Contraceptive methods for men: an unmet need

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ABSTRACT

Improving current contraceptives and discovering novel, easy to use methods with added health benefits would meet the needs of couples who seek alternatives to current methods. Men are underserved and it is time to provide choices and an array of methods to suit their needs and allow men to take control of their reproductive function. The challenges with new male contraception from an ethics perspective include: i) complex rules for informed consent; ii) diverse outcomes for men taking a product and women exposed to the risk of unplanned pregnancy in case of failure; iii) the lack of regulatory guidelines; iv) the time lags of a given product to achieve efficacy and recovery. Male hormonal contraception is the most advanced and non-hormonal methods are not yet in the clinical stage of development except the non-surgical vas occlusion methods already in clinical studies. This paper aims to describe the current trials and expected results, as well as to address the future targets in early stage of research. The search for novel methods must continue in order to offer new options to men and to curb maternal mortality led by multiple pregnancies and unsafe abortions, - still a burden in many countries.

KEYWORDS

Male hormonal contraception, progestin, testosterone, spermatogenesis, non-hormonal methods.

1. INTRODUCTION

1.1 Male contraceptive methods: an unmet need

Currently, nearly half of all pregnancies globally are unintended, totaling 121 million each year. In the United States, about 45% of pregnancies are unintended. Specifically, 27% of all pregnancies were "unscheduled" and 18% of pregnancies were "unwanted" according to a Guttmacher institute survey [1]. A large proportion relates to non-use or failures of contraceptives, including the male condom, which is associated with a 13% failure rate or withdrawal (20% failure rate) [2]. To date, the only effective male contraception is limited to vasectomy, a non- reversible method. Therefore, men are underserved and it is time to develop reversible, effective and safe male contraceptives.

Additional reasons for novel male contraceptive methods to be available include the need for gender equity, as men are willing to share the contraception burden with their partners. Furthermore, the World Health Organization (WHO) has identified development of male contraceptives as a critical step toward achieving gender equality by envisioning family planning as a shared responsibility. *"Like women, men of all ages, married or unmarried, have their own sexual and reproductive health needs. They deserve good-quality services and respectful, supportive, and nonjudgmental counseling"* [3]. In addition, there is a need for more advocacy groups to promote male contraception and increase interest of the pharma industry currently not active in this research field [4,5].

1.2 Surveys: what do men want?

Worldwide studies indicate that >50% of men would opt to use a reversible method [6], and in another international survey, 90% of women confirmed that they would rely on their partner to use a contraceptive [7]. The Heinemann 2005 survey reported 49.3% of men in the United States (US) would be willing to try a male contraceptive if it became available. Results from a more recent US survey reported in 2019 indicated that among the 17 million men aged 18-44, looking for contraceptive methods, 8.1 million indicated they were very likely to use new male methods, and 5.6 million more were somewhat likely to do so [8].

1.3 Preferred methods of administration

In the 2005 survey, in all countries where men were interviewed, daily oral dosing was the preferred route of administration. In Europe and the US, preference for daily oral administration was followed by an annual implant and monthly injection as second and third choices respectively. The annual implant was least often preferred by South American and Indonesian respondents. In Indonesia, a monthly injection and the oral dosing were considered almost equally desirable [6].

In 2019 the Male Contraceptive Initiative survey was conducted, which was an online marketing survey across a sample of 1,500 males ages 18-44 living in the US. More than four out

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of ten men were very interested, and an additional one out of three somewhat interested in a pre-coital birth control pill (44%). Almost as many men were interested in a pill that would be taken regularly (33%), not only prior to having intercourse. Interest in using a topical gel (22%) or getting an injection (28%) was also moderately high, with more than half of men very or somewhat interested in each option. Men interested in an occasion-based pill, a shot, or implant (14%) were likely to have a partner using methods other than the pill [8].

1.4 Acceptability studies

In clinical trials where men experienced a new method of contraception and responded to an acceptability questionnaire, positive responses were recorded. In a clinical trial testing efficacy and safety of a male contraceptive gel a questionnaire was applied to 99 participants and 79/99 answered. Overall, 56% (44/79) of men were satisfied or extremely satisfied with the gel-based method of contraception, and 51% (40/79) reported that they would recommend that method to others. One third of subjects (26/79) reported that they would use this as their primary method of contraception if it were commercially available. However, men with concerns about sexually transmitted diseases were significantly less satisfied than men without such concerns (p=0.03) [9].

In summary, a majority of the men who volunteered to participate in the trial of an experimental male hormonal contraceptive were satisfied with the transdermal male hormonal contraceptive.

2. HORMONAL CONTRACEPTION FOR MEN

Hormonal methods aim to maintain serum concentrations of androgen and progestin relatively constant, either by a continuous release of an implant or a daily administration in order to prevent rebound of sperm output and maintain expected efficacy. Efficacy studies require in their design a first phase of suppression with enrollment of couples before men reach azoospermia or severe oligozoospermia (sperm concentration ≤ 1 million/mL).

Male contraception studies present a unique situation because the treatment is taken by the male, but the efficacy is measured in his partner. Proper counselling to the couple is needed about the possible risk of failure and information on available options in case of pregnancy according to the country regulations.
Surrogate markers of efficacy in the male subject are indicators of efficacy but are not sufficient to document the actual contraceptive effectiveness. A threshold of sperm concentration of ≤ 1 million/mL is proposed for a product to be considered a contraceptive [10].

2.1 Previous Studies

Many studies tested different combinations of progestin and androgen, and a few large studies showed high efficacy but did not reach marketing approval for various reasons. A double blind, multicenter, placebo-controlled study conducted in collaboration between two pharmaceutical companies tested a combination of etonogestrel (ENG) implant and an injectable androgen, testosterone undecanoate (TU) [11]. In this study, 354 healthy men received either a low- or high-release ENG subcutaneous implant combined with intramuscular TU injections (750 mg every 10 or 12 week or 1,000 mg every 12 week) or placebo implant and injections. The treatment duration was of 42 or 44 weeks and the post-treatment follow-up up to 6 months [11]. Overall, spermatogenesis was suppressed to 1 million/mL or less at week 16 in 89% of men, with approximately 94% in two high-release ENG groups. Suppression was maintained up to the end of the treatment period in 91% of men. For all men who completed the treatment, 3% never achieved 1 million/mL or less. Median recovery time to a sperm concentration above 20 million/mL was 15 weeks (mean 17 weeks, 95% confidence interval [CI] 16–18 weeks). Treatment was well tolerated. As compared with the placebo group, more men in the active treatment groups reported adverse events such as weight gain, mood changes, acne, sweating, or libido change. However, it is crucial to underline the importance of the placebo group in that study, as it shows some background information on side-effects occurring also in men who did not receive the treatment. For both spermatogenesis suppression and safety, differences were small between the active treatment groups [11].

In another prospective multicenter study conducted by the WHO and CONRAD in 320 healthy men, aged 18-45 years, and their 18- to 38-year-old female partners, intramuscular injections of 200 mg norethisterone enanthate combined with 1,000 mg TU, were administered every 8 weeks [12]. 95.9% of the 320 participants, suppressed to a sperm concentration less than or equal to 1 million/mL within 24 weeks (95% CI, 92.8-97.9) (Kaplan-Meier method). During the efficacy phase, 4 pregnancies occurred among the partners of the 266 male participants who were treated up to 56 weeks. The pregnancy rate was 1.57 per 100 continuing users (95% CI, 0.59-4.14). The cumulative reversibility of suppression of spermatogenesis after 52 weeks of recovery was 94.8 per 100 continuing users (95% CI, 91.5-97.1). The most common adverse events were acne, injection site pain, increased libido, and mood disorders. The study regimen led to near-complete and reversible suppression of spermatogenesis. However, the frequency of mild to moderate mood disorders was relatively high and consequently, following the recommendation of an external safety review committee, the study was terminated early [12]. The lesson learned from this study was the need to screen subjects for depressive symptoms or history of depression in order not to enroll them in a hormone-based study which may worsen these pre-existing conditions.

2.2 Ongoing Studies

2.2.1 Transdermal gel

Along with the approval of transdermal formulations of testosterone, in the research supported by the Eunice Shriver Kennedy National Institute of Child Health and Human Development (NICHD) in collaboration with the Population Council, a transdermal gel delivering a novel progestin, segesterone acetate (also known as Nestorone®) and testosterone (NES/T) to inhibit sperm production has been evaluated. This transdermal NES/T gel, compared to injections and implants, has the potential to provide more independence and less discomfort for users and has few side effects whilst delivering physiologic doses of androgens. A large international trial of a novel transdermal hormone gel for male contraception is still ongoing. This Phase 2b contraceptive efficacy and safety multi-national study of NES/T transdermal

gel enrolling 462 couples is the first to evaluate contraceptive efficacy of a daily, self- delivered male contraceptive agent. Importantly, with sites in the US, Europe, South America and Sub-Saharan Africa, it will provide information from diverse groups of potential users [13,14]. Early dose-finding clinical studies of NES/T gel have demonstrated high effectiveness at suppressing gonadotropins and sperm production [15], and very high acceptability amongst users [9] who were eager to know when this product would be commercially available for male contraception. In another study [16], the potential for transfer of the transdermal hormones to a partner was reassuring when the gel was used as instructed.

Most men have found transdermal products easy to use and have adapted the daily gel application to their daily schedule. Results to date indicate that the product is highly effective and acceptable to both partners. Large Phase 3 pivotal study (ies) to further demonstrate safety and contraceptive efficacy would be needed for regulatory approval. The transdermal approach to male contraception raises new considerations regarding adherence with the daily gel, as well as concerns about the potential transfer of the gel and the contraceptive hormones to the female partner. One international, multicenter, open-label study of self-administration of a daily combined testosterone and segesterone acetate (Nestorone) gel for male contraception enrolled 462 couples who were in committed relationships [13]. Male partners had baseline normal spermatogenesis and were in good health; female partners were regularly menstruating and at risk of unintended pregnancy. The primary outcome of the study was the rate of pregnancy in couples during the study's 52-week efficacy phase [13]. Secondary endpoints included the proportion of male participants suppressing sperm production and entering the efficacy phase, side effects, hormone concentrations in male participants and their female partners, sexual function, and regimen acceptability. By November 2022 enrollment was closed and the study is still ongoing. However, the successful completion of this and future studies of this formulation may lead to the approval of a first hormonal male contraceptive.

2.2.2 Oral pills

The NICHD is developing several novel modified androgens with a potential to be active orally. Dimethandrolone undecanoate (7-alpha, 11-beta-dimethyl- 19-nortestosterone undecanoate [DMAU]) and 11-beta-methyl- 19-Nortestosterone 17-beta- dodecylcarbonate (11b-MNTDC), are synthetic prodrugs under investigation as both oral and injectable contraceptive agents. DMAU is converted to the active drug, DMA, and 11b-MNTDC to 11b-MNT, *in vivo*, by endogenous esterases. DMA and 11b-MNT activate both androgen and progesterone receptor [17]. These progestogenic androgens have potential to be single-agent male hormonal contraceptives. Neither androgen requires 5-alpha-reduction to exert maximal androgenic action [18] and neither is aromatized to an aromatic A-ring compound [19]. *In vitro*, DMAU is a more androgenic, while 11b-MNTDC has both androgen and progestogenic activity [20,21]; as a consequence, they exert different pharmacodynamics in men.

Initial studies of single oral doses of DMAU and 11b-MNTDC in men demonstrated that concomitant food ingestion is required for effective oral absorption of these synthetic steroids [21–23]. A subsequent dose-finding study in healthy men [21], 100-400 mg of DMAU taken orally once-daily for 28 days, confirmed good tolerability and showed profound suppression of gonadotropins and testosterone [16,24]. The male subjects who received DMAU developed totally suppressed serum testosterone concentrations (<50 ng/dL), but showed only a few or no symptoms of hypogonadism, confirming the androgenic potency observed *in vitro* [20]. A longer study of daily oral DMAU (100-400 mg) to determine its impact on spermatogenesis is underway [25].

2.2.3 Implants

A potent synthetic androgen, 7α-Methyl- 19-nortestosterone (MENT) in a sustained- release formulation, has been proposed for the treatment of hypogonadal symptoms and for male contraception [26]. In previous preclinical studies in rats, the anabolic and anti-gonadotropic potency of MENT was shown to be ten times greater than that of testosterone [27]. Based on the daily production rate of 4-7 mg testosterone in men, it was anticipated that 400-700 μg of MENT per day would maintain anabolic and secondary sexual functions in men. It has been well established that in the prostate, testosterone is 5α reduced to dihydrotestosterone (DHT), which leads to an amplification of its action on this tissue. MENT has an additional advantage in that, unlike testosterone, it does not undergo 5α reduction. Therefore, when MENT is used at a dose that maintains androgen- dependent functions of muscle, pituitary, and kidney, the prostate stimulation will be relatively lower, thus providing a potential health benefit [27].

In the first clinical trial in male volunteers, MENT acetate implants delivering 400 μg/d of MENT for each implant were administered for 1 year. Four implants (1,600 μg/d) were sufficient to suppress gonadotropins and spermatogenesis, that is, azoospermia or sperm counts <1 million/mL in 82% of subjects [28]. Effects on sperm counts were dose related. 82 % of subjects in the 4-implant group reached azoospermia. Side effects generally observed during androgen administration, such as increases in erythrocyte count, hematocrit, and hemoglobin and a decrease in sex hormone binding globulin (SHBG), were also seen in this study and were reversible. Changes in lipid parameters were moderate and transient. Liver enzymes showed small changes. This study demonstrates that MENT acetate, when administered in a sustained release fashion via subdermal implants, can inhibit spermatogenesis over a prolonged period after a single administration and has the potential to be used as a male contraceptive. Full recovery was reached between 2 months and 1 year follow-up. New prototype implants based on a different elastomer technology intend to deliver a higher dose of MENT in order to decrease the number of inserted implants.

3. THE FUTURE

3.1 Promising non-hormonal options

When the human genome was discovered, it triggered research in multiple aspects. The genes involved in reproduction were identified and so was the protein synthesis or enzymes triggered by the genes that are essential for the maturation and activity of the sperm and ovum. Several targets have been identified as

very specific to the testis or to the ovary involved in the process of reproduction. The research is ongoing to identify new molecules that could block their function, but their safety needs to be assessed in toxicology studies and none of the potential avenues for the future has yet reached the clinical stage. The goal is to switch on and off one of these specific targets to induce inability of the sperm or the ovum to fuse or to mature enough to reach fertilization.

These approaches would not interfere with the hormonal system of the body, and for male contraception, they might act more rapidly to suppress sperm function than hormonal methods requiring several weeks to reach sperm suppression. Among the most advanced non-hormonal targets there are several promising alternatives, albeit they have not entered the clinical stage. These include: an Epididymal peptidase inhibitor (EPPIN) [29,30]; a testicular bromodomain protein called bromodomain testis specific protein and development of BRDT specific inhibitor [31]; retinoic acid receptor antagonists; retinoic acid biosynthesis inhibitors [32-34]; CatSper, a novel sperm-specific calcium channel and other sperm ion channels as potential male contraceptives [35,36] and, most recently, an inhibitor of soluble adenylyl cyclase as on demand male contraceptive [37,38].

3.2 Non-surgical vasectomy

The ADAM™ System consists of an injectable hydrogel and delivery apparatus that is intended to provide long-lasting, non-permanent vasal occlusion for men, resulting in azoospermia. ADAM is designed to be inserted into the vasa deferentia through a minimally invasive procedure, similar to the no-scalpel vasectomy. Designed to maintain azoospermia for more than a year, the hydrogel dissolves spontaneously. In animal studies, the ADAM implantation procedure blocks sperm passage through the vas for up to 2 years.

A first clinical study in a small group of 30 volunteers is ongoing and has shown preliminary efficacy with suppression in sperm concentration after 30 days [39]. When the gel does dissolve after one year or more, men should be able to repeat the procedure if they want.

4. REGULATORY CONSIDERATIONS FOR MALE HORMONAL CONTRACEPTION

The future of male contraception and the involvement of the industry in this field of research depends on the establishment of regulatory guidelines as well as the demand for male methods from consumers and advocacy groups. Up to now there is no specific regulatory guidance for male contraception.

Hormonal methods are designed to be reversible. An expert panel recommends assessing the return of sperm concentration to adult male range in phase 2b and 3 studies after 6 months, expecting time to recovery would be about 12 weeks and full recovery at 6 months [40].

The International Council of Harmonization (ICH) guidance recommends for any new product to record safety information (i.e. adverse events, blood pressure, laboratory findings) if the research involves a group of at least 1,500 men in total, with at least 300 men exposed to the product for 6 months and at least 100 men with 1-year product exposure. This guidance would be adjusted to the method for already approved molecules and repurposed for contraception, or for non-hormonal devices that do not deliver new chemical entities. However, no product has yet reached the stage of a new drug application and request for marketing authorization. Therefore, while the expert panels make such recommendations, it is unknown whether the Health Authorities will concur or consider additional requirements to assess safety and efficacy of a new method for male contraception.

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