Male contraception: Expanding reproductive choice

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The development of steroid-based oral contraceptives had revolutionized the availability of contraceptive choice for women. In order to expand the contraceptive options for couples by developing an acceptable, safe and effective male contraceptive, scientists have been experimenting with various steroidal/non-steroidal regimens to suppress testicular sperm production. The non-availability of a long-acting androgen was a limiting factor in the development of a male contraceptive regimen since all currently tested anti-spermatogenic agents also concurrently decrease circulating testosterone levels. A combination regimen of long-acting progestogen and androgen would have advantage over an androgen-alone modality since the dose of androgen required would be much smaller in the combination regimen, thereby decreasing the adverse effects of high steroid load. The progestogen in the combination regimen would act as the primary anti-spermatogenic agent. Currently, a number of combination regimens using progestogen or GnRH analogues combined with androgen are undergoing trials. The side effects of long-term use of androgens and progestogens have also undergone evaluation in primate models and the results of these studies need to be kept in view, while considering steroidal regimens for contraceptive use in men. Efforts are also being made to popularize non-scalpel vasectomy and to develop condoms of greater acceptability. The development of contraceptive vaccines for men, using sperm surface epitopes not expressed in female reproductive tract as source, still requires considerable research efforts.

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The steadily expanding population in developing countries is now of global concern due to its impact on health and societal dynamics. The development of oral contraceptives for women initiated a revolution in contraceptive options. While this was a major landmark in expanding contraceptive choice for women, a similar breakthrough has not taken place in the field of male contraception.

New contraceptive options for men, both hormonal and non-hormonal, are required urgently since vasectomy, withdrawal and condom use are inadequate and have many limitations, which are well known. Attempts to use unique sperm surface epitopes that are not expressed in the female reproductive tract as source to develop contraceptive vaccines for men have not yielded any major successful lead. Increasingly, efforts are being focused on the development of hormonal agents that would induce adequate level of spermatogenic suppression that is not compatible with fertility. This article reviews the recent developments in the area of male contraception and highlights the research done by Indian scientists.

It may be argued that research efforts for developing male oriented methods are not a priority since men are reluctant to opt for contraception, but published data show that men form 26% and 11% of contraceptive users (adopting vasectomy, and condom use, respectively) in developed and developing regions of the world. Even in a setting like India where the contraceptive use of condom and vasectomy by men is a dismal 5% (ref. 2), it was found possible to enhance male involvement by using appropriate intervention strategies. It is also likely that the contraceptive choice of men from different socio-cultural environments and age groups may be different, thus requiring a wider spectrum of options.

Major attempts to develop an effective male contraceptive have focused on different aspects of sperm development, maturation and transport. The present review will focus on research efforts towards (1) prevention of sperm deposition, (2) prevention of sperm transport and, (3) inhibition of spermatogenesis.
Prevention of sperm deposition

Condoms

Condoms have been in use as a barrier method to prevent sperm deposition in the female tract since 1564 when Fallopio used a sheath for “use against venereal disease and numerous bastard offspring”. The history of condom use and research on the development of new generation of condoms have been reviewed earlier.

The coating of condoms with microbicides was presumed to reduce HIV transmission in women. The nonionic detergent nonoxynol-9 (N9), which was considered a spermicide, has been in use for coating condoms. But, the use of vaginal sponges containing N9 was found to increase the risk of HIV infection in female sex workers in Kenya. This was attributed to the cell membrane disrupting action of N9, which acts as an irritant in the epithelium of penis and vagina in approximately 56% of women who were using N9 suppositories four times per day for two weeks. It is clear that the use of spermicides-microbicides would have a significant impact on the role of male and female condoms in contraception and prevention of transmission of sexually transmitted diseases.

Prevention of sperm transport

Contraceptive options for men which are currently available are vasectomy and condom use. Of these, vasectomy or male sterilization is a cheap and an effective method of preventing sperm transport through the vas deferens. Improvement to the method of traditional vasectomy is the “non-scalpel” technique. Various aspects of post-vasectomy complications, vasectomy reversal (vasovasostomy) and pregnancy rate, and long-term health consequences of vasectomy and safety have been reviewed.

In attempts to interfere with sperm passage through the vas deferens, sclerosing agents like quinacrine, ethanol, and silver nitrate have been introduced into the vasal lumen resulting in sclerosis, inflammation, and fibrosis. The occlusion thus induced was irreversible and in some cases, retrograde flow of the agent resulted in testicular atrophy. Intra-vasal injection of polyurethane or silicone rubber resulted in plug formation by polymerization in situ. Since in situ polymerization may be accompanied with the release of potentially toxic compounds, Zaneveld and associates used preformed soft hollow silicone plug called SHUG. Several different SHUG devices and insertion techniques were tested. A high level of contraceptive efficacy was obtained with two SHUG devices. In Indonesia, removable vas occlusion has been achieved by injection of Medical Grade Silicone Rubber (MSR) which cures-in-place to form plugs. The rate of azoospermia, six months after MSR vas occlusion was 98.27% compared to 100% in the vasectomy series.

The partial blocking of vasal lumen by injection of copper resulted in loss in functional capacity of the spermatozoa. Insertion of copper wire into the vas caused decapitation of spermatozoa and resulted in infertility but the effectiveness decreased with time, probably due to erosion of the copper wire. The polymer, Styrene Maleic Anhydride (SMA), when injected into the lumen of the vas deferens in dimethyl sulfoxide is reported to be an effective method of male contraception. Phase I and II clinical trials using the RISUG (trade name of SMA) have been completed. Mishra et al. have reported focal degeneration of seminiferous epithelium in testis of langur monkeys following long-term (540 days) vas occlusion with SMA.

Inhibition of spermatogenesis

Hormone-based approach to male contraception

The development of hormone-based male contraceptive is based on the premise that the suppression of gonadotrophin production will result in the inhibition of spermatogenesis. Gonadotrophin production can be suppressed by the use of (1) steroidal agents like androgen, progestogen, estrogen or combination of these, and (2) by the use of non-steroidal agents. Among the non-steroidal agents, GnRH agonists and antagonists have been evaluated extensively. Suppression of gonadotrophins results in decrease in androgen production leading to clinical manifestations of androgen deficiency. To offset such androgen insufficiency, external androgen supplementation is required. Combination regimens using androgen supplementation need careful monitoring of the dose of androgen to prevent the combination regimen, which suppresses gonadotrophin secretion by interfering with negative feedback control at the pituitary and hypothalamus (e.g. exogenous steroids) or directly by inhibiting the

**Androgen-alone regimen**

Testosterone enanthate

Clinical trials using an androgen alone for male contraception, though carried out for the first time by Indian investigators, is seldom acknowledged. Reddy and Rao\(^\text{15}\) induced uniform azoospermia in men by injecting testosterone propionate (TP) daily. Since daily administration of TP is not feasible for family planning purposes, investigators used thereafter testosterone enanthate (TE) \(^\text{3,5,16,17}\). But, the dose of TE used and schedule of administration were not comparable among the different studies. Further, some of the investigators have used different doses of TE during the induction and maintenance phases to minimize the dose of the drug and thereby reduce the adverse effects. These studies indicated that the androgen-alone modality is able to induce spermatogenic suppression in men to varying degrees depending on the protocol of drug use. Using a standardized protocol, WHO conducted a ten-center seven-country contraceptive efficacy study using weekly injections of TE. No other method of contraception was used once sperm counts decreased to a preset level. The results of this large study showed that during 1486 months of efficacy period, only one pregnancy occurred\(^\text{18}\). The cumulative life table to achieve azoospermia was only 64.5\%. Two interesting observations made out of this study were:

1. the variable response in achievement of azoospermia within six months of exposure to weekly injections of TE, and
2. differences in contraceptive responses in men of Caucasian (60\%) and Chinese (91\%) origin to weekly injections of TE. Subsequent studies also confirmed that androgen alone\(^\text{19-20}\) or in combination with progestins\(^\text{21}\) induced azoospermia in a greater percentage of Asian men than in Caucasian subjects. Body size or pretreatment basal levels of endocrine and semen profile were not related to these ethnic differences in responses. The precise reason for such differences in ethnic response to steroids still needs to be identified.

The contraceptive efficacy of testosterone-induced oligozoospermia was evaluated in a 15-center study undertaken by WHO in which TE-induced suppression of sperm count to \(3 \times 10^9/\text{ml}\) was taken as the cut-off limit to enter the efficacy phase\(^\text{22}\). Four pregnancies were reported during 49.5 person-years of contraceptive efficacy phase in men with sperm count between 0.1 to 3 million/ml. None of the azoospermic men in 230.4 person-years of efficacy phase reported the occurrence of pregnancy.

These landmark multicenter trials carried out by WHO established the fact that hormonally induced azoospermia is compatible with effective contraception. On the basis of these two studies, it was concluded that (1) hormone regimens that induce azoospermia can provide highly effective, sustained and reversible male contraception with minimum side effects\(^\text{18}\) and (2) that, if most of the men were rendered azoospermic, and the rest severely oligozoospermic by a hormonally based agent, this would provide a sustained, reversible level of contraception with an overall level of efficacy similar to that of the combined oral contraceptive pill for the women\(^\text{22}\).

The pharmacokinetic profile of TE, with sharp increase in testosterone levels after injection followed by an exponential fall and short duration of action, were major disadvantages in its use for clinical purposes. The need for a long-acting androgen or improved delivery systems led to the pre-clinical evaluation of a number of promising compounds and evaluation for alternate drug delivery systems. These include testosterone buciclate, injectable testosterone undecanoate, 7α methyl 19-nor testosterone (MENT), testosterone pellets, and transdermal and buccal modes of androgen delivery.

**Testosterone buciclate**

Preclinical evaluation of the pharmacokinetics and pharmacodynamics of testosterone buciclate (TB) in castrated rhesus monkeys showed it to be the longest acting testosterone ester available\(^\text{23,24}\). It was also effective in suppressing spermatogenesis to azoospermia or to severe oligozoospermia, when combined with the long-acting progestogen, levonorgestrel butanoate\(^\text{25}\). The dose of TB was sufficient to maintain circulating androgen levels in the physiological range. But, TB is not available for clinical use due to difficulties in formulation and possible toxicity. When given alone to adult bonnet monkeys at multiple sites, TB decreased sperm count and testicular volume and adversely affected sperm maturation, even though the circulating levels of testosterone were at the upper limit of the physiological range\(^\text{24}\).

**Testosterone undecanoate**

Testosterone undecanoate (TU) has been considered for long as an orally active preparation,
but was not considered suitable for use in contraceptive formulations. Following oral use, marked fluctuations in serum testosterone levels and only partial suppression of gonadotrophin levels occurred. Consequently, spermogonadogenic suppression that occurred was not compatible with the needs of effective contraception.

When dissolved in tea seed oil for injection, TU was found to have favourable pharmacokinetics in castrated monkeys and hypogonadal men. Contraceptive efficacy studies showed that 1000 mg/4w TU induced azoospermia in all 12 Chinese men whereas a 500 mg/4w dose resulted in azoospermia in 11/12 men. The mean time to azoospermia was 12-16 weeks of TU injections. A large efficacy study using TU in 308 men showed that in nine men, spermatogenesis was not suppressed to a sperm concentration of 3 x 10^6/ml or lower within six months. Pregnancies were not reported when sperm concentration remained below 3 x 10^6/ml. But, the same authors reported that when TU was given alone at 1000 mg/8w for 24 weeks, only 67% of men attained azoospermia. The disadvantage of TU is the large diluent volume of 8ml needed for injection. When dissolved in castor oil, the diluent volume for TU is 4ml, as developed by Jena Pharm.

7α-methyl-19-nor testosterone (MENT)
On the basis of stimulation of ventral prostate weight, MENT, a synthetic androgen, has a potency which is 4-5 times greater than that of testosterone. MENT does not undergo 5α-reduction but can be aromatized, and it is not bound by SHBG and is rapidly cleared from the circulation. Two MENT acetate implants inserted in hypogonadal men supported sexual behavior similar to TE. MENT (25 μg) delivered through silastic implants in bonnet monkeys decreased sperm count to oligozoospermia but increasing the dose supported spermatogenesis. MENT has the advantage that it is only twice as potent as testosterone in stimulating prostate growth whereas its potency in suppressing gonadotrophin secretion and stimulating anabolic activity is ten times more than testosterone.

Non-aromatisable androgens — dihydrotestosterone (DHT) and androstanediols
The aromatization of administered testosterone resulting in increased levels of estradiol thereby leading to unwanted side effects was considered undesirable for male contraception. In view of this, the effects of administration of non-aromatisable androgens like DHT and androstanediol were evaluated in rhesus monkeys. In these treated animals, spermatogenesis progressed only to spermatid level in some tubules, while adjacent tubules, showed qualitatively normal spermatogenesis. The absence of ejaculatory response with increase in duration of administration of these non-aromatisable androgens was a major drawback of this regimen. DHT/androstanediol treatment decreased circulating levels of testosterone, but FSH levels were near normal, which may explain the reason for only partial suppression of spermatogenesis. Short-term or long-term exposure to DHT suppressed plasma testosterone and LH in men.

Alternate testosterone delivery systems
Alternate drug delivery modalities were explored by investigators for the delivery of testosterone. These include subdermal fused testosterone implants, transdermal delivery of testosterone intended for scrotal or non-scrotal application and buccal delivery of testosterone. The results of these studies have been reviewed earlier. These modalities of androgen delivery have inherent limitations like: (1) preparation of scrotal skin for patch adhesion, (2) skin irritation in patches with an alcohol base resulting in high discontinuation rate, (3) decreased adherence when patches are applied over a wider area, and (4) visibility.

Progestogen-alone regimens
Progestogens have been tested to assess their potential to suppress spermatogenesis, either alone or in combination with androgen. Progestogens bind to their receptors and suppress gonadotrophin production, besides direct effects on testis by inhibiting androgen biosynthesis and androgen action. Progestogens used for male contraception include derivatives of 19 nor-testosterone (norethindrone acetate, norgestrel, norethisterone enanthate, ethinodiol diacetate), or 17 hydroxyprogesterone derivatives obtained by acetylation of 17 hydroxy group (medroxyprogesterone acetate). New progestogens like desogestrel, gestodene and norgestimate are LNG derivatives. Progestational compounds like levonorgestrel possess inherent androgenic activity, while norethindrone, norethinodrel and ethinodiol diacetate show weak
estrogenicity. These properties of the progestogens would influence their mode of action when used at high doses for suppressing spermatogenesis. In contrast, progestogens like medroxyprogesterone acetate (MPA) obtained by substitution at the 17 and 6 positions of progesterone molecule are devoid of androgenic and estrogenic activities.

Clinical trials carried out by the International Committee for Contraceptive Research of the Population Council, USA using progesterone alone or in combination with androgen showed that azoospermia could be achieved only in 87 of the 191 subjects. It was clear that the dose of progestogen used needs to be increased significantly for effective contraception. Further, the androgen deficiency induced needs to be compensated by use of androgen supplementation.

Progestogen-androgen combination regimens

In combination regimens using progestogen and androgen, the progestogen acts as the primary anti-spermatogenic agent by suppressing gonadotrophin production and action, which is potentiated by androgen co-administration progestogens, in addition to their anti-gonadotrophic effects, also exert direct effects on testis including inhibition of steroidogenesis, inhibition of LH receptor expression and function and on spermatozoa via the non-genomic progesterone receptor.

Medroxyprogesterone acetate (MPA)-androgen combination regimens

Clinical trials have been conducted since 1965 to identify the most effective combination regimens. A consensus has eluded on the dose, schedule, and duration of administration, and on the identity of the progestogen-androgen combination regimen that would induce uniform azoospermia. The contraceptive efficacy of MPA has been evaluated in many clinical trials; the androgen of choice included TE, TU, testosterone cypionate, methyltestosterone or 19 nor-testosterone. Of these androgen preparations used, injectable TE appears most promising. Use of a higher initial loading dose (1000 mg) of DMPA with 250-500 mg TE resulted in 80-100% of men achieving azoospermia, but the lower maintenance doses used were unable to maintain azoospermia with return of spermatogenesis. In the WHO conducted study in Indonesia using 250 mg DMPA plus 200 mg TE/19 nor-testosterone, a higher percentage of subjects became azoospermic (96.7%), compared to trials in Caucasian men, similar to the ethnic differences in response of men to TE. Treated subjects showed gynaecomastia and weight gain. But, the adverse effects on serum lipoproteins and delay in restoration of spermatogenesis due to accumulation of DMPA in the adipose tissue are of concern in the use of the regimen for contraception.

DMPA has also been used in association with percutaneously applied testosterone or DHT; DMPA plus percutaneous androgen induced effective suppression of spermatogenesis, but the side effects in female partner (hirsutism) due to absorption of androgen from the male partner led to the termination of this regimen. Use of transdermal testosterone patches for testosterone delivery also was not acceptable due to allergic skin reactions which were quite severe in some subjects.

Levonorgestrel-androgen combination regimen

19 nor-testosterone-derived progestogens like levonorgestrel are potent gonadotrophin inhibitors. Levonorgestrel has been used orally and as implants in women. In men, orally administered levonorgestrel (LNG; 500 mg/day) combined with weekly injections of TE (100 mg) induced azoospermia in 67% of subjects compared to only 33% azoospermia induced in TE plus placebo group. Levonorgestrel, being a very potent gonadotrophin suppressor was more effective in suppressing spermatogenesis when combined with androgen than the androgen-alone modality. However, the inherent androgenicity of levonorgestrel demonstrated by classical ventral prostate assay requires careful titration of the dose of the progestogen and androgen in the combination regimen to ensure that spermatogenesis remains fully suppressed. This was evident in the dose finding studies carried out in bonnet monkeys using long-acting levonorgestrel butanoate (LNG-B) and TB. Among the three doses used, 1 mg/kg of LNG-B co-administered with 40 mg TB on days 0 and 60 evoked maximum suppression of spermatogenesis to azoospermia or to severe oligozoospermia, while androgen levels were maintained in the physiological range. Thus, the overall androgenic status of the subject appears crucial when progestin-androgen combination regimens are evaluated for suppression of spermatogenesis. Another cause of concern is the androgen related side effects like decrease in HDL-
cholesterol, weight gain and acne. Injectable TU in combination with oral LNG induced azoospermia in only 50% of subjects, possibly due to the high androgen levels. Gui et al. assessed the contraceptive efficacy of LNG implants (75 mg each) in Chinese men combined with TU injections. Insertion of four LNG implants followed 4 weeks later by TU (1000 mg/8w) for 24 weeks resulted in greater number of men attaining azoospermia (90%), compared to men with similar LNG load but only 500 mg TU/8w (62%) or TU (1000 mg/8w) alone (67%), highlighting the greater efficacy of the combination regimen. Adverse effects including changes in serum chemistry were not observed.

Desogestrel-androgen combination regimen
Desogestrel at 300 mg, po daily, combined with 500 mg TE/w or 150 mg, po, daily desogestrel +100 mg TE/w resulted in azoospermia in all treated men, but the number of subjects involved was small. Decreasing the dose of desogestrel or increasing the dose of TE or use of testosterone pellets did not result in uniform induction of azoospermia. It is essential to use a larger number of subjects in such clinical trials to reach reliable conclusions, which is evident in the results of the two-center study (Edinburgh and Shanghai) using 150 or 300 mg desogestrel po, daily for 24 weeks with 400 mg testosterone pellets sc on day one and at 12 weeks. Azoospermia was achieved in greater proportion of men (28/28) in the 300 mg desogestrel group compared to the 150 mg group (22/31). Surprisingly, a trend towards greater spermatogenic suppression was seen in the Caucasian group than in Chinese men, in contrast to the results of the WHO-conducted TE study. Whether this would be substantiated in a closely monitored multicentre study similar to the WHO study remains to be seen. The fall in HDL-cholesterol in Caucasian men was an adverse side effect not reported by Chinese subjects.

Since the active agent of desogestrel is etonogestrel, the contraceptive efficacy of etonogestrel implants (releasing approximately 50 mg of the drug/day) combined with testosterone pellets was compared, however uniform azoospermia was not induced.

Norethisterone-androgen combination regimen
Norethisterone enanthate (NET-en) is a progestogen with approximately 15% of the androgen action of testosterone and is metabolized to ethinyl estradiol and 5α-estradiol. In bonnet monkeys, spermatogenesis could be arrested by 0.8 mg/day NET-en and estradiol valerate, (0.015mg/d) administered via Alzet mini pumps. Preliminary data indicated the high efficacy of TU and NET-en regimen using varying doses of NET-en and mode of application. The results showed that injection of TU/6w combined with 400 mg NET-en/6w is an effective contraceptive modality to suppress spermatogenesis. But side effects included increase in body weight, erythrocytes, hemoglobin and haematocrit and decrease in HDL-cholesterol and alkaline phosphate.

Cypionate acetate-androgen combination regimens
Cypionate acetate (CPA) is an anti-androgen as well as a progestogen and has been in clinical use for treatment of hypersexuality, acne and hirsutism in women and prostate cancer in men. Use of CPA for male contraception requires androgen substitution to offset androgen deficiency caused by its strong anti-androgenicity. This was evident in the results of clinical trials conducted in 1970's using CPA alone. The marked suppression in spermatogenesis achieved by CPA was attributed to its direct effects on testis in addition to its progestational activity since CPA competitively inhibits binding of testosterone and DHT to the androgen receptor.

The first combination regimen of CPA and TE was evaluated in langur monkeys. Spemmatogenesis was suppressed to azoospermia or to severe oligozoospermia. All metabolic parameters were normal.

When CPA was combined with the long-acting androgen TB, uniform azoospermia was induced without any adverse effects. These studies proved that the dose and type of androgen used are critical in the induction and maintenance of azoospermia.

Combination of 25-100 mg/d CPA (oral) with 100 mg/d TE resulted in rapid onset of azoospermia in all subjects. The fall in body weight, hemoglobin concentration and haematocrit was attributed to the anti-androgenicity of CPA. In these studies, CPA did not cause adverse effects on liver function parameters or HDL-cholesterol. At a relatively low dose of 12.5 mg CPA/d, in combination with TU, spermatogenesis was suppressed in men. Cypionate acetate is thus a promising compound for evaluation as a male contraceptive.
contraceptive agent in combination with an appropriate androgen, since CPA is capable of inducing a greater degree of suppression of spermatogenesis at a relatively shorter duration of time, possibly due to its antagonistic role in suppressing even residual intra-testicular testosterone.

**Estrogen-testosterone combination regimens**

While estradiol enhances spermatogenic suppression caused by testosterone, the side effects of estradiol restrict the application of this modality for contraceptive purposes. At best, this approach is of academic interest only.

**GnRH analogues for male contraception**

It was felt that the abolition of gonadotrophin secretion by interference with the action of GnRH on gonadotrophin would be a more direct approach for spermatogenic suppression than the steroidal approach based on interference with the negative feedback action on gonadotrophin secretion. However, hypogonadism thus induced needs to be corrected with androgen supplementation.

**GnRH agonists**

The feasibility of using GnRH agonistic analogues for gonadotrophin suppression and spermatogenic arrest has been evaluated in a number of trials. But, the number of subjects who attained azoospermia was less than in the androgen-alone regimens. This approach was not pursued further.

**GnRH antagonists**

GnRH antagonists have an advantage over agonists since the former cause an immediate and complete suppression of gonadotrophins by competitive GnRH receptor blockage. The resultant hypogonadism is compensated by external androgen supplementation. A number of GnRH antagonists have been evaluated both in primate models and in men and the results have been promising. But, the disadvantages of GnRH antagonists use like high cost of the drug, significant weight loss, incomplete/sustained spermatogenic suppression and allergic reaction at the injection site need to be addressed before this regimen can be extrapolated into large-scale clinical trials.

**Side effects of long-term androgen use**

It is clear from the review of literature that androgen supplementation would form an integral component of a hormonal male contraceptive. Since androgens developed and being evaluated for this purpose should maintain steady-state physiological levels of circulating hormone for relatively long period of time on the other hand, they should not evoke any adverse side effects on systemic and metabolic functions; further, they should be long-acting and affordable.

Androgens for use in male contraception should be evaluated extensively for their long-term effects on cardiovascular, liver and prostate functions. Androgens cause major shifts in lipoprotein fractions in the blood and act as risk factors for ischemic heart disease. High levels of triglycerides in blood have been linked to a high incidence of cardiovascular disease. Androgens are also known to increase liver transaminases in Asians and have been implicated in the occurrence of hepatocellular carcinoma. Adult rhesus monkeys kept under controlled dietary conditions and exposed continuously to 50 mg TE once in 14 days for 32 months showed alterations in lipid profile with increase in LDL-cholesterol and decrease in HDL-cholesterol. Serum transaminases were also markedly elevated in these animals. Elevation in serum transaminases was reported in Chinese men who participated in the WHO multicenter trial using TE. Long-term TE use also induced hypo-insulinemia in monkeys and was attributed to an improvement in tissue sensitivity to the glucoregulatory effects of insulin. Long-term administration of androgen metabolites is known to induce pre-malignant lesions in the prostate of monkeys.

Other side effects of androgen administration are weight gain, acne, and possible effects on bone. Development of long-acting androgens with improved kinetics of absorption may reduce substantially the adverse effects noticed with currently available formulations.

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