Oral Administration of a Retinoic Acid Receptor Antagonist Reversibly Inhibits Spermatogenesis in Mice. Endocrinology 2011;152:2492-2502.
36. Chung SSW, Wang X, Wolgemuth DJ. Prolonged Oral Administration of a Pan-Retinoic Acid Receptor Antagonist Inhibits Spermatogenesis in Mice With a Rapid Recovery and Changes in the Expression of Influx and Efflux Transporters. Endocrinology 2016;157:1601-1612.
37. Lohiya NK, Alam I, Hussain M, Khan SR, Ansari AS. RISUG: an intravasal injectable male contraceptive. Indian J Med Res 2014;140 Suppl:S63-72.
38. 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.
39. Guha SK, Singh G, Ansari S, Kumar S, Srivastava A, Koul V, et al. Phase II clinical trial of a vas deferens injectable contraceptive for the male. Contraception 1997;56:245-250.
40. Lohiya NK, Manivannan B, Mishra PK. Repeated vas occlusion and non-invasive reversal with styrene maleic anhydride for male contraception in langur monkeys. Int J Androl 2000;23:36-42.
41. Aribarg A, Chanprasit Y, Sukcharoen N, Ngeamvijawat J, Kriangsinyos R. Suppression of spermatogenesis by testosterone enanthate in Thai men. J Med Assoc Thai 1996;79:624-629.