CURRENT OPINION

Testosterone and male contraception

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Purpose of review
Rates of unintended pregnancy have remained relatively stagnant for many years, despite a broad array of female contraceptive options. Recent restrictions on access to abortion in some countries have increased the urgency for expanding contraceptive options. Increasing data suggest men are keen to utilize novel reversible male contraceptives.

Recent findings
Despite decades of clinical research in male contraception, no reversible hormonal product currently exists. Nestorone/testosterone, among other novel androgens, shows promise to finally move to pivotal Phase 3 studies and introduction to the marketplace.

Summary
Hormonal male contraception utilizes androgens or androgen-progestin combinations to exploit negative feedback that regulates the hypothalamic-pituitary-testicular axis. By suppressing release of gonadotropins, these agents markedly decrease endogenous testosterone production, lower intratesticular testosterone and suppress spermatogenesis. The addition of a progestin enhances the degree and speed of sperm suppression. The androgen component preserves a state of symptomatic eugonadism in the male. There is growing demand and acceptance of male contraceptive options in various forms. As these formulations progress through stages of drug development, regulatory oversight and communication with developers around safety and efficacy standards and garnering industry support for advancing the production of male contraceptives will be imperative.

Keywords
androgens, male contraception, nestorone/testosterone, testosterone

INTRODUCTION

Unintended pregnancies result in considerable social, economic, and medical burdens for women and are associated with significant adverse family outcomes [1]. Despite considerable expansion of female contraceptive options, over the last 3 decades, the global rate of unintended pregnancies has only modestly declined, with notable increases in the percentage ending in abortion [2]. With considerable global restrictions on access to safe abortion, and in some cases like the United States *increasing* restrictions to access, there is an urgent need to prevent unplanned pregnancies. While there are multiple female contraceptive options on the market, some with intolerable side effects or contraindications for use, male contraceptive methods are severely limited. The condom, introduced in the 18th century [3] and associated with a high failure rate (13%) [4] and vasectomy, which is invasive, costly, and not easily or reliably reversible [5] make up the entire male contraceptive menu. Novel male contraceptives are urgently needed to reduce unplanned pregnancies and androgen-based hormonal male contraceptives (HMCs) are likely to be part of the future male contraceptive mix.

Development of contraceptive options for males has biological and social undercurrents. Historically, the burden of contraception has been borne by women, who face the physical and economic consequences of pregnancy. Additionally, there are long-held beliefs that women will not trust men to reliably use a contraceptive method or find contraceptives unappealing. However, more recent surveys have demonstrated that men welcome the concept of male-driven contraceptives [6,7] and that women in stable relationships would trust their

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KEY POINTS

- There is an unmet need for novel methods to prevent unplanned pregnancy; male hormonal contraceptive methods which are reversible and effective could help fill this gap within the next decade.
- Male hormonal contraception utilizes exogenous androgen, usually testosterone, plus a progestin to interrupt normal hypothalamic-pituitary-testes endocrine homeostasis resulting in suppression of spermatogenesis.
- Clinical efficacy trials of more than 2000 couples have demonstrated the male hormonal methods are well tolerated, effective, reversible and acceptable to users; a pivotal Phase 3 study involving 5–10 000 couples will likely be required to get these methods to the market.
- Exogenous testosterone, or an equivalent androgen, is a necessary component of male hormonal contraceptive regimens and can be given at physiologic dosing; data support that dosing in the physiologic range is well tolerated and effective for men using these methods.

partners to use them [8,9]. Physiologic challenges in developing male methods have included blocking production of the millions of sperm men make each day while quantifying sperm thresholds compatible with effective contraception. Furthermore, a full cycle of spermatogenesis spans 74 days [10], thereby conferring a time lag of 4–12 weeks before both becoming effective and reversal. The addition of progestogenic agents to testosterone as male hormonal contraceptives has enhanced the speed and degree of suppression of spermatogenesis, largely overcoming these challenges [11].

Herein, we review the seminal work that has advanced the field of male hormonal contraception, highlight the current agents in development and attempt to forecast advances in the years ahead.

PHYSIOLOGY OF MALE REPRODUCTION

In healthy men (Fig. 1a), gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and released into the hypophyseal portal circulation where it acts on the anterior pituitary to release gonadotropins – luteinizing hormone (LH) and follicle stimulating hormone (FSH)-into the circulation. Within the testes, LH stimulates Leydig cells to secrete testosterone, a vital prerequisite for spermatogenesis [12,13], while FSH stimulates Sertoli cells facilitating spermatogenesis. Systemically, testosterone binds to androgen receptors to exert androgenic activity in nongonadal tissues and exerts negative feedback upon the hypothalamus and pituitary to suppress GnRH and gonadotropin production. Testosterone is also aromatized to estradiol, which further contributes to the suppression of GnRH and gonadotropin production [14]. Testosterone is also reduced by 5-alpha-reductase to dihydrotestosterone [15], primarily acting within the prostate and hair follicles.

HMC methods disrupt the hypothalamic-pituitary-testicular axis to suppress spermatogenesis (Fig. 1b). Like female hormonal contraceptives, exogenous sex-steroids suppress the release of GnRH, LH and FSH thereby interrupting spermatogenesis. Meanwhile, nongonadal sex-steroid sensitive tissues are maintained by the exogenously provided androgen, historically exogenous testosterone. Progestins also exert negative feedback at the hypothalamus and pituitary and their inclusion in HMC results in more

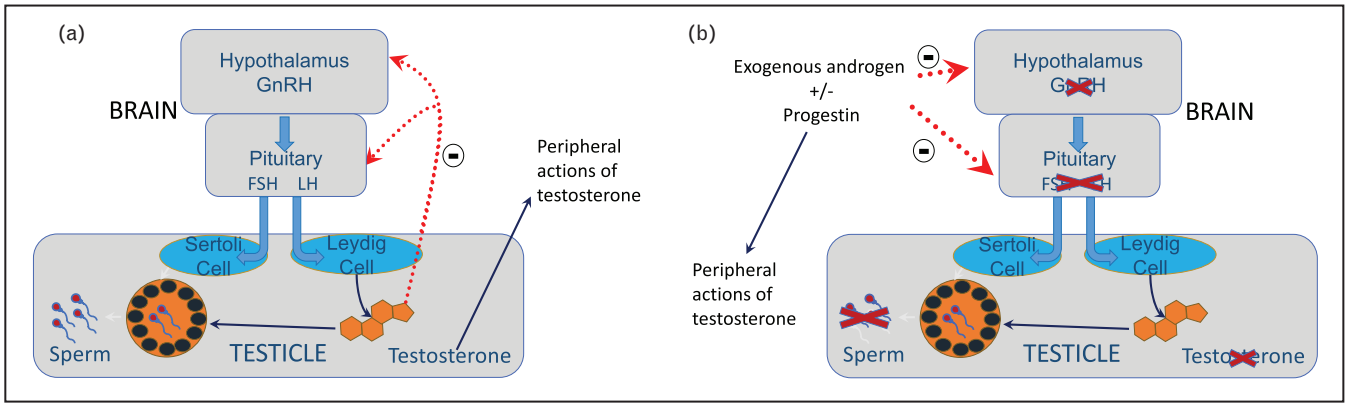

FIGURE 1. Hypothalamic-pituitary-gonadal axis physiology and with contraceptive agents. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T, testosterone. (a) shows the normal functioning of the axis with the feedback inhibition exerted by T to keep the loop in check. (b) shows the functioning of the axis under the effects of a male hormonal contraceptive regimen, whereby the production of endogenous T and sperm is inhibited, yet maintaining peripheral actions of T. Figure reused with permission from Thirumalai and Page [16] (License number: 5815380841177).

rapid and profound suppression of spermatogenesis [17]. Importantly, all these effects are entirely reversible with cessation of HMC [18].

Clinical development of effective HMC has unique challenges. Following Phase 1 trials demonstrating safety and tolerability in men, Phase 2 studies must demonstrate effectiveness in suppressing spermatogenesis prior to evaluation as a contraceptive. Phase 2b efficacy trials must evaluate the effectiveness of these novel methods at preventing pregnancy and therefore enroll couples who rely solely on the investigational regimen for contraception. Phase 2b studies employ study designs that help minimize pregnancy risk by, for example, measuring sperm counts during the efficacy period. To date, despite several successful Phase 2b trials, no HMC has reached a Phase 3 study wherein enrolled couples would use the investigational HMC as their sole contraceptive with minimal monitoring during use to allow for calculation of a 'typical use' pregnancy rate. This hurdle must be overcome for HMC to reach the market.

HORMONAL MALE CONTRACEPTIVE EFFICACY TRIALS

HMC efficacy trials conducted over the last 5 decades are outlined in detail in prior reviews [19,20] and encapsulated in Table 1. Two initial efficacy trials conducted by the WHO used intramuscular (i.m.) testosterone enanthate dosed supra-physiologically (200 mg i.m./week). The first used a strict criterion of azoospermia (zero sperm in ejaculate) to allow couples to enter the study efficacy phase; one pregnancy occurred but only 70% of the participants reached azoospermia and qualified for the efficacy phase [21]. In the second study, a more permissive threshold of 3 million sperm/ml or less of ejaculate (severe oligozoospermia) was used to enter efficacy; 98% of men achieved this with a failure rate of 1.4%, comparable to typical use of the female contraceptive pill [22]. However, the high dose of androgen in these trials was associated with side effects, including mood changes, changes in libido, acne, polycythemia, weight gain and hypertension. The weekly injection regimen was also burdensome and discontinuation rates in these trials were high (33–55%). Importantly, the WHO trials demonstrated that a sperm threshold of 1 million sperm/ml or less of ejaculate optimizes contraceptive efficacy comparable to female oral contraceptives with 90–95% of men reaching that threshold.

To avoid the need for weekly injections, implantable testosterone preparations dosed every 3 months were evaluated [24]. While 70% of men achieved threshold sperm suppression and no pregnancies were observed in 214 months of exposure, there was concern around painful implant extrusion in some participants. Similarly, testosterone pellets implanted very 4–6 months in combination with depot intramuscular medroxyprogesterone acetate (DMPA) 300 mg every 3 months was studied by Turner *et al.* [25]. Notably, this was the first HMC efficacy trial to utilize an androgen-progestin combination. Over 96% of participants achieved the target sperm threshold of less than 1 million/ml of ejaculate and maintained it during the 1-year efficacy phase during which no pregnancies occurred.

Concurrently, Gu *et al.* [26] evaluated the contraceptive efficacy of i.m. testosterone undecanoate every month in China. Ninety-seven percent of men achieved azoospermia or severe oligozoospermia (<3 million sperm/ml of ejaculate) during the 6-month suppression phase, and there were no pregnancies during the 6-month efficacy phase in men who maintained that degree of sperm suppression. Two percent of men demonstrated sperm rebound above the suppression thresholds and one pregnancy, attributed to sperm rebound, resulted in overall nearly 95% contraceptive efficacy. A subsequent Phase 2 efficacy trial of the same regimen, using a sperm suppression threshold of 1 million/ml or less to enter efficacy [27] noted an overall failure rate of 6.1%, including 4.8% failure to suppress, 1.3% postsuppression sperm rebound, and nine pregnancies during the 24-month efficacy phase. The most common side effects included acne in 7% of participants, and severe coughing lasting minutes after the large volume injections. Overall, despite these promising results, there has been a move away from androgen-only male contraceptive regimens due to concerns regarding long-term, supraphysiologic testosterone exposure.

A large Phase 2 efficacy study across four continents [28] using i.m. testosterone undecanoate in combination with i.m. norethisterone enanthate (progestin), dosed every 8 weeks was completed in 2012. Ninety-six percent of men achieved the sperm suppression threshold of less than 1 million/ml within 26 weeks, and a 56-week efficacy phase was planned. However, the study was terminated prematurely by an independent safety committee, due to concerns for increased frequency of moderate to severe depression reported predominantly at one study site. Other side effects included weight gain, erythrocytosis, acne, altered libido and injection site pain. Four pregnancies occurred during the trial. Despite early termination of the study, more than 90% of participants, including both men and women, reported they would have continued using the method if it had been available. Overall, this

Table 1. Male contraceptive efficacy studies: T alone and T plus progestin

Study (Reference)	Progestin	Androgen	Sperm threshold	Individuals completing suppression phase N	Individuals reaching sperm threshold N (%)	Number completing efficacy	Number of pregnancies	Failure rate[a]
T alone								
WHO 1990 [21]	none	TE 200 mg/week	0	225	157 (69.8)	119	1	0.8 (0–4.5)
WHO 1996 [22]	none	TE 200 mg/week	<3 million/ml	357	349 (97.8)	209	4	1.4 (0.4–3.7)
McLachlan *et al.* [24]	none	T implants 800 or 1200 mg/4 months	<1 million/ml	29	21 (72)	16	0	–
Gu *et al.* [26]	none	TU 1 g load + 500 mg/month	<3 million/ml	308	299 (97.1)	280	1 (in sperm rebound)	2.3 (0.5–4.2)
Gu *et al.* [27]	none	TU 1 g load + 500 mg/month	<1 million/ml	898	855 (95.2)	733	9	1.1 (0.4–1.8)
T plus progestin								
Turner *et al.* [25]	depot medroxyprogesterone acetate (DMPA)	T implants 4–6 monthly + DMPA 300 mg/3 months	<1 million/ml	55	53 (94)	30	0	-
Soufir *et al.* [58] [b]	medroxyprogesterone acetate (MPA)	T gel (50–125 mg/day) + MPA 20 mg/day	<1 million/ml	29	27 (93)	25	1	0.3
Behre *et al.* [28]	norethisterone enanthate (NET)	TU 1000 mg + NET 200 mg/8 weeks	<1 million/ml	283	274 (95.9)	111[c]	4	2.2 (0.8–5.8)

T, testosterone; TE, testosterone enanthate; TU, testosterone undecanoate.
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[a]Failure rate: pearl rate (95% confidence interval) per 100 couple-years (can only be calculated if there are any pregnancies).
[b]This was a pilot study that had a subset of men enter an efficacy phase of the trial.
[c]Study terminated early.

study contributed significantly to understanding the effectiveness of HMC and highlighted the importance of evaluating any potential mental health impacts of HMC going forward.

Most recently, a large phase 2b efficacy trial of a combined testosterone and segesterone acetate (Nestorone) transdermal gel, spanning 17 sites across 4 continents, is expected to conclude in 2024 [29▪]. A prior 24-week study compared sperm suppression in men receiving either testosterone gel alone or testosterone gel in combination with Nestorone gel (8–12 mg/day) found that 23% of men in the testosterone-alone arm suppressed sperm production to less than 1 million/ml, while in the combination group, more than 88% of men achieved this threshold [30]. Adverse events were minimal, and only 5 of 99 enrolled men discontinued due to (possibly) drug-related side effects. This novel regimen is the first user-administered HMC to be evaluated in a multisite efficacy study. User-driven methods may appeal to some men given the ease of use; however, user-administered methods may increase nonadherence and complicate interpretation of method failure. Concerns regarding hormone transfer to nonusers with transdermal hormone delivery have been raised [31] prompting evaluation of transfer of Nestorone/Testosterone gel. Similar to testosterone transdermal gels (prescribed to treat male hypogonadism), users of Nestorone/Testosterone gel wearing a shirt during prolonged, intense skin to skin contact or showering 2 h after gel application mitigates transfer to others [32]. Results of the Phase 2b efficacy trial are expected in early 2025, with positive results perhaps supporting the first Phase 3 HMC trial.

ADDITIONAL HORMONAL CONTRACEPTIVE METHODS USING TESTOSTERONE OR NOVEL ANDROGENS

Gonadotropin-releasing hormone antagonists

While 90–95% of men in testosterone-progestin HMC trials reach contraceptive sperm thresholds (<1 million sperm/ml) maximal sperm suppression is not universal. In addition, some men experience increases in sperm production, termed 'sperm rebound' despite reporting adherence to the HMC method. No definitive mechanism underlying incomplete sperm suppression and sperm rebound has been demonstrated but, in some cases, incomplete gonadotropin suppression may contribute. In an attempt augment gonadotropin suppression beyond that provided by exogenous testosterone with or without progestins, GnRH antagonists have been evaluated to augment HMC. A daily subcutaneous injection of the GnRH antagonist Nal-Glu in combination with weekly injections of i.m. testosterone enanthate, showed initial promise [33,34], but the combination failed to confer any benefit in contraceptive effectiveness over testosterone monotherapy [35]. The GnRH antagonist cetrorelix, in conjunction with 19-nortestosterone showed effective suppression to azoospermia in a small pilot study, but daily subcutaneous injections are suboptimal for contraception [36]. The GnRH antagonist, acyline has a 2-week duration of action, is a more practical adjunct; however, the incorporation of acyline into a regimen of testosterone and DMPA failed to accelerate or enhance the spermatogenic suppression achieved by the testosterone-DMPA combination [37]. With the introduction of oral GnRH antagonists [38] and testosterone [39], there is the potential to re-evaluate GnRH antagonists as part of an oral androgen-based HMC in the future.

7-Alpha-methyl-19-nortestosterone

MENT, a 19-nortestosterone derivative, was investigated as an implantable, long-acting HMC in the early 2000 s. MENT is aromatized but not 5-alpha reduced, and thus is considered 'prostate sparing' given the high concentration of 5-alpha reductase within the prostate [40,41]. MENT implants plus etonorgestrel were compared to equivalent doses of testosterone pellets plus etonorgestrel in a 12-month sperm suppression study. While both regimens resulted in sperm suppression at 12 weeks, in the MENT group, suppression was not sustained over the 12-month follow-up period [42]. Pharmacokinetic data demonstrated inconsistent MENT release from the implants as the likely explanation for sperm rebound, but further development of MENT has stalled. Conceptually, MENT remains a viable and attractive androgen for male contraceptive development.

Dimethandrolone undecanoate and 11-beta-methyl-19-nortestosterone

Two orally bioavailable 19-nortestosterone derivatives, 7-alpha, 11-beta-dimethyl-19-nortestosteorne undecanoate (DMAU) and 11-beta-methyl-19-nortestosterone (11βMNTDC) are under investigation as oral, daily administered male contraceptives. Both are converted *in vivo* by esterases to their respective active compounds, DMA and 11βMNT, which activate both androgen and progesterone receptors [43], conferring the potential to act as single-agent HMC. Neither DMA nor 11βMNT require 5-alpha reduction to achieve androgenic

effects [44], and neither is aromatized to an aromatic A-ring compound [45]. Preclinical studies of DMAU and 11βMNT demonstrated reversible suppression of gonadotropins, spermatogenesis and fertility, while preserving nongonadal androgenic action in animal studies [46–48]. Two formulations of DMAU are in clinical trials, oral and injectable. Both oral DMAU and 11βMNT require co-administration with a meal to achieve maximal and effective absorption [49]. A 28-day dose finding study of oral DMAU 100–400 mg demonstrated safety and tolerability in healthy men, with suppression of serum gonadotropins to less than 1 IU/l and testosterone to less than 50 ng/dl [50]. Despite these very low levels of testosterone, the participants did not experience significant hypogonadal symptoms, likely due to the high affinity of DMA for the androgen receptor (approximately four-fold that of testosterone) [43] supporting peripheral androgen effects. Weight gain (1.5–3.8 kg), increased hematocrit (up to 2%), reduction in HDL cholesterol (6–15 mg/dl), acne and altered libido were reported, also likely due to androgen effects. Interestingly, a posthoc analysis found that despite its lack of aromatization, DMAU administration was associated with a significant increase in serum P1NP, a marker of bone formation, with no changes to bone resorption markers [51], suggesting minimal short-term impact on bone. A subsequent 12-week study of oral DMAU alone or in combination with low-dose oral levonorgestrel to evaluate sperm suppression has been conducted (NCT03455075) and an injectable form of DMAU is also in human trials (NCT02927210). Like DMAU, a 28-day daily dosing study of 11βMNTDC demonstrated profound suppression of serum testosterone levels and gonadotropins [52]. Side effects were similar to those observed with DMAU, although some men reported decreased libido (16%), altered mood (13%), fatigue (13%) and erectile or ejaculatory dysfunction (10%), suggesting at the doses used 11βMNTDC may not be as androgenic as DMAU and may favor progestational activity. Such differences in androgen and progestin activity likely underlie the modest differences in metabolic effects of these 19-nortestesterone derivatives [53]. Future development of DMAU and 11βMNTDC as oral male contraceptives are contingent on demonstrating effective sperm suppression in longer studies.

CONCLUSION: FUTURE DEVELOPMENT OF HORMONAL MALE CONTRACEPTIVES

Clinical trials over the last 50 years have demonstrated the effectiveness and safety of androgen-based HMC. Importantly, recent data from older men has provided additional reassurance regarding the safety of exogenous testosterone when given at physiologic dosing [54–56], the backbone of combined androgen-progestin HMC. So why is there no HMC on the market? To perform pivotal Phase 3 studies, both funding and regulatory guidance is required to allow developers to appropriately evaluate longer term safety and efficacy. Surveys of men and women suggest a rapidly expanding desire for male contraceptive options and interest in sharing the burden of contraception [57]. Co-ordinated efforts between investigators, regulators, investors and the public are required to get male contraceptives to the market, a need that is increasingly urgent in the face of the economic and health impacts of unplanned pregnancies. Such efforts will hopefully result in novel, reversible male contraceptives in the next decade.

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- ■■ of outstanding interest

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