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Male contraception

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Currently approved male-directed contraceptive methods include condoms and vas occlusion. Vas occlusion is very effective but is intended to be non-reversible. Condoms have a relatively high failure rate, at least partially due to compliance problems and are not accepted by many couples. The only other male-oriented methods in clinical trials utilize the administration of testosterone alone or its combination with another gonadotropin-suppressing agent such as a progestin or a gonadotropin-releasing hormone antagonist. Studies published in the 1990s demonstrated that a testosterone-containing hormonal contraceptive method suppressed spermatogenesis to azoospermia in most men and severe oligozoospermia in the remaining. The contraceptive efficacy after treatment with testosterone alone was comparable to that of female hormonal methods. Having proven that reversible male contraception is a reality, present trials are attempting to identify the best androgen delivery system and the most effective androgen plus progestin preparation. It is likely that the first marketed male hormonal contraceptive method will be a long-acting (injectable or implant) combination of an androgen plus a progestin. Research is continuing to identify other target areas for male contraceptive development, including agents with post-testicular and epididymal sites of action.

Key words: hormonal male contraception; androgens; gonadotropin-suppressing agents.

CURRENT MALE METHODS

Condoms

About 10% of couples in the reproductive age range use male methods of contraception. The methods currently available are the male condom and vas occlusion. Condoms used appropriately have the added benefit of prevention of sexually transmitted infections (STIs) including the human immunodeficiency virus. The contraceptive failure of the condom in general use is about 12%.[1] Some condoms contain a spermicide to give added protection. Recent improvements include substitution of latex by polyurethane. Although the acceptability of condoms amongst couples is variable, this remains the

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recommended contraceptive and preventive method for sexually transmitted diseases in couples in casual relationships.

Vas occlusion

Vas occlusion is used by 5–10% of couples as a method of contraception. The prevalence varies greatly from country to country. Vas occlusion is performed mostly in the USA, UK, Netherlands, China, Thailand, Indonesia, Korea and India. Vas occlusion is offered by family planning services as a non-reversible method. The introduction of no-scalpel vasectomy has improved significantly the complications and morbidity of vasectomy.[2] The operation includes removal of a piece of vas, and fascial interposition can be included as a means to prevent recanalization. Other methods of vas occlusion introduced in China include intra-vasal injection of occlusive agents[3] or cured-in-place medical polymer[4] or silicone plugs. The former is mainly approved for use in China, whereas the latter is still undergoing investigations to introduce the appropriate volume of the silicone-in-place silicone to be injected without rupturing the vas.

The failure rate of vas occlusion methods is $< 1\%$ although recent data from long-term follow-up studies suggest higher failure rates. With good surgical techniques, early failure rates due to surgical failures are very uncommon. Late failure with reappearance of sperm is usually due to re-canalization of the vas. Current research includes studying the effect of cauterizing the ends of the vas on the long-term success rate. It should be noted that vas occlusion has a delayed effect; it takes several weeks before the residual spermatozoa are emptied from the ejaculatory system. In present practice, a man is asked to use other methods of contraception for at least 20 ejaculations in the post-vas occlusion period. Alternatively, the man is required to return for post-vasectomy surveillance until two consecutive semen analyses show azoospermia.

HORMONAL METHODS OF MALE CONTRACEPTION

The hormonal methods currently in development are based on the exogenous administration of an androgen alone or an androgen plus a gonadotropin-suppressing agent, such as a progestin or gonadotropin-releasing hormone antagonist (GnRH antagonist). These exogenously administered agents suppress the hypothalamic pulsatile secretion of GnRH and decrease the synthesis and secretion of both the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Decreased LH production will result in decreases in intra-testicular testosterone. The suppression of FSH together with a low intra-testicular testosterone concentration will lead to the suppression of spermatogenesis. Loss of sperm cells occurs by acceleration of programmed cell death (apoptosis) of spermatids and spermatocytes. Because the spermatogonia are not affected by hormonal suppressive agents, withdrawal of exogenous hormonal administration results in renewed proliferation of germ cells without concomitant increased germ cell death. Because hormonal methods of male contraception act by suppression of spermatogenesis and the human spermatogenic cycle requires about 72 days to complete, it can take between 8 and 12 weeks before maximum suppression is observed. Because suppression of LH secretion results in low circulating androgen levels, androgen replacement is an essential component of all hormonal male contraception regimens (Figure 1). Hormonal methods of male contraception do not prevent STIs; thus, this method is most applicable to couples

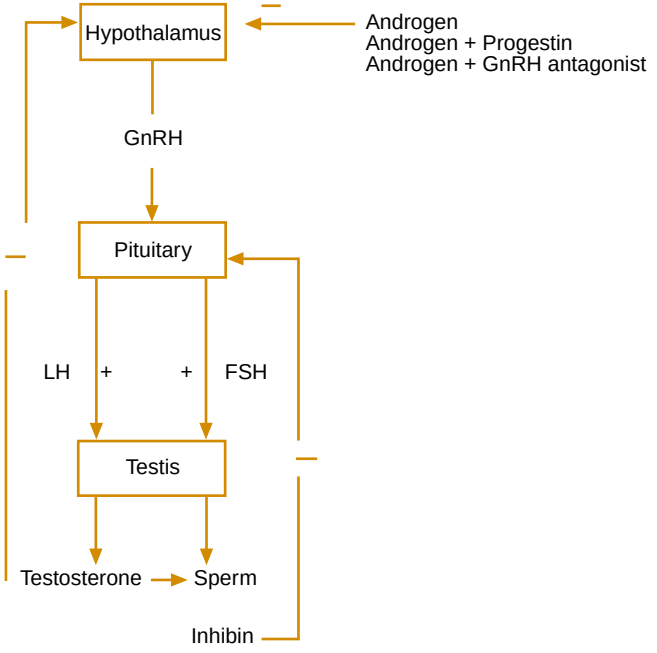

Figure 1. Hormonal methods of male contraception.

with monogamous relationships or combined with condoms to improve efficacy and protect against STIs.

Androgens alone

Injectable testosterone ester (testosterone enanthate) was tested in the 1970s in the USA and Europe in male contraceptive trials.[5] These earlier studies showed that when it is administered in supra-physiological doses (200 mg i.m. once weekly), testosterone enanthate induced azoospermia in about 40–50% and severe oligozoospermia in another 35–45% of healthy white volunteers.[6,7] Between 1985 and 1995, the World Health Organization (WHO) and the Contraceptive and Development Program supported two multi-national multi-centre contraceptive efficacy studies to show that once azoospermia[8] and/or severe oligozoospermia[9] were induced by exogenous androgens, high contraceptive efficacy was achieved. In the second pivotal study, testosterone enanthate 200 mg/week was administered to the male partner of over 500 couples for 18 months. During the first 6 months, while waiting for three consecutive samples to attain azoospermia or severe oligozoospermia (defined as sperm concentration $< 3 \times 10^6$/ml for these studies), the couple used another method of contraception. Once this threshold was reached, the couple used this male hormonal method as the sole method of contraception. As shown in Table 1, there was only one pregnancy in over 1400 months of exposure when the subjects reached consistent azoospermia.[8] If severe oligozoospermia (sperm count $< 3 \times 10^6$/ml) was used as the threshold, there were four pregnancies in about 280 person-years of exposure.[9] This gives a Pearl index of 1.4 per 100 person-years, which is similar to female hormonal contraceptive methods such as the oral pill, the injectables or the

Table 1. Contraceptive efficacy studies of testosterone-induced azoospermia and severe oligozoospermia.

Number of couples	Threshold	Efficacy phase (Years)	Pregnancies	Pearl rate per 100 person-years
WHO 1990				
157	Azoospermia	123.8	1	0.8
WHO 1996				
349	Azoospermia	230.4	0	0.0
	Oligozoospermia	49.5	4	8.1
	Azoospermia + Oligozoospermia	279.9	4	1.4

*Sperm concentration $< 3 \times 10^6$/ml.

new trans-dermal patches. The pregnancy rate was proportional to the residual sperm concentration in the ejaculate of the subjects. Only eight out of the 357 (2.2%) men failed to suppress sperm production to $<3 \times 10^6$/ml by 6 months. Moreover, once azoospermia is achieved, return of spermatozoa in the ejaculate is extremely rare during continuous treatment. The weekly testosterone enanthate injections were well tolerated by the subjects. The main adverse events included weight gain, oiliness of skin, acne and increased haematocrit. Though the subjects tolerated the injections well, this method of weekly intramuscular delivery of testosterone is not practical. Moreover, the serum testosterone levels achieved were above the physiological range at the peak and were at the upper normal range at the trough.

In the past decade, longer-acting testosterone preparations have been developed and some have been tested for efficacy of spermatogenesis suppression (Table 2). These include testosterone implants and testosterone buciclate and undecanoate.[10–14] Testosterone implants (1200 mg) gave the same suppression of spermatogenesis as weekly injections of testosterone enanthate.[10] Testosterone undecanoate administered at 500 or 1000 mg every 4 weeks in Chinese men[14] or 1000 mg every 6 weeks in Caucasian men[15] also resulted in suppression of sperm production to a similar degree as testosterone enanthate.

Table 2. Androgens plus progestins used in male contraceptive trials.

Androgen	Progestin
Injectables	*Injectables*
Testosterone enanthate	Medroxyprogesterone acetate
Testosterone undecanoate	Testosterone enanthate
Testosterone decanoate	
Oral	*Oral*
Testosterone undecanoate (not effective)	Levonorgestrel
	Desogestrel
	Cyproterone acetate
Implants	*Implants*
Testosterone	Levonorgestrel
7α-Methyl-19-nortestosterone	Etonogestrel
Transdermal	*Transdermal*
Testosterone patch (not effective)	Not tested

Androgens increase lean body mass and bone mineral density and decrease body fat. These health benefits can be potentially helpful in men especially in developing countries. Supra-physiological doses of testosterone have the potential to induce weight gain and acne. At least two safety issues remain unsettled. These include whether supra-physiological doses of androgens have potential adverse effects on the prostate gland and cardiovascular system. It is clear that androgens are required for the growth and development of the prostate. Although long-term follow up has not been assessed, there is no evidence to show that androgens will result in benign prostatic hyperplasia. Most of the prostate cancers in men are androgen-dependent, thus testosterone replacement must not be used until the presence of prostate cancer is excluded. There is also no evidence that androgen treatment will induce the development of prostate cancer or the progression of histological to clinical cancer.[16–18] Androgens for contraceptive purposes will be administered to younger men whose partners are in the reproductive age group. Prostate cancer is extremely uncommon in men before the age of 55. Thus the risk of androgens, if any, on prostate diseases cannot be tested until a hormonal male contraceptive method becomes available and introduced as a family planning method. At this time, large-scale, long-term epidemiological studies cannot be done. Testosterone administered exogenously causes a small decrease in serum HDL-cholesterol levels without affecting LDL-cholesterol or triglycerides. Serum total cholesterol shows no change, or a slight decrease. The clinical significance of a slight decrease in HDL-cholesterol levels within the normal range is unknown. Recent studies have demonstrated a direct vasodilatory effect of testosterone on the coronary arteries. Other lipids, coagulation-and fibrinolytic factors are also affected by androgens. Thus, despite the early evidence of decreased HDL-cholesterol concentrations, it is unlikely that the use of androgen in younger adult men will result in an increased cardiovascular disease risk even after long-term administration.[16–18] Nevertheless, long-term carefully performed safety studies are needed to resolve these issues.

Androgens and progestin combinations

It has been proposed that the addition of another gonadotropin-suppressing agent such as a progestin will have synergistic effects with androgens and allow the dose of androgens to be reduced. A number of testosterone and progestins had been tested in the past.[19] A more recent study comparing testosterone alone (testosterone enanthate 100 mg i.m./week) versus testosterone plus levonorgestrel (250 μg/day, oral administration) confirmed that the combination suppressed spermatogenesis to azoospermia and severe oligozoospermia more effectively (combination 94%, testosterone alone 61%) and more rapidly (combination 8.9 weeks; testosterone alone, 14.4 weeks).[20] Subsequently, studies by this group showed that the dose of oral levonorgestrel can be further reduced to 125 μg/day without decreasing spermatogenic suppression but decreasing the weight gain and the suppression of serum HDL levels observed with the oral progestin.[21] Table 2 shows the combination of androgens and progestins that has been tested in clinical trials up to now.

Testosterone enanthate has been studied together with medroxy-progesterone acetate (DMPA) injections[22], oral desogestrel[23,24] and cyproterone acetate (a progestin with anti-androgenic action).[25,26] All of these studies showed an enhancing effect of progestin on androgens. Testosterone undecanoate has been studied with oral levonogestrel (250 μg/day)[15] and norethisterone enanthate injections (200 mg/6 weeks, i.m.).[27] The combination of testosterone undecanoate with norethisterone enanthate was very effective in suppressing spermatogenesis to azoospermia but not

when combined with oral levonorgestrel. Similarly, testosterone pellets (800 mg) administered with DMPA (300 mg injections) were very effective in achieving azoospermia.[28] In contrast to injectable androgens, testosterone patches used in combination with levonorgestrel[29] administered either orally or as implants (unpublished data from our centre) had little suppressive effect on the testes, with only about 25–30% of men treated acheiving azoospermia. Studies just completed, ongoing, or planned include: 1) testosterone undecanoate with norethisterone enanthate injections, DMPA injections, etonogestrel implants; 2) testosterone pellets with DMPA injections, or levonorgestrel or etonogestrel implants; 3) 7-α methyl-19-nor-testosterone(MENT) implants with levonorgestrel implants; and 4), testosterone decanoate injections with etonogestrel oral or implants.

Cyproterone acetate (CPA) is an oral potent progestin with anti-androgenic properties. When used alone, CPA decreases serum testosterone levels resulting in hypogonadism.[30] In combination with testosterone enanthate (100 mg/week or 250 mg/2 or 3 weeks), treatment resulted in azoospermia or near azoospermia in all of the small number of men tested. There was no change in serum lipids. High doses of CPA (50 mg or above) result in decreases in haematocrit even when used with physiological doses of testosterone.[25] Reducing the dose of CPA to 20 mg/day eliminated the changes in haematocrit.[26] CPA is not available for male contraceptive development. Another progestin with anti-androgenic action is dienogest; studies are planned to use this anti-androgen/progestin with androgens in small-scale clinical trials.

Selective androgen and progestin receptor modulators

Selective steroid receptor modulators are designer molecules that can be agonistic to the steroid at one target tissue and antagonist to the same steroid at other sites.[31] Examples of such modulators include selective oestrogen receptor modulators (SERMS), such as tamoxifen and raloxifen which have agonistic oestrogen actions on the bones and antagonistic effects at the breast. Tamoxifen acts as an agonist on the uterus, raloxifen does not. MENT is a selective androgen receptor modulator (SARM) with very potent agonist actions in the pituitary and muscle and much less potent activity in stimulating prostate growth than testosterone.[32] MENT has been shown in clinical studies to maintain sexual function in androgen-deficient men.[33] Several members of the pharmaceutical industry are proceeding with the development of once-a-day orally active agents that have agonistic effect as androgens on the hypothalamus/pituitary, bone, muscle, bone marrow, and antagonistic or neutral effects on the prostate. Similarly, selective progesterone receptor modulators (SPRM) are also being developed. These SPRMs should have the gonadotropin-suppressive effects of progesterone but minimal effects on lipid and carbohydrate metabolism. It is also conceivable that a hybrid with both SARM and SPRM properties could be created for hormonal male contraception.

Androgens and GnRH antagonists

Unlike in the female, where GnRH agonists are very effective in suppressing ovulation, GnRH agonists are not predictably effective agents in suppressing spermatogenesis in men. GnRH agonists, when administered in high doses or as an infusion together with an androgen in men, result in suppression of serum LH and FSH but fail to decrease sperm concentration to azoospermia or severe oligozoospermia for effective contraception.[34–36] By contrast, GnRH antagonists (administered as a daily subcutaneous

injection) in combination with androgens are very efficient suppressors of gonadotropins and spermatogenesis.[37–39] These earlier GnRH antagonists caused local skin reaction in most men; more recently developed GnRH antagonists do not have observable local histamine-like adverse effects.[40] Despite their effects, GnRH antagonists are expensive to synthesize. Because GnRH antagonist suppresses serum FSH and LH usually to non-detectable levels, the testosterone used will be required only as a replacement to prevent hypogonadism. The dose of testosterone used with a GnRH antagonist will most probably be lower than the dose employed in androgen plus progestin combinations.

A recent study conducted in two centres in the USA (Harbor-UCLA and University of Washington) showed that when spermatogenesis was suppressed to azoospermia or severe oligozoospermia with a combined GnRH antagonist (daily subcutaneous injection) and testosterone (testosterone enanthate injections 100 mg/week), the suppression of spermatogenesis could be maintained by the testosterone preparation alone.[41] This is of clinical and practical importance because it demonstrated that when the testicular production of sperm is severely suppressed, the maintenance of suppression requires only an androgen. It is conceivable that the azoospermia/oligozoospermia induced by androgen plus progestin might also be maintained by androgens alone.

Androgen and oestrogen combination

Studies in rats and monkeys showed that addition of oestradiol implants to testosterone implants resulted in suppression of spermatogenesis that appeared to be more complete.[42] Oestrogens may have the potential side-effect of inducing more gynaecomastia but have beneficial effects on bone and reverse the decreases in HDL cholesterol associated with androgen therapy. A small-scale study performed in human subjects did not show an additive suppressive effect on spermatogenesis by oestradiol and testosterone combination treatments.[49]

Observed ethnic differences in the suppression of spermatogenesis

When testosterone enanthate injections were administered to healthy volunteers in the multi-centre studies initiated by the WHO, it was noted that in Asian centres the suppression of spermatogenesis to azoospermia was achieved in $>90\%$ of Asian men. In non-Asian centres using a similar treatment, azoospermia was achieved in only 60% of men.[8,9] Similarly, when testosterone was administered with DMPA to Indonesian men, azoospermia was achieved in $>95\%$ of the volunteers compared to the 60–70% observed in non-Asian volunteers.[21] Despite efforts by several groups to unravel this disparity, it is not clear why Asian men appear to be more susceptible to suppression of spermatogenesis to azoospermia by exogenous hormones. It has been suggested that incomplete suppression of intra-testicular androgens, (e.g. dihydrotestosterone) could be responsible for this ethnic disparity.[43] As yet, strong supportive evidence for this concept has not emerged. Studies from our group have suggested that the suppression of the secretory pulse amplitude of LH by testosterone occurred more rapidly in Asian versus non-Asian men.[44] Others have demonstrated that the basal testosterone production rate is lower in Asian men though the metabolic clearance rate of testosterone is similar.[45] Our group also demonstrated in autopsy samples that the daily sperm production rate per man might be lower in Asian versus Hispanic or Caucasian men.[46] We have also shown that the basal germ cell apoptosis rate is higher in Asian men.[47] These studies suggest that genetic/geographical groups might respond

differently to hormonal administration. Some hormonal contraceptive methods might work better in some regions and populations.

OTHER APPROACHES TO MALE CONTRACEPTION

Gossypol (cotton seed oil) has been proposed to have contraceptive potential in studies carried out in the 1980s in China. When studied in normal volunteers, gossypol induced severe suppression of germ cell development. In 10–25% of subjects administered varying doses of gossypol, the sperm concentration did not return to normal range. Thus administration of gossypol does not lead to reversible contraception.[48]

Agents which affect the function of the spermatozoa within the epididymis or others which change the intra-epididymal environment have also been studied. Such agents would have a fast onset and would not cause any perturbations to the hypothalamic–pituitary–testis axis. A major research effort sponsored by national and international collaboration is working to identify agents that will fulfil this role.

Auto-immune infertility in the male is caused by auto-antibodies in the reproductive tract resulting in dysfunction of sperm. Active investigation is ongoing to identify sperm membrane antigens critical to fertilization. Antibodies have been developed against these sperm antigens and are being tested in non-human primate models. None of these immuno-contraceptive methods has proceeded to clinical trials in men.

SUMMARY

Currently available methods of male contraception include condoms and vasectomy. Condoms have a failure rate of about 12%. Vasectomy is considered an irreversible method. These methods are not acceptable to all couples.

Hormonal methods are based on reversible suppression of gonadotropins (both LH and FSH) and inhibition of intra-testicular steroid and sperm production. In 1990 and 1996, the WHO published results from two studies using testosterone injections as a prototype hormonal method. These studies demonstrate for the first time that if a hormonal method can render most of the men azoospermic and the remainder severely oligozoospermic (<3 million/ml ejaculate), this would provide efficacious contraception. The current research efforts in male methods of contraception consist of, firstly, developing more user-friendly androgen delivery systems. Recent advances in the understanding of androgen receptor actions are leading to the synthesis of non-steroid androgen receptor agonists that could have tissue specificity. These agents, which can be taken orally, could provide selective androgen agonistic effects on gonadotropin and sperm suppression but without any effect on the prostate or on synthesis of lipoproteins in the liver. The other approach is to use progestins or other gonadotropin suppressors together with androgens. The rationale is that the combination will synergistically lead to greater suppression of spermatogenesis. The dose of androgens can be lowered to reduce the possibility of long-term adverse effects. Current research is in progress to define the most effective and safe combinations of androgens and progestins. GnRH antagonists interfere with the action of GnRH at the pituitary. When administered as a daily subcutaneous injection, GnRH antagonists suppress gonadotropins, and hence spermatogenesis, in a more rapid and complete fashion. Molecular modelling will allow the development of non-peptide GnRH antagonists which then can be administered orally.

Agents acting directly on the testis have not undergone further development because of the problem of irreversibility. New approaches in decreasing functional capacity of the spermatozoa while in the epididymis are being investigated in collaborative projects amongst researchers.

The future of male contraceptive development lies in the development of androgen and progesterone receptor modulators which have strong gonadotropin suppressive activity while maintaining sexual function, bone and muscle mass but will have little or no effect on the prostate or serum lipids. Mechanisms to shorten the time lag between the start of hormone administration and suppression of spermatogenesis have to be identified. Combination of agents directly acting on the testis or the epididymis together with a hormonal method could accelerate the development of more complete but reversible suppression of spermatogenesis which can then be maintained by lower doses of the hormone.

Research agenda

- new or improved methods of vas occlusion
- identification of the best androgen and progestin combination for efficacy studies in large numbers of subjects
- development of selective androgen (SARMS) and/or progestin receptor (PRMS) modulators
- non-peptide GnRH antagonist and user-friendly GnRH antagonist delivery systems
- new post-testicular leads or targets for male contraception

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