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Pharmacologic Development of Male Hormonal Contraceptive Agents

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Abstract

The world population continues to increase dramatically despite the existence of contraceptive technology. The use of male hormonal contraception may help in preventing unintended pregnancies and managing future population growth. Male hormonal contraception relies on the administration of exogenous hormones to suppress spermatogenesis. Clinical trials have tested several regimens using testosterone, alone or in combination with a progestin. These regimens were shown to be >90% effective in preventing conception and were not associated with serious adverse events.

MALE HORMONAL CONTRACEPTION

Currently, the world population is ~6.9 billion, and it is increasing at the rate of 80 million persons a year.¹ It has been projected that the global population will exceed 9 billion by 2050, causing an unprecedented strain on global ecology and food supplies.² Much of the population growth is attributable to inadequate use of or lack of access to contraception.³ Improved methods of contraception are needed. In particular, little progress has been made in the development of new methods of male contraception. A survey revealed that a majority of men would be willing to use a reversible contraceptive,⁴ and women said they would be willing to rely on their male partner using contraception to avoid pregnancy.⁵

Research aimed at developing a male hormonal contraceptive has been under way for several decades. Male hormonal contraceptives suppress the function of the hypothalamic–pituitary–testicular axis to inhibit spermatogenesis. Normally, men secrete gonadotropin-releasing hormone in a pulsatile manner from the hypothalamus. This hormone stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LH binds to Leydig cells in the testicular interstitium to stimulate the production of testosterone, which is present in the testes at concentrations 100–200× those observed in the serum.⁶ This intratesticular testosterone diffuses into the seminiferous tubules, where it promotes spermatogenesis in conjunction with FSH-mediated stimulation of Sertoli cells. Testosterone synthesized in the testes also enters the bloodstream and, in combination with estradiol, serves to regulate its own production by negative feedback at the level of the hypothalamus and pituitary gland.

Male hormonal contraception capitalizes on this negative-feedback function of testosterone. Specifically, the administration of exogenous testosterone to men suppresses the secretion of LH and FSH, depriving the testes of the signals required for spermatogenesis and leading to markedly suppressed sperm counts in most men (Figure 1). Importantly, suppression of spermatogenesis by exogenous hormones appears to be uniformly reversible. Most men have normal sperm parameters within 6 months of discontinuing hormonal contraceptive regimens; however, in some men, the levels may take up to a year to return to baseline.⁷ However, in a minority of men, administration of testosterone alone fails to completely suppress sperm production. Therefore, recent research has studied combinations of testosterone and progestins, which synergistically suppress LH and FSH, to optimize suppression of spermatogenesis and contraceptive efficacy. The doses of testosterone and progestins studied were thought to be sufficient to suppress gonadotropins; are similar to those used for other indications, such as treatment of male hypogonadism and female contraceptives; and result in hormone levels being maintained within or near the normal range. There are minimal data to suggest that there are significant differences in gonadotropin or sperm suppression between different formulations of testosterone or progestins. Overall, no serious adverse events have been associated with male hormonal contraceptive regimens. Common adverse events include acne, suppression of high-density lipoprotein cholesterol, reversible reduction in testicular volume, and increase in hematocrit.⁸

In normal men, sperm concentrations exceed 15 million/ml ejaculate. The absence of sperm in the ejaculate, a condition called “azoospermia,” makes fertilization impossible. Therefore, universal induction of azoospermia in all men undergoing treatment is the ultimate goal of male hormonal contraceptive development. However, a sperm concentration <1 million/ml ejaculate—“severe oligozoospermia”—is associated with a risk of pregnancy of ~1% per year⁹ and is considered a reasonable goal for development of male contraceptive¹⁰ because it would confer an efficacy similar to that of female hormonal contraceptives.¹¹

Male hormonal contraceptives act by inhibiting sperm production, and in most men it takes 2–3 months for sperm concentration to be suppressed to the point of severe oligozoospermia;¹² this is similar to the interval required for a vasectomy to become fully effective. In addition, there are race-related differences in the response to testosterone-only male hormonal contraceptive regimens. In particular, Asian men exhibit rates of azoospermia in the 90–100% range on testosterone-alone regimens, whereas studies carried out in men in Europe, North America, and Australia show rates of azoospermia closer to 60% on very similar regimens.^{9,13} Although the reason for this difference is unclear, it is an important consideration when study results are compared between populations.

In this article, we review the hormonal agents that are currently in development for use as a male contraceptive. We review the recent clinical trials as well as the challenges and impediments to the development of a male hormonal contraceptive.

TESTOSTERONE UNDECANOATE

The first studies examining the contraceptive efficacy of a male hormonal contraceptive in couples were conducted by the World Health Organization and used testosterone enanthate administered as weekly intramuscular injections.^{9,13} These studies demonstrated that testosterone alone can function as an effective contraceptive agent in the majority of men. However, in some men, the administration of testosterone alone fails to suppress spermatogenesis to an extent sufficient for contraceptive purposes. In addition, 12% of the men withdrew from these studies because of their dislike of the weekly intramuscular injections.

More recent studies of testosterone as a single agent for male hormonal contraception have examined the very-long-acting formulation testosterone undecanoate (TU), which can be administered once every 10–12 weeks for testosterone replacement in men with hypogonadism.¹⁴ Two large studies in China have investigated the efficacy of TU used as a single agent for male contraception. The first enrolled 308 healthy men and their partners and administered TU to the men at a dosage of 500 mg once a month for 12 months.¹⁵ During the study, 299 men showed suppression in sperm concentrations to <3 million sperm/ml ejaculate, whereas nine men did not show suppression to this extent. Of the 299 men in whom sperm concentrations were suppressed to <3 million sperm/ml ejaculate, 296 entered an efficacy phase in which they and their respective sexual partners relied on the TU injections as their sole method of contraception. Among these 296 couples, six subsequently found it necessary to restart other forms of contraception because of rising sperm counts. One pregnancy occurred in this group, giving an overall efficacy rate of 95%. The hormonal and semen parameters of all the men returned to baseline values during the recovery period.

A larger phase III study, also in China, enrolled 1,045 men and their partners for a 30-month treatment period.¹⁶ Using a similar 500-mg monthly dosage of TU, this group also showed a 95% rate of suppression of spermatogenesis and a 95% contraceptive efficacy rate. With few dropouts from both studies, TU seems to be a highly acceptable, effective, safe, and reversible method of male contraception in Chinese men (Table 1). Unfortunately, TU was not approved for contraceptive purposes in China because of concerns on the part of regulatory authorities; however, it may prove to be a useful component of hormonal contraceptive regimens in other countries.

TU + PROGESTINS

TU has also been studied in combination with various progesterone agents because combined hormone treatments using testosterone and a progestin agent have shown higher rates of efficacy.^{7,17,18} Etonogestrel was originally designed as a long-acting contraceptive implant for women. A recent international, multicenter, double-blind, randomized, controlled trial evaluated two doses of etonogestrel implants combined with three-dose regimens of long-acting TU.¹⁹ A total of 354 healthy men, 98% of whom were Caucasian, were treated for a total of 42 or 44 weeks, depending on the dosing regimen. In the high-dose etonogestrel groups, 94% of the men showed suppression of spermatogenesis to ≤1 million/ml ejaculate, and these levels returned to baseline values in all the men after cessation of therapy. This method of contraception was well tolerated, safe, and effective; but the authors noted that alterations in the dosing regimen could potentially improve the efficacy rate.

Norethistrone enanthate, a long-acting injectable progestin with weak androgenic and estrogenic activity, shows great promise as an adjunct agent in combination with TU for male hormonal contraception. As with TU, norethistrone enanthate can be dosed at intervals; this allows for a combined injectable contraceptive regimen. A prospective 6-month contraceptive trial in 40 men, comparing TU alone vs. TU + norethistrone enanthate, showed more consistent suppression of spermatogenesis and serum gonadotropins with the combined regimen.²⁰ The World Health Organization is currently sponsoring a phase IIb contraceptive trial in 400 couples using TU and norethistrone enanthate injected once every 8 weeks for 48 weeks. This trial will provide additional data regarding the efficacy, safety, and tolerability of an injectable contraceptive regimen for men. Injections of medroxyprogesterone acetate have also been used in combination with injections of TU every 8 weeks, and this combination also resulted in similar, profound suppression of spermatogenesis (Figure 2).²¹

TRANSDERMAL TESTOSTERONE + PROGESTINS

Testosterone patches are a successful approach to the treatment of male hypogonadism but do not appear to be an effective method of androgen administration for male contraception, probably because lower peak serum levels of testosterone are less effective at suppressing gonadotropin secretion from the pituitary gland. In addition, skin reactions to the patch are a problem. For example, in a study combining testosterone patches with the progestin desogestrel, 24% of participants withdrew because of skin irritation from the patches.²²

Recently, testosterone gels have been marketed for treatment of hypogonadism. These gels achieve higher serum testosterone concentrations and are less irritating to the skin than the patches.²³ Testosterone gel was recently used as the androgen in a contraceptive trial in combination with injectable medroxyprogesterone acetate, resulting in good suppression of spermatogenesis.²⁴ Importantly, the gel appeared to be acceptable to a majority of the men enrolled in the study,²⁵ who stated that they would be interested in using this form of contraception were it available.

Transdermal gels can also be combined with transdermal progestins to create a completely noninjectable form of male hormonal contraceptive. One candidate for such a transdermal progestin is nestorone, a 19-norprogesterone derivative that lacks androgen or estrogen receptor binding activity.²⁶ Nestorone, initially developed as a female contraceptive, has negligible bio-availability when administered orally but is well absorbed as part of a transdermal gel. Recently, a multicenter, prospective, open-label, randomized trial was conducted to investigate the effect of nestorone, alone and in combination with testosterone gel, on gonadotropin suppression.²⁷ This study demonstrated that nestorone alone can suppress gonadotropins, and the combination resulted in dramatic reductions in serum levels of both LH and FSH, consistent with a good contraceptive effect. A 6-month contraceptive trial using the combination of nestorone and testosterone gels is currently under way to study the effect on spermatogenesis, acceptability, and long-term side effects of this gel/gel approach to male hormonal contraception.

FUTURE ANDROGENS FOR MALE HORMONAL CONTRACEPTION

Dimethandrolone undecanoate (DMAU) is a potent synthetic androgen that binds strongly to the progesterone receptor. DMAU can be administered either orally or by injection and has the potential to be a single-agent male hormonal contraceptive because it combines the necessary properties of testosterone and a progestin agent.²⁸ A 60-day study in rabbits comparing 2.5 and 5.0 mg/kg/day of DMAU showed suppression of gonadotropins and serum testosterone and severe oligospermia in all the rabbits in the 2.5 mg/kg/day dosage group.²⁹ Mating trials with the oligospermic rabbits showed that they were rendered infertile by DMAU treatment. Serum hormones and sperm parameters returned to normal in all the rabbits after cessation of DMAU therapy. To date, studies of DMAU have not been performed in humans, but such studies are in the planning stages.

Whereas several contraceptive regimens work to disrupt the hypothalamic–pituitary–gonadal axis using hormones similar to those naturally produced in men, there are also new nonhormonal medications being developed that may utilize the positive effects of hormones while avoiding some of the side effects. Several nonsteroidal, selective androgen receptor modulators have been described in the chemical literature,³⁰ similar to the selective estrogen receptor modulators developed for use in women. Selective androgen receptor modulators have the potential to act as agonists in some tissues while acting as antagonists in other androgen-responsive tissues. One such compound was shown to suppress spermatogenesis in rats by 75% after 10 weeks of treatment, but it had little effect on prostate growth.³¹ Although further animal testing will be required before these types of compounds can be

studied in humans, they are particularly appealing because they might allow for oral administration of the androgen component of future male contraceptive regimens and could, in theory, minimize adverse effects on the prostate and/or serum lipoproteins.

CONCLUSIONS

Studies have demonstrated the feasibility, acceptability, and efficacy of a hormonal approach to male contraception. Male hormonal contraceptive regimens have proven to be safe and reversible, with high efficacy and a low rate of side effects. Ongoing studies are attempting to further improve efficacy because not all men achieve adequate suppression of spermatogenesis despite high degrees of gonadotropin suppression. Hopefully, ongoing studies will result in efficacy rates that are high enough to lead to phase III testing.

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Figure 1.

The mechanism of action of male hormonal contraception. The normal stimulation of the hypothalamic–pituitary–testicular axis is highlighted with green arrows. Exogenous testosterone, alone or in combination with a progestin, mimics the negative feedback of endogenous testosterone at the hypothalamus and pituitary, thereby suppressing LH and FSH secretion. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Figure 2.

Mean sperm concentrations in men treated with 1,000 mg TU every 8 weeks alone (diamonds) or in combination with 150 mg (squares) or 300 mg (triangles) of MPA every 8 weeks (arrows). All 20 subjects in the TU/MPA groups achieved azoospermia by week 20 of treatment. MPA, medroxyprogesterone acetate; TU, testosterone undecanoate. Reprinted from ref. 19. Copyright 2004 The Endocrine Society.

Table 1

Trials of male hormonal contraceptives examining effectiveness at preventing pregnancy

Study	Regimen	Number of couples	Azoospermic (%)	Oligozoospermic (%)	Failure to suppress (%)	Pregnancies (%)	Total failures (%)	Overall efficacy (95% CI)
WHO ⁹	Testosterone enanthate 200 mg i.m. weekly	357	268 (75)	81 (23)	8 (2.2)	11 (3.1)	19 (5.3)	94.7 (92–97)
Gu <i>et al.</i> ¹⁵	Testosterone undecanoate 500 mg i.m. monthly	305	130 (43)	166 (54)	9 (2.9)	1 (0.3)	10 (3.3)	96.7 (95–98)
Turner <i>et al.</i> ¹⁷	Testosterone implant + medroxyprogesterone 300 mg i.m. every 3 months	53	49 (93)	2 (3.6)	2 (3.6)	0 (0.0)	2 (3.6)	96.4 (91–100)
Gu <i>et al.</i> ¹⁶	Testosterone undecanoate 500 mg i.m. monthly	898		855 ^a (95.2)	43 (4.8)	9 (1.0)	52 (5.8)	94.2 (93–96)

CI, confidence interval; IM, intramuscularly; WHO, World Health Organization.

^a855 Men in this study suppressed spermatogenesis to <1 million sperm/ml ejaculate.