

Review Article

Pharmaceutical Approaches and Advancements in Male Contraception

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Abstract

Currently available contraceptive methods offer a variety of options for women, but only very few for men which include surgical methods, condom and hormonal methods. Non-surgical and non-hormonal methods are under investigation. Among these, hormonal contraceptive approaches, including injections, oral and transdermal delivery systems of testosterone, have attracted the attention of investigators. Also non-hormonal approaches based on chemicals extracted from different plants such as cotton seed plant, Neem tree, *Trypterigium wilfordii* and *Momordica Charantia* seed, are known to have effect on male fertility. Additionally, alkylated imino sugars, Ca⁺⁺ channel blockers, indenopyridines, indazole-3-carboxylic acid analogues, reversible inhibition of sperm under guidance (RISUG) which involves injection of stericmaleic anhydride with dimethyl sulfoxide, spermicide-microbicide (including gel formulations) and vaccine approaches are intended to interfere in a certain fertilization step. Information obtained from multi-center studies in several countries on both men or women shows the necessity for additional reversible male contraceptive methods. Results from recent surveys clearly indicate that there is a market and a need for novel pharmaceutical preparations for male contraception.

Keywords: Male Contraception, Contraceptive agents, Hormonal methods

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INTRODUCTION

Recent available contraceptive methods offer a variety of options for women, but only very few (condom and sterilization) for men. The choice of method either for women or men depends very much on the cultural background of the user-groups. It has been observed that, world-wide, approximately 20 – 30 % of couples using contraceptives employ a male method, and the only available reversible male methods are condom and vasectomy [1-3]. Recent surveys indicate that approximately 90 % of partners tend to be active in choosing a suitable contraception method, and more than 50 % of men want to take responsibility [3]. The socio-economic status and religion of couples, as well as government policies and actions influence the type and usage of contraception in a country. Men's age and level of education have been found to have a significant influence on the acceptance of contraceptive methods in developing countries [4].

Information obtained from multi-center studies in different societies will be useful in the design of future products and introduction of a near ideal method. For example, when men attending a multi-center study were asked to rank condoms, a daily pill, a three-monthly injection and long-term implant, men from Edinburgh showed preference for a male pill, and an implant was the least prevalent first choice. By contrast, an implant was the second favored choice, and a pill the least favored among men from Shanghai [1,5]. Among women involved in a multi-center survey performed in the United Kingdom, South Africa and China, over 65 % agreed that the responsibility for contraception falls too heavily on women while over 71 % felt that developing a "male pill" would be a good idea [6]. Additionally, various opinion polls have shown a generally high acceptance rate of a potential hormonal male contraceptive by men as well as women [7]. Generally, results from recent surveys clearly implicate that there is a market and a

need for a novel male contraceptive method [5-8].

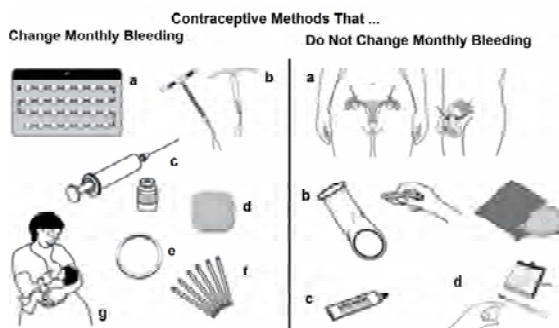


Fig. 1: Illustration of contraceptive methods. **Left side:** a) Combined and progestin-only contraceptives, b) copper and hormonal IUDs, c) injectables d) patch, e) vaginal ring, f) implant (these all alter monthly bleeding to varying degrees), and g) lactational amenorrhea method (LAM)—breastfeeding in a way that reliably postpones the return of fertility. **Right side,** a) Female and male sterilization, b) barrier methods (female condom and diaphragm, male condom), c) spermicides, and d) fertility awareness-based methods do not change monthly bleeding [9].

Currently available methods presented in Figure 1 [9] can be summarized as surgical methods, condom, hormonal methods, non-surgical and non-hormonal methods [1,3]. Hormonal contraceptive approaches try to induce suppression of spermatogenesis or bring about azoospermia by suppressing the gonadotrophins and thereby eliminating intratesticular testosterone (T) through the use of T alone or in combination with gestagens as a standard regimen [10]. Strategies investigated for T administrations include injections, oral or transdermal delivery systems at weekly or longer intervals [10-13].

Non-hormonal approaches for men tend to hinder sperm function and maturation [8,10]. These approaches have been carried out using chemicals such as gossypol extracted from cotton seed plant (*Gossypium sp.*) and triptolide extracted from *Tripterigium wilfordii*; these were promising non-hormonal agents

in the 1980s and 1990s in China [8,14-16]. Also, the Asian tree, Neem (*Azadirachta indica*) and the methanol extract of *Momordica Charantia* seed, are known to have an effect on male fertility [2,17].

Non-hormonal approaches have a number of potential advantages over hormonal methods, such as rapidity of onset and lack of interference with non-reproductive androgen-dependent function. However, the azoospermia effect of gossypium was found to be irreversible in 20 % of men who had taken it for prolonged periods [8]. Additionally, alkylated imino sugars [18], Ca⁺⁺ channel blockers [19-20], indenopyridines [16,20,21], indazole-3-carboxylic acid analogues [10,20], reversible inhibition of sperm under guidance (RISUG) which involves injection of stericmaleic anhydride (SMA) combined with dimethyl sulfoxide (DMSO) [1,16,20,22], spermicide-microbicide (including gel formulations) [23] and vaccine approaches [1,16,20,24] are intended to interfere in a specific fertilization step [1,25]. These non-hormonal methods include attempts to decrease sperm production or motility or to block the ability of sperm to fertilize the ovum [10,16].

Vaccine approaches involves the use of antigens/antibodies to target different aspects of gamete production and function as a means of inducing infertility [8,26-29]. For example, vaccines based on luteinizing hormone-releasing hormone/gonadotropin releasing hormone (GnRH) have been tested, and they have been shown to affect testosterone production, resulting in decrease in testis and prostate weights [30,31].

Researchers have attached more importance to hormonal methods which require the administration of exogenous T combined with a progestogen to suppress the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland [10,32]. Most early studies have used T alone because of the expediency that

gonadotrophin suppression and androgen replacement can be achieved with a single agent. However, oral bioavailability of unmodified T is poor because of hepatic first-pass metabolism and orally active 17-alkylated T analogues are hepatotoxic. The daily physiological requirement of T in men can only be achieved with depot preparations of injectable T esters or implantable T pellets [8,16,33].

To deliver T, most male hormonal contraceptive regimens have relied on injectable or implantable formulations of T. However, the relatively frequent injections required to maintain serum T levels necessitate frequent clinic visits and can be painful [34-36].

Because of the shortcomings of currently available methods of male contraception, efforts have been made to develop additional forms of contraception for men. Recent trials with newer, long-acting forms of injectable T, which can be administered every 8 weeks, combined with progestogens, administered either orally or by long-acting implant, have yielded promising results and may soon result in the marketing of a safe, reversible, and effective hormonal contraceptive for men [37-39].

At this point, an ideal male hormonal contraceptive should meet some of the features highlighted in Table 1 [40];

Table 1: Features of an ideal male-directed (hormonal) contraceptive [40]

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- **High efficacy**
 - Universally effective (i.e., can be used by all men)
 - Equivalent to female-directed methods
 - **Reversible**
 - **Safe**
 - Short-term side effects
 - Long-term health risks
 - **Acceptable to couples**
 - Convenient
 - Economical
 - **Rapid onset of action and recovery**
 - **Affordable and available**
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The mechanism of action of hormonal contraceptives is presented in Figure 2 [41], and hormonal contraceptive regimes can be summarized under three headings [32];

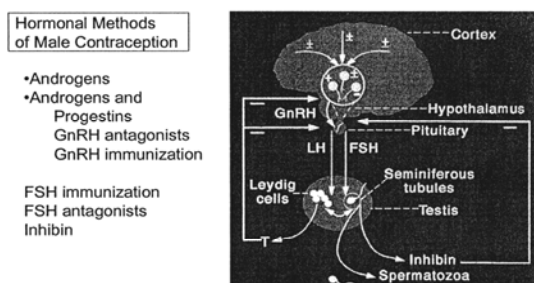


Fig 2: The hypothalamic-pituitary-testis axis showing the negative feedback of gonadal steroids and inhibin on GnRH, FSH, or LH secretion. The hormonal method of male contraception works by inhibition of secretion of both FSH and LH [41].

1. Androgen only

Due to poor oral bioavailability of unmodified T and hepatotoxicity of orally active 17-alkylated T analogues, daily physiological requirement for milligram amounts of T in men can be achieved with injectable depot preparations or transdermal formulations of T esters or implantable pellets containing crystalline T [33,42,43].

Testosterone undecanoate (TU) is an unsaturated ester of T with a long hydrophobic aliphatic fatty acid side chain which renders it highly fat-soluble. Formulation of TU in tea seed oil (125 mg/ml) and castor oil (Nebido™ 250 mg/ml) yielded long-acting depot preparations for intramuscular use. TU (in castor oil) has a long half-life of 70 days with more stable pharmacokinetics when administered at 4–8 weekly intervals. TU (in tea seed oil) 500 mg monthly i.m. can induce azoospermia or oligozoospermia (< 3 million/ml) in 97 % of Chinese subjects with high contraceptive efficacy (one pregnancy in 143 person years exposure, i.e., a failure rate of 2.3 (95 % CI 0.5 – 4.2) per 100 couple-years) [33,44]. These encouraging results are being followed-up by phase 3 studies involving

>1000 men in 10 centers in China where a new and more concentrated formulation of TU in soybean oil (250 mg/ml) is also under investigation [33].

Scrotal transdermal T patches were introduced in the late 1980s [16]. Several novel transdermal delivery systems (patches and gels) of T have become available recently. While self-administration and maintenance of physiological T blood levels offer obvious convenience and advantages in androgen replacement for hypogonadism, the requirement for daily application and higher levels of variability in skin absorption raises an important issue of compliance, not to mention the high incidence of skin irritation with the reservoir patch. Unsurprisingly, transdermal T on its own has not been investigated as a potential contraceptive formulation [10,16,33].

7 α -Methyl-19-nortestosterone (MENT) is a highly potent synthetic androgen which is resistant to 5-reductase but sensitive to aromatase. In a preliminary dose-finding study, four sub-dermal MENT acetate implants (each delivering 400 μ g/day) have been shown to suppress gonadotrophins and induce azoospermia in 64 % of men with a suggestion of reduction in prostate volume by 10–17% after 6 months [33,45].

2. Progestin/androgen combinations

Exogenous progestins can inhibit gonadotrophin secretion in men, and suppress spermatogenesis. Combining a progestin with androgens for male contraception exploits the synergistic actions of the two steroids so that they can be used at lower doses thus minimizing the potential for side effects [8,33].

It has been reviewed that, depot medroxyprogesterone acetate (DMPA) has an azoospermia effect in approximately 50 % of men, according to WHO [8]. DMPA has been combined with 19-nortestosterone (19-NT), Testosterone enanthate (TE) and T

implants. Studies with 19-NT and TE in combination with DMPA in Indonesian men indicate azoospermia rates of 98 % [8,33]. A male contraceptive study has been performed using daily self-administration of T-gel in combination with injections of DMPA every 3 months in normal men [46]. This study demonstrated that the improved T delivery of the gel results in sperm suppression similar to that achieved with frequent injections of intramuscular T combined with a progestogen [46,47].

While the addition of an androgenic progestin to T is a rational choice, the use of an antiandrogenic progestin without T appears not quite logical. An attempt to create a male pill by co-administration of oral TU with an orally active antiandrogen and progestogen cyproterone acetate (CPA) led to suppression of spermatogenesis, but had to be discontinued due to an antiandrogen-caused decrease in hemoglobin and hematocrit [8,16,48].

CPA combines anti-gonadotrophic and anti-androgenic properties which may be particularly favorable for suppression of spermatogenesis, especially in high doses (200 mg/day) [8]. Oral CPA at doses of 25 – 100 mg/day combined with TE 100 mg/week resulted in rapid onset of azoospermia in the subjects, whereas the same dose of TE alone was less effective [8,16,33,49].

Testosterone patches have been combined with oral levonorgestrel (LNG, 125 g daily) and long-acting LNG implants (four rods, Norplant II). Relatively poor sperm suppression (severe oligozoospermia in < 60 %) probably relates to the unreliable administration or absorption of T so that circulating levels in the low normal range only can be achieved [8,33].

However, when LNG was administered in four capsules delivering about 160 g LNG (Norplant II, Jadelle) per day together with weekly injections of 100 mg TE, 93 % of the subjects achieved azoospermia and all

suppressed oligozoospermia to < 1×10^6 sperm/ml. Long-acting LNG implants (four rods of Norplant II) combined with injectable TE were significantly more effective than LNG (125 µg daily) combined with T patches [50]. As effective as this combination may be, it brings us back to weekly T injections, making the approach impractical for general use. The combination of levonorgestrel implants with long-acting testosterone preparations (ideally also implants) might be a solution and requires investigation [51].

Desogestrel (DSG) is an oral third generation synthetic progestin with potent progestational activity but lower androgenicity. These potentially favourable properties led to the study of desogestrel in combination with TE. A cross-national study confirmed that oral DSG (150 or 300 g daily) in combination with injectable TE or 400 mg T pellets (every 12 weeks) can induce azoospermia in virtually all men in the 300 g group with a significant decline in HDL-C in Caucasian men only [15,32,51]. Further study of this promising progestin implant in combination with TU injections is in progress.

Norethisterone (NET) is an androgenic progestin which can be delivered as NET enanthate (NETE), an i.m. aqueous depot preparation available in Europe for female contraception. NETE 400 mg and TU 1000 mg administered at 6-weekly intervals induced azoospermia in 92% of men. In another study, men who received the combination of 1000 mg TU and 200 mg NET for every 6 week achieved azoospermia after 32 weeks of treatment. It was demonstrated that high rates of azoospermia (90%) can be maintained when TU and NETE are administered for 8 weeks intervals, but not for dosed every 12 weeks. This promising regime consisting of two long-acting depot injectable preparations is being further investigated in planned multi-centre studies [8,11,16].

A buccal dosage unit is provided for administering a contraceptive composition to

fertile mammalian males has been granted a patent in 2001. The buccal dosage unit comprises an androgenic agent (testosterone or ester forms of testosterone) and a progestin in a polymeric carrier that bioerodes and provides for delivery of the active agents throughout a predetermined drug delivery period that is preferably in the range of approximately 8 to 24 h [53].

Currently injectable T combined with gestagens or administered as implants are being tested for possible licensing. Although scrotal and non-scrotal T patches, orally administered TU and T gels are generally well tolerated and provide stable T levels in the normal range, their use showed generally disappointing efficacy due to insufficient gonadotropin suppression. Further large multi-centre studies are required to establish the contraceptive efficacy of the most promising steroid combinations [54].

The latest progestin to be tested for male contraceptive purposes is the orally effective dienogest. As dienogest has only mild antiandrogenic activity, this substance may be a possible candidate for future trials [51].

3. GnRH antagonists

GnRH antagonists are competitive blockers of GnRH receptor binding and suppress gonadotrophins within 24 h. Studies have shown very rapid spermatogenic suppression with a high rate of azoospermia. Whilst these complex synthetic peptides clearly have contraceptive potential (main advantage is being faster suppression than sex steroids), they have disadvantages like high cost, short half-life and the need for frequent subcutaneous injection. New long-acting depot preparations of potent GnRH antagonists may, therefore, have a place in male contraception where rapid induction of spermatogenic suppression can subsequently be maintained by testosterone with or without progestins [33].

GnRH antagonists in combination with testosterone lead to a more rapid onset and complete suppression of sperm [55], but the preparations currently available require daily or weekly injections and are expensive [51]. GnRH antagonist Nal-Glu, administered by daily subcutaneous injection, in combination with T is one of the trials on GnRH analogs. In the initial studies with Nal-Glu, after two weeks of administration, azoospermia was induced in 14 of 16 men [8,16].

A literature search by Hoesl et al [56] provides strong support for the male contraception approach. Their findings, presented as a cross-cultural survey, show men's willingness to bear contraceptive responsibility. Clinical trials substantiate that hormonal contraception involving suppression of gonadotropins holds the best promise to provide a male pharmacological contraceptive. Androgens have been demonstrated to induce reversible infertility particularly in combination with certain progestins and GnRH antagonists. Advances in non-endocrine contraception include intervention with triptolide derivatives, alkylated imino sugars, and immunization by eppin. With respect to pharmacology, the male contraceptive has been considerably advanced in recent years. Long-term studies involving a greater number of subjects may result in a safe, reversible and effective means. Asia is likely to be the first market for male hormonal contraceptive methods. The clinical evaluation of non-endocrine approaches may ultimately lead to an alternative to hormone-based male contraception.

Hormonal methods are closer to becoming an available method compared to non-hormonal methods. However, the combination of two hormones, requiring also two modes of delivery, is complex and might not appear attractive to users [10]. Further research is needed to assess the long-term safety, continuation rates, satisfaction among users and issues related to service delivery [35]. An intensive search for a second-generation of

male contraceptive drugs is ongoing, supported by several organizations such as World Health Organization (WHO), National Institutes of Health (NIH), Contraceptive Research and Development Program (CONRAD), the Population Council and several other medical research councils [10,57].

CONCLUSION

The drawback of surgical approaches (such as vasectomy) especially patient compliance and the low success rates with condoms has spurred research on hormonal contraceptive dosage forms. There is a dearth of investigations in the development of pharmaceutical preparations. Evolving technology in the 21st century as well as improvement in living standards further underline the need for new male contraception approaches, especially those that entail new drug delivery methods.

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