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Male contraception

Jing Chao, MD^a, Stephanie T. Page, MD, PhD^a [Professor], and Richard A. Anderson, MD, PhD, FRCOG^{b,*} [Professor]

^aDivision of Endocrinology and Diabetes, University of Washington, Seattle, USA

^bMRC Centre for Reproductive Health, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Abstract

Clear evidence shows that many men and women would welcome new male methods of contraception, but none have become available. The hormonal approach is based on suppression of gonadotropins and thus of testicular function and spermatogenesis, and has been investigated for several decades. This approach can achieve sufficient suppression of spermatogenesis for effective contraception in most men, but not all; the basis for these men responding insufficiently is unclear. Alternatively, the nonhormonal approach is based on identifying specific processes in sperm development, maturation and function. A range of targets has been identified in animal models, and targeted effectively. This approach, however, remains in the pre-clinical domain at present. There are, therefore, grounds for considering that safe, effective and reversible methods of contraception for men can be developed.

Keywords

spermatogenesis; contraception; testis; testosterone

Introduction

Childbearing and rearing directly affect women's health, lifestyle, and economy. As a result, research and efforts in family planning have traditionally focused more on female methods of contraception. A wide range of reversible contraceptive choices have become available to women over the past 50 years; however, male contraceptive methods remain limited. Condoms, introduced 300–400 years ago, provide protection against sexually transmitted diseases when used properly, but are associated with high contraception failure rates, with 12 out of 100 couples conceiving during their first year of use. Vasectomy, a safe and simple outpatient surgical procedure, has a failure rate of less than 1%, but may require several months to achieve full contraceptive efficacy, and vasectomy reversal is costly and

*Corresponding author. Tel.: +44 1312426386. Richard.anderson@ed.ac.uk (R.A. Anderson).

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unreliable. Recent studies have shown that both men and women of different races, religions, and ethnicities are increasingly interested in novel male methods of contraception [1–3]. The ideal male contraception would rapidly achieve consistent and fully reversible azoospermia without adverse effects, such as interference with libido or prostatic enlargement. Optimally, it would provide additional health benefits such as chemoprevention or an increase in quality of life.

Hormonal and non-hormonal pharmacological methods are being investigated for male contraception. Hormonally based male contraceptive methods are based on suppression of the hypothalamic–pituitary–gonadal axis and thus of spermatogenesis (Fig. 1). Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus leads to pulsatile release of luteinising hormone and follicle-stimulating hormone (FSH) from the pituitary gland into the circulation. Luteinising hormone stimulates Leydig cells of the testes, leading to testosterone production. Follicle stimulating hormone interacts with Sertoli cells, supporting spermatogenesis. Both FSH and luteinising hormone are required for normal spermatogenesis to occur in men. Maximal suppression of both hormones usually results in azoospermia [4], although, in many of the studies described below, a proportion of men continue to produce low concentrations of sperm in the ejaculate. This dual hormonal control of spermatogenesis is regulated by the negative feedback of testosterone (and to a lesser extent of inhibin B) to the hypothalamus and pituitary gland. Therefore, administration of exogenous testosterone suppresses the production of GnRH, luteinising hormone, and FSH, causing a reversible inhibition on endogenous testosterone production and spermatogenesis.

Non-hormonal contraceptive agents aim at disrupting spermatogenesis or the sperm-egg interactions by interfering with sperm motility or processes involved in fertilisation. The theoretical advantages of non-hormonal contraception include target specificity, which could minimise the systemic side-effects that may be associated with the hormonally based agents, and the possibility of having a more rapid onset of action.

In this review, we first summarise recent advances in male contraception, with emphasis on newer regimens that may be introduced into clinical practice in the near future.

Male hormonal contraceptive methods

The goal of male hormonal contraception is the sufficient inhibition of spermatogenesis to result in azoospermia; however, early studies of male hormonal contraception showed that a sperm concentration less than 1 million/ml, classified as ‘severe oligospermia’ is associated with a low pregnancy rate (about 1% per year), an efficacy similar to that of the female hormonal contraceptives [5]. Therefore, severe oligospermia is considered a standard for a male hormonal contraceptive, and is currently used as an end point in clinical development of these methods. An interval of 2–3 months is required for male hormonal contraceptives to reach their full effect, similar to the time required for vasectomy to become fully effective.

Hormonal contraceptive agents lead to the suppression of endogenous testosterone production via negative feedback on the hypothalamus and the pituitary gland. Therefore, it is important to replace peripheral testosterone with sufficient androgen administration to

prevent the development of symptoms related to androgen deficiency, such as low libido, erectile dysfunction, changes in mood and behaviours, and disturbance of certain metabolic processes. On the contrary, supraphysiological dosing of testosterone may be associated with unwanted side-effects, such as acne, an increase in haemoglobin concentrations, and a decrease in high-density lipoprotein (HDL) cholesterol. Therefore, it is prudent for hormonal regimens to aim to maintain serum testosterone levels, and, by extension, androgen action at target tissues, within the normal, physiologic range.

Testosterone alone as a male hormonal contraceptive

Testosterone enanthate—After many years of development studies, The World Health Organization (WHO) conducted two large, multicentre, male hormonal contraceptive efficacy trials between the late 1980s and early 1990s, using intramuscular testosterone enanthate as a single agent contraceptive. These ‘proof of concept’ trials showed that testosterone enanthate is a reversible and effective contraceptive regimen in most men. In the first study [6], 65% of the men became azoospermic after a mean of 4 months, with 0–0.8 pregnancies per 100 person-years, equivalent to an efficacy rate of over 99%. An additional 30% of men became oligospermic (<3 million sperm/ml). The second WHO study enrolled 399 mostly Asian men who were given 200mg testosterone enanthate by weekly injection [5]. All but eight men (2%) became azoospermic or oligospermic, with overall fertility decreasing to a rate of 8.1 pregnancies per 100 person-years. Notably, none of the men who became azoospermic fathered a pregnancy. After the cessation of testosterone injections, sperm production of all subjects returned to normal.

No serious adverse events occurred in these trials, and well-being, quality of life, sexual function, and cognitive function were maintained or slightly improved in men receiving testosterone enanthate compared with baseline. [7,8] Several major disadvantages, however, render testosterone enanthate as a single agent hormonal contraceptive impractical: a delay between first dose to contraceptive effectiveness of 3–4 months, the potential for fertility in the few men who fail to suppress their sperm concentration to below 1 million sperm/ml, and the inconvenient frequency of weekly injections. Side-effects seemed to be dose-related and reversible, including acne, weight gain, a decrease in testicular volume, an increase in haemoglobin, and a 10–15% decrease in serum HDL cholesterol reflecting the supraphysiologic levels of serum testosterone from this regimen. Nevertheless, these were important studies that demonstrated reversible contraceptive efficacy in large numbers of men.

Testosterone undecanoate—The development of a long-acting formulation of injectable testosterone took a long time to reach clinical practice. Injectable testosterone undecanoate allows for one injection every 10–12 weeks for testosterone replacement in men with hypogonadism. Two large studies conducted in China showed that testosterone undecanoate is a highly acceptable, effective, and safe agent for male contraception. Both studies administered 500 mg of testosterone undecanoate monthly as a single agent. The first study found that 299 out of 308 men enrolled achieved either azoospermia or oligospermia (<3 million sperm/ml) [9], and went on use testosterone undecanoate injections as a sole means of contraception for 1 year. Six men were subsequently found to have rising sperm

concentrations despite testosterone undecanoate injections, and the overall contraceptive efficacy was 96.7%. A subsequent phase III study conducted in China enrolled 1045 men and showed that 94% of the men in the study attained severe oligospermia, with a fertility rate of 1.1 per 100 men after 30 months of treatment, and a similar overall contraceptive efficacy of 95% [10].

Testosterone undecanoate treatment resulted in a slower recovery time for spermatogenesis compared with testosterone enanthate. Discomfort at the site of injection was the main adverse effect, followed by acne (reflecting the supraphysiological dose of testosterone), and a small decrease in testis volume. Other dose-related side-effects, including increases in haemoglobin, are of particular concern for the widespread application of this approach.

Most importantly, the contraceptive efficacy of testosterone-only regimens is not uniform. Although Asian men attain high rates of azoospermia (90–100%), only 60% of white men do so [11]. The basis of these ethnic differences has not been elucidated, but adjunctive therapies are clearly required to achieve appropriate efficacy in combination with testosterone across ethnic groups.

Testosterone pellets—Implantable testosterone pellets offer an alternative route of delivery, achieve steady testosterone concentrations, and need to be replaced only every 3–6 months. Testosterone pellets have been investigated alone but, as with injectable testosterone, combinations with progestogens were more effective. Two contraceptive studies have examined the efficacy of testosterone pellets combined with etonogestrel implants, and found an overall rate of azoospermia of 85% (83 out of 98 men) [12,13]. Similarly, the combination of testosterone pellets and depomedroxyprogesterone (DMPA) was both efficacious and well tolerated in a pilot efficacy study among couples in Australia [14] (discussed below). Testosterone given in the form of pellets seems to have only minor, if any, affect on HDL cholesterol, and these regimens had few side-effects. Although the long-term clinical implications remain unclear, minimising the non-reproductive effects of contraceptive regimens remains desirable for widespread use.

Transdermal testosterone—Transdermal testosterone may be delivered via patches or gels. The former has been used successfully to restore eugonadism in men with hypogonadism. Even when testosterone patches are combined with a progestin, however, they have not proven to be an effective method for male contraception [15,16], with fewer than 50% of men achieving oligo- or azoospermia, presumably because lower amounts of testosterone were delivered overall as well as a lack of high peak levels incompletely suppressing the secretion of the gonadotropins. Moreover, patches are associated with a high frequency of skin irritation, leading to the discontinuation in nearly one-quarter of the participants in one study [16].

Testosterone gel has shown efficacy in the treatment of hypogonadism and superior suppression of spermatogenesis compared with the testosterone patches when combined with a progestin. Testosterone gel alone has not been tested as a contraceptive. The combination of daily testosterone gel and intramuscular DMPA every 3 months resulted in severe oligospermia in 90% of participants [17] (see below). Side-effects of this regimen

were well-tolerated and reversible, and included mild acne, mild weight gain, a small decrease in HDL cholesterol and total cholesterol, whereas the haematocrit remained unaffected, the latter reflecting the lack of high peak levels of testosterone [18].

Contraceptive regimens using testosterone gels cause less skin irritation and are quite acceptable to men [19]. Disadvantages include the need for daily application and the potential for transfer to female partners or children. This can be avoided if these products are used as directed, however, and men are counselled about appropriate timing of application and washing.

Testosterone–progestin combinations

Progestins act as adjunct male contraceptive agent with testosterone, enhancing inhibition of gonadotropin secretion leading to improved sperm suppression [20]. Progestins may also have direct testicular effects, which may further modulate spermatogenesis or spermatation [21].

A variety of progestins have been used in combination with testosterone in contraceptive trials (Table 1). These steroids vary in structure, resulting in degrees of androgenic compared with purely progestational activity. First- and second-generation progestins (estrans and first-generation gonanes, respectively) are derivatives of 19-nortestosterone and tend to be androgenic (although such considerations are more relevant for female administration than for men), whereas third- and fourth-generation progestins have less androgenic activity.

Levonorgestrel and testosterone—Levonorgestrel is a first-generation gonane that has been used extensively in women, and has the advantage of good oral bioavailability. It has been used in a number of small male hormonal contraceptive trials in combination with testosterone, including a series of studies examining low-dose titration in an effort to limit side-effects. A randomised-controlled trial that enrolled 36 white men showed that the combination of levonorgestrel and testosterone enanthate led to higher incidence of azoospermia and severe oligospermia compared with testosterone enanthate alone [22]. The levonorgestrel-testosterone enanthate combination group had more weight gain and greater decline in HDL cholesterol. When levonorgestrel was used at a much lower dose, sperm suppression was not compromised, and these side-effects were minimised [23,24]. Levonorgestrel has also been used successfully as an implant in combination with long-acting testosterone undecanoate injections. A trial enrolling 62 Chinese men used a long-acting levonorgestrel implant with testosterone undecanoate, and found that 90% of the men attained azoospermia, and all became severely oligospermic [25]. In a second study involving both Chinese and non-Chinese men, testosterone implants alone were not effective in non-Chinese men; however, the combination of levonorgestrel with testosterone resulted in nearly 90% of the men achieving severe oligospermia in both groups [26].

Etonogestrel and testosterone—Etonogestrel, the active metabolite of orally administered desogestrel, is a third-generation progestin originally formulated as a contraceptive agent for women and delivered via an implant, providing 3 years of contraception. A pilot study examined etonogestrel's potential as part of a male hormonal

contraceptive regimen in combination with testosterone pellets was promising [27], leading to an international multicentre phase II study that enrolled 130 men and used combinations of etonogestrel implants with testosterone decanoate for 48 weeks [28]. A total of 78–85% of the men achieved azoospermia, with a low incidence of side-effects. This regimen was further optimised by using testosterone undecanoate injections evaluated in a trial that included 354 men [29]. In the group who received high-dose etonogestrel, 94% achieved severe oligospermia. This study notably included a placebo group for the etonogestrel arm to allow clearer identification of side-effects. It also used an innovative centralised semen analysis method based on fluorescent detection: this allowed detection of low numbers of sperm, and accounted for the low azoospermia rate in that study. Side-effects associated with the combination were minimal and well-tolerated, with no change in HDL cholesterol concentrations.

Norethisterone enanthate and testosterone—Norethisterone enanthate (NETE) is a long-acting injectable, second-generation progestin with both antiandrogenic and antiestrogenic effects. Pilot studies have shown that testosterone undecanoate combined with NETE given intramuscularly or orally resulted in azoospermia in 90% of the men and severe oligospermia in the remaining 10%. Follow-up studies further investigated the optimal dosing interval for NETE when combined with testosterone undecanoate for the suppression of spermatogenesis [30], and this combination was selected by WHO and CONRAD for further exploration in a multinational phase II efficacy trial, with the intention of recruiting 400 couples who would use the 80-week injection regimen (200mg NETE with 1000 mg testosterone undecanoate) for contraception for a year when the man's sperm concentration had fallen below 1 million per ml. Although the detailed findings have not been published, preliminary reports suggest that the combination of testosterone undecanoate and NETE was well-tolerated and had a high contraceptive efficacy rate.

Depot medroxyprogesterone acetate and testosterone—Depot medroxyprogesterone acetate (DMPA) is a long-acting progestin with a long history of use as a female contraceptive agent. The first testosterone-DMPA male contraceptive efficacy trial enrolled 55 men in Australia and used the combination of testosterone pellets every 4–6 months and DMPA injections every 3 months [14]. Fifty-three men achieved severe oligospermia and entered the efficacy phase, during which no pregnancies occurred. A similar study in China randomised 30 men to receive either alone or testosterone undecanoate with DMPA [31]. Rebound in sperm concentrations occurred only in the testosterone undecanoate-alone group. As mentioned above, a more recent trial randomised 44 men to receive transdermal testosterone gel and DMPA with or without the GnRH antagonist acyline. [17] In this study, 90% of the men developed severe oligospermia. Safety outcomes of all three trials were reassuring, with no severe adverse events. In both the Australian and Chinese studies, an increase in haemoglobin concentration and modest weight gain was observed, whereas transdermal T resulted in minimal changes in weight and serum lipid concentrations. When used in women, DMPA can result in persisting contraceptive effects, making reversibility less predictable. As persisting DMPA may continue to suppress gonadotropins beyond the duration of testosterone administration during the initial recovery phase, this may induce temporary hypogonadism in some men.

Nestorone, cyproterone acetate, and testosterone—Nestorone is a 19-norprogesterone-derived progestin with potent gonadotropin suppression developed as a gel, allowing an ‘all-gel’ approach for male hormonal contraception. Of 99 participants enrolled in a study of this approach, 89% achieved azoospermia or severe oligospermia [18]. A rebound in sperm production during drug exposure was observed in four men. No significant adverse event occurred, and reported side-effects included mild acne in one-fifth of participants, weight gain, a small decrease in serum HDL cholesterol, and a small increase in fasting serum glucose that remained within the normal range in all men. A combined nestorone–testosterone gel is currently being developed, and could be a promising contraceptive option for men.

Cyproterone acetate (CPA) is an anti-androgenic progestin that, when combined with testosterone, yielded profound spermatogenic suppression with few adverse effects. In contrast to other regimens, CPA plus testosterone resulted in mild weight loss and a slight decrease in haemoglobin concentration, both of which are dose-dependent and attributed to CPA’s anti-androgenic properties, with rapid and profound sperm suppression [32]. Although the antiandrogenic properties of CPA may have had a direct testicular affect that enhances sperm suppression, higher doses of testosterone enanthate, when combined with CPA did not further the contraceptive potential of the combination, and, in fact, were associated with lower rates of azoospermia. In a follow-up study, longer acting testosterone undecanoate injections combined with daily, oral, CPA resulted in azoospermia or severe oligospermia in 100% of participants [33] and could be maintained by testosterone undecanoate alone or testosterone undecanoate plus CPA for another 32 weeks. Despite high concentrations of testosterone, a fall in haemoglobin was observed in men receiving the combination of testosterone and CPA. Although these results are promising, CPA has not been available for further evaluation.

The paradoxical lack of enhanced suppression of sperm production in the setting of higher doses of exogenous testosterone combined with CPA highlight a conundrum in male hormonal contraceptive development. Why do a proportion of men fail to completely suppress sperm production despite hormonal manipulation? Initial studies focused on the possibility of incomplete gonadotropin suppression in some individuals, but this has not been borne out [34]. Baseline hormone levels and sperm concentration similarly do not predict men who are treatment ‘failures’ [4]. It is possible that residual, non-gonadotropin dependent intratesticular androgen production might support persistent, low-level spermatogenesis in some men. This hypothesis is supported by work in mice deficient in luteinising hormone, in which low levels of non-LH dependent intratesticular androgens appear to support spermatogenesis [21]. Although small, pilot studies in men have failed to corroborate a linear relationship between intratesticular androgen concentrations and spermatogenesis, recent work has demonstrated the potency of ketoconazole with and without dutasteride (a 5 α reductase inhibitor) to lower intratesticular androgens further in men undergoing male hormonal contraceptive treatment. Use of these agents, together with androgen plus progestin regimens, will allow for experimental testing of the effectiveness of further suppression of non-gonadotropin dependent intratesticular androgen production on

spermatogenesis in men over the next few years and may provide a target for further treatment of those men who fail to achieve azoospermia.

Gonadotropin-releasing hormone antagonists as adjuncts in male hormonal contraceptive treatment

Despite improved efficacy with the addition of progestins to testosterone, persistent spermatogenesis in a small number of men has been problematic. One potential mechanism whereby men might escape full suppression is via persistent, low level gonadotropin production, below the limit of detection for many gonadotropin assays. Unlike the GnRH agonists that initially increase gonadotropin production, GnRH antagonists are capable of potently suppressing the production of FSH and luteinising hormone within hours of administration. This property has been exploited experimentally to augment the contraceptive effects of hormone-based regimens at the level of the pituitary, particularly as 'induction' agents to shut down the gonadal axis in an effort to decrease the time to maximal sperm suppression.

Three trials have evaluated the efficacy of the GnRH antagonist peptide Nal-Glu as an adjunct to testosterone for male contraception [4]. The first two small trials found reversible azoospermia in 14 of the 16 men receiving the combination of testosterone enanthate and daily subcutaneous injections of Nal-Glu; however, one-third trial failed to demonstrate an additive effect of Nal-Glu compared with testosterone enanthate alone. Nal-Glu was also tested as a potential agent for the induction of azoospermia, and, when combined with testosterone enanthate, led to oligospermia or azoospermia in 14 of the 15 men within 12–16 weeks [35]. Another trial showed that the combined administration of 19-nortestosterone and the GnRH antagonist cetrorelix effectively suppressed spermatogenesis to azoospermia in all six participants within 12 weeks [36].

Both Nal-Glu and cetrorelix required daily subcutaneous administration, which is not feasible as a part of a long-term contraceptive regimen. Acyline is a longer-acting GnRH antagonist that suppresses gonadotropins for up to 2 weeks [17], and is also active after oral administration [37]. Although the addition of acyline did not accelerate spermatogenic suppression or improve the rates of severe oligospermia when used in combination with testosterone enanthate and DMPA [17], the high efficacy of testosterone enanthate plus DMPA might have obscured any benefit of acyline. Oral acyline and other formulations of novel GnRH antagonists have yet to be evaluated as adjuncts to androgens for male contraception. Unlike progestins, the GnRH antagonists are unlikely to be associated with additional metabolic side effects when used with testosterone and thus deserve further evaluation in this context.

Alternative androgens for hormonal contraception

7-Alpha-methyl-19-nortestosterone—7-Alpha-methyl-19-nortestosterone (MENT) is an androgenic-anabolic steroid, and is five times more androgenic than testosterone *in vitro*. It has been successfully formulated as an implant, with a goal to develop implants requiring only annual, or even less frequent, placement. The addition of a methyl group at the 7-carbon position renders MENT resistant to 5-alpha-reduction, a potentially attractive property in an

androgen for male hormonal contraception as it renders MENT relatively ‘prostate-sparing’ in animal models. 5 α -reductases are highly expressed in the prostate, and reduction of androgens by these enzymes can result in more potent metabolites, such as dihydrotestosterone in the case of testosterone, which may amplify androgen action in these tissues. In addition, MENT is aromatised to an oestrogen, which may be important for supporting bone health in long-term users [38].

The first dose-finding study in healthy men showed that MENT implants can provide a sustained release of MENT sufficient to suppress gonadotropins and spermatogenesis for 1 year [39]. In this study, eight out of the 11 men receiving four implants achieved and maintained azoospermia for 12 months, with recovery to normal levels of spermatogenesis within 3 months of implant removal. Results from trials combining MENT implants with etonogestrel and levonorgestrel implants, however, have been disappointing, with low rates of azoospermia (50–60%) and inconsistent maintenance of sperm suppression [40]. This lack of efficacy, however, may be specific to the MENT implants used, as they did not provide sufficient and sustained release of MENT into the circulation, compared with earlier formulations. New MENT implants are in development to improve delivery, and will be tested in future trials.

Dimethandrolone undecanoate—Dimethandrolone undecanoate (DMAU) (7 α , 11 β -dimethyl-19-nortestosterone 17 β -undecanoate) is a potent synthetic 19-norandrogen. Both DMAU and its more potent metabolite dimethandrolone (DMA) bind androgen and progesterone receptors, resulting in androgenic and progestational activity *in vitro* and *in vivo*. This dual activity gives DMAU and DMA the potential to serve as a single agent for male contraception. Moreover, DMAU is both orally and intramuscularly bioavailable, giving it the potential to be either a single agent ‘male pill’ or a long-acting, single agent injectable. A promising study in rabbits demonstrated reversible contraception with daily, oral, DMAU [41]. Moreover, DMAU administered to rats had favourable anabolic effects, including maintenance of lean body mass and bone mineral density and prevention of fat mass accumulation and weight gain.

On the basis of these promising results in animals, evaluation of DMAU in men is currently under way. A Phase 1, single-dose, dose-ranging safety study in healthy men demonstrated that a single dose of oral DMAU partially suppressed gonadotropins and testosterone (Page et al.: manuscript submitted). Effective drug concentrations were only achieved when this formulation of DMAU was ingested with a fatty meal. This is similar to observations with oral testosterone undecanoate, which requires lymphatic absorption to optimise serum concentrations. Efforts are currently underway to improve the bioavailability of oral DMAU and to examine the effectiveness of intramuscular DMAU as a long acting, reversible, single-agent male hormonal contraceptive.

Male non-hormonal contraceptive methods

In addition to the hormonal agents that disrupt spermatogenesis, ongoing research also focuses on developing non-hormonal male contraceptive agents by targeting sperm formation and maturation within the testis or epididymis, or sperm motility.

Testicular targets

Gossypol—Gossypol, a natural phenol derived from the cotton plant, is one of the earliest compounds to be tested as a non-hormonal contraceptive agent. Several large trials conducted in China in the 1980s demonstrated that gossypol targets resulted in severe oligospermia in more than 90% of men. Unfortunately, gossypol led to irreversible antifertility effects in 20% of the men, as well as clinically significant hypokalemia even at lower doses [42], and its development was abandoned.

Indenopyridines—The indenopyridines (CDB-4022) were initially developed as new antihistamines and inadvertently discovered to possess antispermatogenic activity during toxicology testing. Administration of indenopyridine led to the depletion of germ cells of the seminiferous epithelium in dogs and rats without gonadotropin suppression, indicating a direct testicular effect, although the exact mechanism of action remains unclear. Administration of CDB-4022 to rats resulted in irreversible damage to the seminiferous tubules, but pretreatment with the GnRH antagonist acyline led to reversible infertility [43]. A primate study showed that a 7-day treatment with l-CDB-4022 was associated with severe oligospermia in all four monkeys from day 7 to week 6, with complete recovery of sperm counts by week 16 [44]. Circulating levels of gonadotropins and testosterone, were unaffected, and no overt toxicities were observed. Long-term studies of CDB-4022 in animals will be needed to confirm reversibility of infertility and safety before studies in humans may be conducted.

Lonidamine derivatives: 2-gamendazole and adjudin—Lonidamine was originally synthesised as an anticancer drug. It disrupts Sertoli-germ cell junctions, inducing the release of immature spermatids [45,46]. Because lonidamine has a narrow therapeutic window and is associated with a number of undesirable side-effects, safer and more efficacious analogs were developed, such as adjudin (AF-2364), which results in complete but reversible infertility in rats [47]. In some animals, however, adjudin caused liver inflammation and muscle atrophy. A conjugated form of adjudin using a FSH beta subunit mutant was subsequently developed and was effective in reducing the adjudin dose [48]. The possibility of developing anti-FSH autoantibody may also compromise reversibility [4].

A further derivative, H2-gamendazole resulted in complete infertility in rats although reversibility was incomplete [49]. Further dose-finding experiments are required to define the therapeutic window and reversibility, which will aid in preparation of an investigational new drug application to proceed to human testing in the near future.

JQ1—JQ1 is a small-molecule inhibitor of the testis-specific bromodomain (BRDT), which is an epigenetic reader protein essential for chromatin remodeling during spermatogenesis [50]. A proof-of-principle study showed that JQ1 led to a reduction in sperm count and motility, resulting in a complete and reversible contraception in mice, without affecting mating behaviours and serum hormones and without apparent toxicity. These promising results support the development of derivatives that possess higher affinity and specificity for BRDT to reduce possible long-term adverse effects that may be associated with a pan-BET bromodomain inhibitor.

Retinoic acid receptor antagonist: BMS-189453 and WIN 18,446—Vitamin A and its metabolites are required for initiation and maintenance of spermatogenesis. Vitamin A deficiency and retinoic acid receptor (RAR)-knockout renders male animals infertile, demonstrating the potential of targeting retinoic acid synthesis or the RARs for male contraception.

BMS-189453 is an orally active retinoic acid receptor antagonist that binds all three RARs (α , β , and γ), and causes the spermatids to fail to align at the lumen for spermiogenesis [51]. Administration of BMS-189453 resulted in complete and reversible infertility in all mice and no abnormalities in haematology, serum chemistry, hormonal or pathological evaluations [51]. Ongoing research focuses on the development of a RAR α -specific antagonist to minimise off-target effects. The first two RAR α -specific antagonists (BMS-189532 and BMS-195614) failed to induce infertility in mice when the drugs were administered orally [52]. Data from this study will aid the development of new RAR α -selective antagonists for pharmaceutical application.

The ability for the bisdichloroacetyldiamine WIN 18,446 to safely and reversibly inhibit spermatogenesis in human was discovered in the 1960s [53]. Sixty men were treated with Win 18,446 for up to 1 year and achieved severe oligospermia [53]. When they consumed alcohol, however, they developed an unpleasant disulfiram reaction, which halted the development of this compound as a male contraceptive agent. Testicular biopsies demonstrated a complete arrest of spermatogenesis at the stage of spermatogonia [54], and a recent study using a rabbit model demonstrated a decrease in intratesticular retinoic acid concentration preceding the reversible azoospermia by inhibition of aldehyde dehydrogenase 1a2 (ALDH1a2) [55], required for the conversion of vitamin A to retinoic acid. Development of a compound that specifically inhibits testicular aldehyde dehydrogenase without an effect on alcohol metabolism is under way.

Epididymal targets: HE6 and CRISP-1

HE6 and CRISP-1 are potential targets for male contraception, and the development of appropriate and specific pharmacologic agents against these proteins for clinical use is under way. The G-protein coupled receptor (GPCR) HE6 displays a preferred epididymis-specific expression pattern and HE6 knockout mice have markedly reduced fertility without other hormonal or systemic abnormalities, probably through, a defect in reabsorption of testicular fluids in the efferent epididymal ductules [56]. As a GPCR, it offers a drugable target for male contraceptive development.

CRISP-1, a glycoprotein secreted by the epididymal epithelium, has been found to suppress sperm capacitation and inhibit sperm-egg fusion in rats and mammals [57].

Targeting sperm motility or sperm-egg fusion

N-butyldeoxynojirimycin—Agents targeting sperm motility are not always effective across species, and miglustat is such an example. Studies in mice demonstrated that N-butyldeoxynojirimycin (Miglustat), a glycosphingolipid biosynthesis inhibitor, leads to reversible infertility [58]. Administration of therapeutic doses of miglustat, however, does

not seem to affect human spermatogenesis, with no change in the concentration, motility, or morphology of sperm [59].

CatSper—CatSper ion channels are a family of tetrameric, alkalization-activated calcium-permeable ion channels unique to sperm. Flux of calcium through CatSper triggers hyperactivation of sperm, and progesterone appears to have a permissive role in CatSper function [60]. To date, CatSper is the only calcium channel whose function has been confirmed by whole-cell patch clamping technique in sperm. Disruption of the CatSper genes results in sterility in male mice, with a marked decrease in sperm motility and inability to fertilise intact eggs. Moreover, mutations or deletions in CatSper1 and CatSper2 are associated with infertility in humans [61]. CatSper's specificity for sperm makes them attractive targets for male contraceptive development and the search for specific inhibitors is under way. Such molecules might facilitate 'on demand' male contraception as they target a late stage of fertilisation, and could conceivably be delivered through either the male or perhaps be administered to women specifically to the reproductive tract, thus minimising off target and longterm exposure.

3-Phosphate dehydrogenase-S—Sperm motility is essential to the process of fertilisation and requires adenosine triphosphate, which is synthesised through aerobic glycolysis. 3-Phosphate dehydrogenase-S (GAPDS) is an enzyme essential for the sperm-specific glycolysis: disruption renders male mice infertile. [62] Several small molecule inhibitors have been identified [63]. Like CatSper, this approach also has the potential for longer and shorter acting contraception. The biggest challenges are minimising cross reactivity and off-target effects, and achieving effective drug concentrations within the testes, female reproductive tract, or both.

Conclusion

The hormonal approach to male contraception continues to progress slowly. A number of promising targets for non-hormonal male contraception have also been identified. Presently, one of the biggest hurdles in the male contraceptive development lies in identifying pharmacological agents that reliably render males infertile and are fully reversible and safe for long-term use, as men might use these medications for many years. Therefore, development of new drugs and careful monitoring of their safety parameters are of paramount importance.

A major setback to new male contraceptive methods occurred several years ago when the major pharmaceutical sponsors of male hormonal contraceptive research withdrew their support. Funding remains limited in this area despite support from the Contraceptive Discovery and Development Branch of NIH. As the world's population soars above 7.1 billion, and 800 women a day continue to die in childbirth worldwide, additional resources are needed [64]. The goal is to address the ongoing public health and disparity issues of unwanted pregnancies by delivering pragmatic contraceptive choices for both men and their female partners.

References

1. Heinemann K, Saad F, Wiesemes M, et al. Attitudes toward male fertility control: results of a multinational survey on four continents. *Hum Reprod.* 2005; 20:549–56. [PubMed: 15608042]
2. Glasier AF, Anakwe R, Everington D, et al. Would women trust their partners to use a male pill? *Hum Reprod.* 2000; 15:646–9. [PubMed: 10686212]
3. Martin CW, Anderson RA, Cheng L, et al. Potential impact of hormonal male contraception: cross-cultural implications for development of novel preparations. *Hum Reprod.* 2000; 15:637–45. [PubMed: 10686211]
4. Page ST, Amory JK, Bremner WJ. Advances in male contraception. *Endocr Rev.* 2008; 29:465–93. [PubMed: 18436704]
- *5. 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; 65:821–9. [PubMed: 8654646]
6. Contraceptive efficacy of testosterone-induced azoospermia in normal men. World Health Organization Task Force on methods for the regulation of male fertility. *Lancet.* 1990; 336:955–9. [PubMed: 1977002]
7. Bagatell CJ, Heiman JR, Matsumoto AM, et al. Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. *J Clin Endocrinol Metab.* 1994; 79:561–7. [PubMed: 8045977]
8. Sjogren B, Gottlieb C. Testosterone for male contraception during one year: attitudes, well-being and quality of sex life. *Contraception.* 2001; 64:59–65. [PubMed: 11535215]
9. Gu YQ, Wang XH, Xu D, et al. A multicenter contraceptive efficacy study of injectable testosterone undecanoate in healthy Chinese men. *J Clin Endocrinol Metab.* 2003; 88:562–8. [PubMed: 12574181]
- *10. Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. *J Clin Endocrinol Metab.* 2009; 94:1910–5. [PubMed: 19293262]
11. Handelsman DJ, Farley TM, Peregoudov A, et al. Factors in nonuniform induction of azoospermia by testosterone enanthate in normal men. World Health Organization Task Force on Methods for the Regulation of Male Fertility *Fertil Steril.* 1995; 63:125–33. [PubMed: 7805901]
12. Kinniburgh D, Zhu H, Cheng L, et al. Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. *Hum Reprod.* 2002; 17:1490–501. [PubMed: 12042267]
13. Anderson RA, Van Der Spuy ZM, Dada OA, et al. Investigation of hormonal male contraception in African men: suppression of spermatogenesis by oral desogestrel with depot testosterone. *Hum Reprod.* 2002; 17:2869–77. [PubMed: 12407041]
- *14. Turner L, Conway AJ, Jimenez M, et al. Contraceptive efficacy of a depot progestin and androgen combination in men. *J Clin Endocrinol Metab.* 2003; 88:4659–67. [PubMed: 14557437]
15. Buchter D, von Eckardstein S, von Eckardstein A, et al. Clinical trial of transdermal testosterone and oral levonorgestrel for male contraception. *J Clin Endocrinol Metab.* 1999; 84:1244–9. [PubMed: 10199762]
16. Gonzalo IT, Swerdloff RS, Nelson AL, et al. Levonorgestrel implants (Norplant II) for male contraception clinical trials: combination with transdermal and injectable testosterone. *J Clin Endocrinol Metab.* 2002; 87:3562–72. [PubMed: 12161475]
17. Page ST, Amory JK, Anawalt BD, et al. Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. *J Clin Endocrinol Metab.* 2006; 91:4374–80. [PubMed: 16940442]
18. Ilani N, Roth MY, Amory JK, et al. A new combination of testosterone and nesterone transdermal gels for male hormonal contraception. *J Clin Endocrinol Metab.* 2012; 97:3476–86. [PubMed: 22791756]

19. Amory JK, Page ST, Anawalt BD, et al. Acceptability of a combination testosterone gel and depomedroxyprogesterone acetate male contraceptive regimen. *Contraception*. 2007; 75:218–23. [PubMed: 17303493]
20. Liu PY, Swerdloff RS, Christenson PD, et al. Hormonal male contraception summit group. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet*. 2006; 367:1412–20. [PubMed: 16650651]
- *21. Zhang FP, Pakarainen T, Poutanen M, et al. The low gonadotropin-independent constitutive production of testicular testosterone is sufficient to maintain spermatogenesis. *Proc Natl Acad Sci USA*. 2003; 100:13692–7. [PubMed: 14585929]
22. Bebb RA, Anawalt BD, Christensen RB, et al. 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; 81:757–62. [PubMed: 8636300]
23. Anawalt BD, Amory JK, Herbst KL, 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; 26:405–13. [PubMed: 15867009]
24. Herbst KL, Anawalt BD, Amory JK, et al. The male contraceptive regimen of testosterone and levonorgestrel significantly increases lean mass in healthy young men in 4 weeks, but attenuates a decrease in fat mass induced by testosterone alone. *J Clin Endocrinol Metab*. 2003; 88:1167–73. [PubMed: 12629101]
25. Gui YL, He CH, Amory JK, et al. Male hormonal contraception: suppression of spermatogenesis by injectable testosterone undecanoate alone or with levonorgestrel implants in Chinese men. *J Androl*. 2004; 25:720–7. [PubMed: 15292101]
26. Wang C, Wang XH, Nelson AL, et al. Levonorgestrel implants enhanced the suppression of spermatogenesis by testosterone implants: comparison between Chinese and non-Chinese men. *J Clin Endocrinol Metab*. 2006; 91:460–70. [PubMed: 16278260]
27. Anderson RA, Kinniburgh D, Baird DT. Suppression of spermatogenesis by etonogestrel implants with depot testosterone: potential for long-acting male contraception. *J Clin Endocrinol Metab*. 2002; 87:3640–9. [PubMed: 12161488]
28. Brady BM, Amory J, Perheentupa A, et al. A multi-centre study investigating subcutaneous etonogestrel implants with injectable testosterone decanoate as a potential long-acting male contraceptive. *Hum Reprod*. 2006; 21:285–94. [PubMed: 16172147]
- *29. Mommers E, Kersemaekers WM, Elliesen J, et al. Male hormonal contraception: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2008; 93:2572–80. [PubMed: 18413423]
- *30. Meriggiola MC, Costantino A, Saad F, et al. Norethisterone enanthate plus testosterone undecanoate for male contraception: effects of various injection intervals on spermatogenesis, reproductive hormones, testis, and prostate. *J Clin Endocrinol Metab*. 2005; 90:2005–14. [PubMed: 15634716]
31. Gu YQ, Tong JS, Ma DZ, 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; 89:2254–62. [PubMed: 15126550]
32. Meriggiola MC, Bremner WJ, Costantino A, et al. Low dose of cyproterone acetate and testosterone enanthate for contraception in men. *Hum Reprod*. 1998; 13:1225–9. [PubMed: 9647551]
33. Meriggiola MC, Costantino A, Cerpolini S, et al. Testosterone undecanoate maintains spermatogenic suppression induced by cyproterone acetate plus testosterone undecanoate in normal men. *J Clin Endocrinol Metab*. 2003; 88:5818–26. [PubMed: 14671175]
- *34. Liu PY, Swerdloff RS, Anawalt BD, et al. Determinants of the rate and extent of spermatogenic suppression during hormonal male contraception: an integrated analysis. *J Clin Endocrinol Metab*. 2008; 93:1774–83. [PubMed: 18303073]
35. Swerdloff RS, Bagatell CJ, Wang C, et al. Suppression of spermatogenesis in man induced by Nal-Glu gonadotropin releasing hormone antagonist and testosterone enanthate (TE) is maintained by TE alone. *J Clin Endocrinol Metab*. 1998; 83:3527–33. [PubMed: 9768659]

36. Behre HM, Kliesch S, Lemcke B, et al. Suppression of spermatogenesis to azoospermia by combined administration of GnRH antagonist and 19-nortestosterone cannot be maintained by this non-aromatizable androgen alone. *Hum Reprod.* 2001; 16:2570–7. [PubMed: 11726576]
37. Amory JK, Leonard TW, Page ST, et al. Oral administration of the GnRH antagonist acyline, in a GIPET-enhanced tablet form, acutely suppresses serum testosterone in normal men: single-dose pharmacokinetics and pharmacodynamics. *Cancer Chemother Pharmacol.* 2009; 64:641–5. [PubMed: 19479252]
- *38. Anderson RA, Wallace AM, Sattar N, et al. Evidence for tissue selectivity of the synthetic androgen 7 α -methyl-19-nortestosterone in hypogonadal men. *J Clin Endocrinol.* 2003; 88:2784–893.
39. von Eckardstein S, Noe G, Brache V, et al. A clinical trial of 7 α -methyl-19-nortestosterone implants for possible use as a long-acting contraceptive for men. *J Clin Endocrinol Metab.* 2003; 88:5232–9. [PubMed: 14602755]
40. Walton MJ, Kumar N, Baird DT, et al. 7 α -methyl-19-nortestosterone (MENT) vs testosterone in combination with etonogestrel implants for spermatogenic suppression in healthy men. *J Androl.* 2007; 28:679–88. [PubMed: 17460095]
41. Attardi BJ, Engbring JA, Gropp D, et al. Development of dimethandrolone 17 β -undecanoate (DMAU) as an oral male hormonal contraceptive: induction of infertility and recovery of fertility in adult male rabbits. *J Androl.* 2011; 32:530–40. [PubMed: 21164142]
42. Waites GM, Wang C, Griffin PD. Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. *Int J Androl.* 1998; 21:8–12. [PubMed: 9639146]
43. Hild SA, Attardi BJ, Reel JR. The ability of a gonadotropin-releasing hormone antagonist, acyline, to prevent irreversible infertility induced by the indenopyridine, CDB-4022, in adult male rats: the role of testosterone. *Biol Reprod.* 2004; 71:348–58. [PubMed: 15044265]
44. Hild SA, Marshall GR, Attardi BJ, et al. Development of 1-CDB-4022 as a nonsteroidal male oral contraceptive: induction and recovery from severe oligospermia in the adult male cynomolgus monkey (*Macaca fascicularis*). *Endocrinology.* 2007; 148:1784–96. [PubMed: 17218411]
45. Marcante ML, Natali PG, Floridi A, et al. Effects of AF 1312/TS and lonidamine on cultured sertoli cells. *Chemotherapy.* 1981; 27(Suppl 2):43–9. [PubMed: 7285637]
46. De Martino C, Malcorni W, Bellocchi M, et al. Effects of AF 1312 TS and lonidamine on mammalian testis. A morphological study. *Chemotherapy.* 1981; 27(Suppl 2):27–42. [PubMed: 7285636]
47. Grima J, Silvestrini B, Cheng CY. Reversible inhibition of spermatogenesis in rats using a new male contraceptive, 1-(2,4-dichlorobenzyl)-indazole-3-carbohydrazide. *Biol Reprod.* 2001; 64:1500–8. [PubMed: 11319158]
48. Mok KW, Mruk DD, Lie PP, et al. Adjudin, a potential male contraceptive, exerts its effects locally in the seminiferous epithelium of mammalian testes. *Reproduction.* 2011; 141:571–80. [PubMed: 21307270]
49. Tash JS, Attardi B, Hild SA, et al. A novel potent indazole carboxylic acid derivative blocks spermatogenesis and is contraceptive in rats after a single oral dose. *Biol Reprod.* 2008; 78:1127–38. [PubMed: 18218612]
- *50. Matzuk MM, McKeown MR, Filippakopoulos P, et al. Small-molecule inhibition of BRDT for male contraception. *Cell.* 2012; 150:673–84. [PubMed: 22901802]
51. Chung SS, Wang X, Roberts SS, et al. Oral administration of a retinoic acid receptor antagonist reversibly inhibits spermatogenesis in mice. *Endocrinology.* 2011; 152:2492–502. [PubMed: 21505053]
52. Chung SS, Cuellar RA, Wang X, et al. Pharmacological activity of retinoic acid receptor α -selective antagonists and. *ACS Med Chem Lett.* 2013; 4:446–50. [PubMed: 24040487]
53. Heller CG, Moore DJ, Paulsen CA. Suppression of spermatogenesis and chronic toxicity in men by a new series of bis-(dichloroacetyl) diamines. *Toxicol Appl Pharmacol.* 1961; 3:1–11. [PubMed: 13713106]
54. Heller CG, Flageolle BY, Matson LJ. Histopathology of the human testes as affected by bis(dichloroacetyl)diamines. *Exp Mol Pathol Suppl.* 1963; 2:107–14. [PubMed: 14089658]

- *55. Amory JK, Muller CH, Shimshoni JA, et al. Suppression of spermatogenesis by bisdichloroacetyldiamines is mediated by inhibition of testicular retinoic acid biosynthesis. *J Androl.* 2011; 32:111–9. [PubMed: 20705791]
56. Davies B, Baumann C, Kirchhoff C, et al. Targeted deletion of the epididymal receptor HE6 results in fluid dysregulation and male infertility. *Mol Cell Biol.* 2004; 24:8642–8. [PubMed: 15367682]
57. Roberts KP, Ensrud KM, Wooters JL, et al. Epididymal secreted protein Crisp-1 and sperm function. *Mol Cell Endocrinol.* 2006; 250:122–7. [PubMed: 16414181]
58. van der Spoel AC, Jeyakumar M, Butters TD, et al. Reversible infertility in male mice after oral administration of alkylated imino sugars: a nonhormonal approach to male contraception. *Proc Natl Acad Sci USA.* 2002; 99:17173–8. [PubMed: 12477936]
59. Amory JK, Muller CH, Page ST, et al. Miglustat has no apparent effect on spermatogenesis in normal men. *Hum Reprod.* 2007; 22:702–7. [PubMed: 17067996]
60. Ren D. Sperm and the proton channel. *N Engl J Med.* 2010; 362:1934–5. [PubMed: 20484401]
61. Lishko PV, Kirichok Y, Ren D, et al. The control of male fertility by spermatozoan ion channels. *Ann Rev Physiol.* 2012; 74:453–75. [PubMed: 22017176]
62. Miki K, Qu W, Goulding EH, et al. Glyceraldehyde 3-phosphate dehydrogenase-S, a sperm-specific glycolytic enzyme, is required for sperm motility and male fertility. *Proc Natl Acad Sci USA.* 2004; 101:16501–6. [PubMed: 15546993]
63. Sexton JZ, Danshina PV, Lamson DR, et al. Development and implementation of a high throughput screen for the human sperm-specific isoform of glyceraldehyde 3-phosphate dehydrogenase (GAPDHS). *Curr Chem Genomics.* 2011; 5:30–41. [PubMed: 21760877]
64. Sengupta, S. New York Times. Feb 12. 2014 U.N. report says progress for women is unequal.

Research agenda

- Identification of mechanisms of non-suppression of spermatogenesis.
- Optimisation of long-acting testosterone administration.
- Clarification of importance of key metabolic indicators of excess or insufficient steroid administration.
- Development of animal models of spermatogenesis and epididymal function of human relevance.

Fig. 1.

The basis for the hormonal approach to male contraception. Left: normal male reproductive function. The gonadotropins luteinising hormone and follicle-stimulating hormone, respectively, support Leydig cell and Sertoli cell function in the testis, and thus spermatogenesis. Testosterone production supports normal male function throughout the body, and contributes to feedback control of hypothalamic–pituitary activity. In the hormonal approach (right), exogenous testosterone, progestogens or gonadotropin-releasing hormone antagonists suppress luteinising hormone and follicle-stimulating hormone secretion, and thus spermatogenesis and testosterone production. The administration of testosterone is therefore required to support normal male physiological functions as well as contributing to gonadotropin suppression. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinising hormone; T, testosterone.

Table 1

Key attributes of testosterone-based approaches to male contraception.

Preparation	Major features
Testosterone alone (injections, pellets, gel)	High doses needed so androgenic side-effects; relatively low rates of azoospermia especially in white men.
With levonorgestrel	Good efficacy; HDL-cholesterol changes; oral and implant options for LNG.
With etonogestrel	Implant formulation; low metabolic effects.
With norethisterone enanthate	Long-acting injectable; potential for co-formulation with testosterone undecanoate; currently being investigated in efficacy trial.
With medroxyprogesterone acetate	Used with testosterone pellets and gel; occasional prolonged duration of action.
With nesterone	Novel non-androgenic progestogen.
With cyproterone acetate	Anti-androgenic activity; may be relevant to metabolic effects and contraceptive efficacy.
With GnRH antagonists	Peptides, thus require frequent injection; expensive compared with progestogens; no metabolic effects; potentially useful for initial suppression of spermatogenesis; novel oral agents becoming available.

HDL, high-density lipoprotein; LNG, levonorgestrel.