Chapter 30
What male contraceptives currently exist and what is the outlook for male hormonal contraception?

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Current male contraception: Vasectomy and condoms

There currently exist two efficacious, approved contraceptive options for men: vasectomy and condoms. Together, condoms and vasectomy account for 20-30% of contraception in the US. In other countries, the use of condoms and vasectomy vary significant based on local availability and cultural acceptability.

Vasectomy is a safe outpatient surgery usually performed under local anesthesia. During a vasectomy, the vas deferens is severed and the ends ligated or cauterized through a small scrotal incision. Vasectomies are a highly effective method of permanent contraception with a failure rate of less than 1%. Most failures occur early after the procedure and before all the sperm have been cleared from the proximal vas, although late failures due to vas re-canalization have been reported. Most surgeons currently utilize the "no scalpel" technique pioneered in China, in which a puncture is made midline in the scrotal raphe with scissors. Drawbacks to vasectomy include a 3-4 month delay in the onset of azoospermia, post-vasectomy pain (<5%) and rare infections. While most post-vasectomy pain resolves quickly, a small number of men will experience chronic scrotal discomfort requiring reversal. Vasectomy is most appropriate for men who no longer wish to father children, since surgical reversal does not always restore fertility and is costly.

Condoms made of animal intestine have been used as a means of male fertility control for at least several hundred years. Since around 1920, most condoms have been made of latex rubber, have improved reliability and are less expensive than other options. The use of condoms during sex also affords some protection against most sexually transmitted diseases including HIV/AIDS. Unfortunately,

condoms have a middling contraceptive efficacy long term, with pregnancy rates of 10-15% per year in couples using condoms as a sole method of contraception; this contrasts with female contraceptive methods such as intrauterine devices and oral pills which have failure rates of 1 and 9% respectively with typical use. Condom failure is frequently due to inconsistent use or breakage, although pregnancy can occur even with correct and consistent use. In addition, latex allergies can be a problem for some users. For these men, polyurethane condoms are a reasonable alternative.

Experimental hormonal male contraceptives

Efforts are ongoing to develop new methods of contraception for men. The approach that has been tested most extensively are hormonal male contraceptives. Hormonal male contraceptives rely on the administration of testosterone, which functions as a contraceptive by suppressing the secretion of luteinizing hormone (LH) and follicle-stimulating (FSH) hormone from the pituitary (Fig. 1). The absence of normal circulating concentrations of LH and FSH deprives the Leydig cell of the signal necessary for steroidogenesis leading to markedly reduced concentrations of intratesticular testosterone. The low intratesticular testosterone coupled with the low FSH deprives the seminiferous tubules of the signals needed to promote spermatogenesis and results in effective contraception in a majority of men. Male hormonal contraception is well tolerated, fully reversible, and appears be associated with a low rate of serious adverse effects. Unfortunately, regimens in which testosterone is used alone fail to completely suppress spermatogenesis in a subset of men. Therefore, combinations of testosterone and progestins, which synergistically suppress gonadotropins, are currently employed in most studies.

In most fertile men, sperm concentrations exceed 15 million/ml (normal range 15-200 million/ml). The absence of detectable sperm in the ejaculate, a condition called azoospermia, makes fertilization impossible. In prior male contraceptive studies, a sperm concentration suppressed to below 1 million/ml, “severe oligospermia,” is associated with a pregnancy risk of approximately 1% per year. Therefore, achieving severe oligospermia in all men is considered a reasonable near-term goal of male contraceptive development. In addition, because male hormonal contraceptives inhibit sperm production, it takes 3-4 months of treatment until the sperm concentration in most men is suppressed to under 1 million/ml.

Several large male contraceptive efficacy studies have been performed using hormonal contraceptives. The first two were conducted by the World Health Organization conducted two large, multicenter trials of weekly injections of testosterone enanthate for male and enrolled over 600 couples. The first demonstrated the high efficacy of hormonally-induced azoospermia. The second also allowed men with either azoospermia or oligozoospermia to rely on the regimen of testosterone injections for contraception. In this second study, there were no pregnancies fathered by the men who

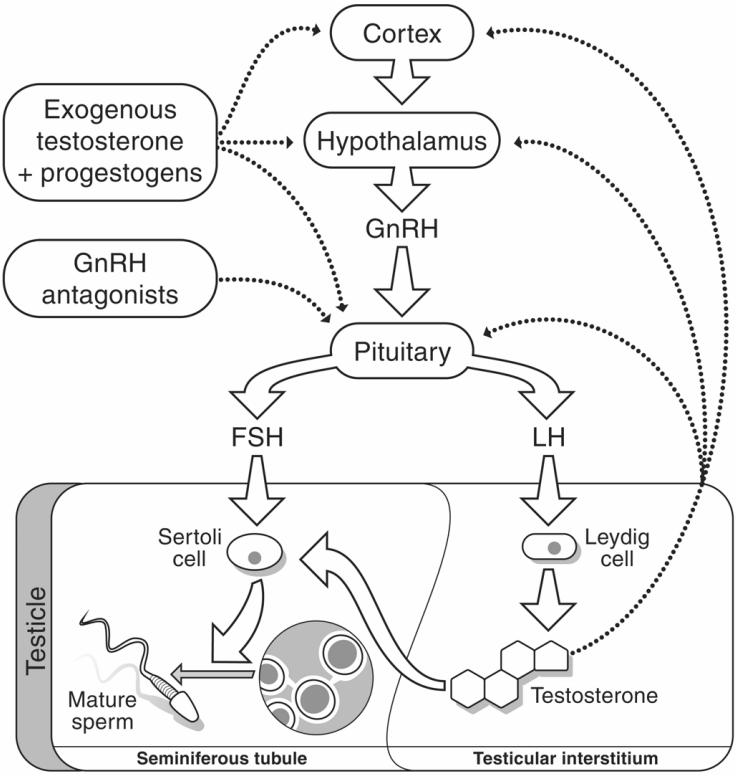

Figure 1. Spermatogenesis and male hormonal contraception. Solid arrows, promotes spermatogenesis; dashed arrows, inhibits spermatogenesis. Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone. Negative feedback of testosterone occurs at the level of the pituitary, the hypothalamus and the cortex.

became azoospermic, and fertility was reduced to 8.1 pregnancies per 100-person years in the men who suppressed to less than 3 million sperm/ml for an overall failure rate of 3.4%. Recovery to normal sperm concentrations occurred in all participants after the testosterone injections were discontinued. These two studies demonstrated that testosterone injections are a safe, reversible and highly effective contraceptive in a majority of men. However, they also demonstrate that pregnancy remains possible even at very low sperm concentrations and, for unknown reasons, a small group of men continue to exhibit low level spermatogenesis despite hormonally-mediated gonadotropin suppression.

Side effects in these trials included a 10-20% decrease in serum HDL- cholesterol, occasional acne attributable to the supraphysiologic testosterone dosing, and small, reversible reductions in testicular volume. Importantly, cognitive function, well-being, quality of life and sexual function were not adversely affected. The regimen was found to be better than expected by a majority of subjects; however, the requirement for weekly intramuscular injections led twelve percent of the subjects to discontinue participation.

Since the WHO trials research in hormonal male contraception has focused on formulations of testosterone that can be administered less frequently, such as testosterone undecanoate and combinations of testosterone and progestins to maximize gonadotropin suppression. Monthly injections of testosterone undecanoate have been studied in over 1000 Chinese men with a contraceptive efficacy of 95%. Injections of a combination of testosterone undecanoate and noresthisterone acetate were studied in a third WHO sponsored study and appeared promising in terms of contraceptive, but this study was ended early due to mood disorders in some men. Currently, the NIH is sponsoring a large, multinational contraceptive efficacy trial employing a combination of testosterone and nestorone topical gels, which had shown excellent suppression of spermatogenesis in earlier studies. Data from this study should be available in 2023-24. Lastly, the NIH has two promising novel steroids, dimethandrolone and 11-beta-methyl nortestosterone, that have inherent androgenic and progestational activity and are orally bioavailable that seem promising in early clinical studies as a single agent “male pill”.

Underlying this work is a mystery. Why do a small minority of men fail to fully suppress their spermatogenesis despite profound suppression of gonadotropins by male hormonal contraceptives?

Since there are no significant differences in the gonadotropin levels during treatment among men who suppress to azoospermia and those who do not, the degree of gonadotropin suppression itself is not the answer. Therefore, genetic, dietary or other factors likely play a role. Further studies of the control of spermatogenesis are needed to optimize this approach to male contraception.

Summary

Vasectomy and condoms are widely used, effective forms of male contraception. Experimental testosterone-progestin based male hormonal contraceptives reversibly suppress human spermatogenesis without severe side effects in most men; however, a uniformly effective regimen has remained elusive. Nevertheless, it is possible that improvements in this approach may soon result in the clinical introduction of a safe, reversible and effective form of male contraception.

Suggested reading

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