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Male contraception: Another holy grail ☆

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ABSTRACT

The idea that men should participate in family planning by playing an active role in contraception has become more acceptable in recent years. Up to the present the condom and vasectomy have been the main methods of male contraception. There have been and continue to be efforts to develop an acceptable hormonal contraceptive involving testosterone (T) suppression. However the off target affects, delivery of the analogs and the need for T replacement have proven difficult obstacles to this technology. Research into the development of non-hormonal contraception for men is progressing in several laboratories and this will be the subject of the present review. A number of promising targets for the male pill are being investigated. These involve disruption of spermatogenesis by compromising the integrity of the germinal epithelium, interfering with sperm production at the level of meiosis, attacking specific sperm proteins to disrupt fertilizing ability, or interfering with the assembly of seminal fluid components required by ejaculated sperm for acquisition of motility. Blocking contractility of the vas deferens smooth muscle vasculature to prevent ejaculation is a unique approach that prevents sperm from reaching the egg. We shall note the lack of interest by big pharma with most of the support for male contraception provided by the NIH.

Family planning, or contraception has generally been the responsibility of the female partner in a relationship. After all, it's the woman who gets pregnant. This doesn't mean that men can't or shouldn't accept the contraceptor's role. In fact, in some partnerships this becomes a necessity, if the woman is unable for health reasons to use the birth control pill. Presently, there is a concerted research effort to develop a male pill.

That man realized he provided the seed that produced the baby dates to ancient times as evidenced by the reference in Genesis 38:9 to Onan spilling his seed on the ground to avoid impregnating his brother's widow. Awareness that some natural products could decrease male fertility also traces to antiquity. The use of plants stems from at least the first century CE when Dioscorides included that hemp seeds 'extinguished conception' in his extensive compilation of natural materials for medicinal use.[1] This documents what may have been a long history of attempts to use plant seeds, leaves and extracts for birth control and perhaps the beginning of men taking an active role in this process. In fact, it is likely that contraception, whether used by women or men, was not a topic for public discussion in polite society until the advent of the "pill" for use by women. It was not long after this that sex came out from under the covers. And then the idea of sharing the contraceptive burden, at least in a stable relationship, motivated research into developing the 'male pill'.

Directed research in male contraceptive development is relatively new. It is also fraught with difficulties because the goal is to provide a drug that can be used safely by healthy individuals of reproductive age (the fact that the same is true for a woman doesn't seem to have been a real problem). The burden for demonstration of safety, efficacy, and reversibility by regulatory agencies and the consumer is high. This burden may even include the assurance of no deleterious effects to the future offspring. This perhaps is a major reason that 'Big Pharma' rapidly lost interest in pursuing a birth control pill for men. As a consequence, the National Institutes of Health (NIH) is the major, if not sole source of funding to develop a male pill in the United States. Perusal of the 124 currently open clinical trials retrieved under the search term 'contraception' that are registered at the National Library of Medicine revealed only one that was concerned with the development of a male contraceptive drug, dimethandrolone undecanoate, discussed below.[2,3] The lack of pharmaceutical support can be argued to have more to do with the slow progress in this field than anything else.

In the United States, condoms and vasectomy are the only two methods of contraception available for use by men. Of these two methods, only condom use is reliably reversible. Condoms serve as exterior barriers to block fertilization and have in one form or another been used for perhaps thousands of years.[4] Not only are condoms widely available, even in rather esoteric shapes and sizes, but nowadays packages are prominently displayed in pharmacies

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compared to behind the counter location in the 'old days'. The failure rate for typical use is as high as 18%.[5] Condoms also serve the dual function of protecting against STD's, and should be used with or without the pill in casual sexual relationships.

Vasectomy, an invasive procedure, is used by only an estimated 6% of U.S. couples.[6] Efficacy is extremely high and complications are relatively rare. Vasovasostomy (re-anastomoses of the vas) by skilled surgeons is relatively straight forward, with patency rates (return of sperm to semen) ranging from 70–95% dependent on the procedure and time elapse since vasectomy.[7] Pregnancy rates of the partner are considerably lower at 30–76%, which may reflect a host of variables including the woman's age. In addition, there is evidence that vasectomized men develop antibodies to sperm that lead to infertility which of course defeats the purpose of the vasovasostomy. Therefore, vasectomy is not an ideal choice for men who plan to have a family in the future. Cultural and other barriers also contribute to its low level of use in the United States.[6] The prospect of developing a non-invasive, reversible, physically satisfying, and safe pharmaceutical contraceptive for use by men is worthwhile. But first we might ask why?

Nearly half of all pregnancies in the United States are unintended.[8] This statistic illustrates the urgent need to develop new methods of male contraception and overcome uncontrolled fertility. While a variety of options are available for female contraception, there is no safe, effective, and reversible contraceptive drug product in the market for men. There is however a rather startling array of instructions for the preparation of homemade contraceptive brews for men available on the Internet. This unsubstantiated collection must represent the need and interest of men seeking out reversible contraceptive choices. It is astonishing, that in the 21st century, the reversible contraceptive choices for a man differ little from the first century.

Development of a male contraceptive targeting the hormonal control of spermatogenesis, consisting of a progestin and testosterone, is the most developed pharmaceutical option at this time, though nothing will be on the market in the US in the near future. The strategy is to down-regulate pituitary release of LH and FSH resulting in decreased production of testosterone in the testis and impaired spermatogenesis.[9–12] Concerns about a hormonal male contraceptive are raised by studies that have revealed an array of physiological changes with short-term administration of testosterone derivatives that were undesirable. These included metabolic disturbances such as weight gain, decreased HDL/LDL ratios, and increased serum glucose levels. Acne, decreased libido, reduced testis size, and mood changes have also been commonly reported. In addition, a significant percentage of men do not achieve sufficient suppression of spermatogenesis for contraception and, although not understood, this is influenced by ethnic background.[13] The need to routinely inject some formulations is likely to reduce acceptance by many men. There is a promising recent report of a clinical trial that combined delivery of testosterone (T) and nestorone (a nonandrogenic progestin) by transdermal gels for the suppression of spermatogenesis.[14] Transdermal gels are a more acceptable method of delivery and efficacy across diverse ethnic groups was achieved with 88–89% of treated men achieving sperm concentrations below 1 million/ml. The authors concluded that a combination of daily NES+T gels suppressed sperm concentration to contraceptive levels, with minimal adverse effects, and may be further studied as a male transdermal hormonal contraceptive. The same research group has phase 1 studies underway to assess safety and tolerability of dimethandrolone undecanoate (DMAU); an androgen with progestin activity.[2,15]

In addition to approaches based on the hormonal control of spermatogenesis, there is a need to develop non-hormonal methods by identifying novel targets for contraceptive intervention. We have no bias as far as hormones are concerned, but the diverse targets available for non-steroidal suppression of spermatogenesis hold the promise of development of an efficacious drug with minimal side effects and acceptable routes of delivery. The remainder of this review will focus on the clinical and research progress towards development of non-hormonal contraceptive methods.

There are a number of exciting, potential drug targets that are being pursued. The challenge is that the delivery must be simple and that the effects of the drug be non-toxic, specific to the target and reliably reversible in affecting fertility. Levels of attack are the testes, epididymis, and spermatozoa. The goal may be to either suppress spermatogenesis (i.e., reduce sperm counts) or to render sperm non-functional. That is, in order to reach the egg, sperm must be motile and in order to penetrate the outer coat, the zona pellucida of an egg, sperm must undergo a maturation process, called capacitation, in the female reproductive tract. All these steps must take place before fertilization can occur providing multiple targets for contraceptive intervention.

Drug discovery is a complicated process requiring collaborations with medicinal chemists, structural biologists, practitioners in pharmacokinetics, and in this arena, reproductive biologists. Medicinal chemistry procedures are well established, but complex and costly. The process involves target identification and high throughput screens (HTS) to identify active compounds. Requirements for activity, selectivity, and physicochemical properties must be supported by bioassay and computational methods and, where possible, biophysical measurements and protein crystallography. HTS triage (selection of compounds for follow-up) requires that each compound that is screened must also be tagged as a confirmed active, a non-confirmed active, or an inactive compound. Because most of the data collected is proprietary the information about targeting described below is limited. Figure 1 shows the chemical structures of the non-steroidal compounds with potential for male contraception discussed below.

The mammalian testis is a dual function organ responsible for maintaining the body's hormonal homeostasis as well as being the site of sperm production. Testosterone (T) is the most familiar and important hormone for sexual behavior as well general physical well-being. There are no shortages of ads promoting T to not only improve men's sex lives but also enhance their business acumen and social behavior. Usually T levels decline with age and there is research, which will not be addressed here, on such studies. The point in this context is that an endocrine method of birth control in men, which affects hormonal balance must be carefully adjusted and the difficulty in accomplishing the appropriate treatment regime is one of the major complications in hormonal intervention for male birth control. For this reason, an alternative approach aimed at discovery of a non-androgenic compound to disrupt sperm production or sperm function is attractive.

Vitamin A metabolism has long been considered as a target for male contraception.[16] Meiosis in both male and female germ cells requires retinoic acid.[17,18] Vitamin A deficient rodents and retinoic acid receptor (RAR) alpha knock-out mice are infertile in the male.[17,19] The phenotypic defects in spermiation are similar in both models. Recently, a RAR antagonist (BMS-189453) that binds all three RARs (α,β,γ) has been studied for contraception in male mice.[20] It causes a failure of spermatid alignment and sperm release and is extremely effective, highly reversible, and shows low off-target effects. This research is at the stage of trying to develop an RARα-specific antagonist to minimize off-target effects.[21] The RARα-selective antagonists, BMS-189532 and BMS-195614 displayed selective activity *in vitro*, both compounds failed to suppress spermatogenesis with oral administration to mice. These investigators plan to build on these results, which they suggest are crucial for designing new RARα-selective antagonists for pharmaceutical application.