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Male contraception

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Clear evidence shows that many men and women would welcome new male methods of contraception, but none have become available. The hormonal approach is based on suppression of gonadotropins and thus of testicular function and spermatogenesis, and has been investigated for several decades. This approach can achieve sufficient suppression of spermatogenesis for effective contraception in most men, but not all; the basis for these men responding insufficiently is unclear. Alternatively, the non-hormonal approach is based on identifying specific processes in sperm development, maturation and function. A range of targets has been identified in animal models, and targeted effectively. This approach, however, remains in the pre-clinical domain at present. There are, therefore, grounds for considering that safe, effective and reversible methods of contraception for men can be developed.

Introduction

Childbearing and rearing directly affect women's health, lifestyle, and economy. As a result, research and efforts in family planning have traditionally focused more on female methods of contraception. A wide range of reversible contraceptive choices have become available to women over the past 50 years; however, male contraceptive methods remain limited. Condoms, introduced 300–400 years ago, provide protection against sexually transmitted diseases when used properly, but are associated with high contraception failure rates, with 12 out of 100 couples conceiving during their first year of use.

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Vasectomy, a safe and simple outpatient surgical procedure, has a failure rate of less than 1%, but may require several months to achieve full contraceptive efficacy, and vasectomy reversal is costly and unreliable. Recent studies have shown that both men and women of different races, religions, and ethnicities are increasingly interested in novel male methods of contraception [1–3]. The ideal male contraception would rapidly achieve consistent and fully reversible azoospermia without adverse effects, such as interference with libido or prostatic enlargement. Optimally, it would provide additional health benefits such as chemoprevention or an increase in quality of life.

Hormonal and non-hormonal pharmacological methods are being investigated for male contraception. Hormonally based male contraceptive methods are based on suppression of the hypothalamic–pituitary–gonadal axis and thus of spermatogenesis (Fig. 1). Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus leads to pulsatile release of luteinising hormone and follicle-stimulating hormone (FSH) from the pituitary gland into the circulation. Luteinising hormone stimulates Leydig cells of the testes, leading to testosterone production. Follicle stimulating hormone interacts with Sertoli cells, supporting spermatogenesis. Both FSH and luteinising hormone are required for normal spermatogenesis to occur in men. Maximal suppression of both hormones usually results in azoospermia [4], although, in many of the studies described below, a proportion of men continue to produce low concentrations of sperm in the ejaculate. This dual hormonal control of spermatogenesis is regulated by the negative feedback of testosterone (and to a lesser extent of inhibin B) to the hypothalamus and pituitary gland. Therefore, administration of exogenous testosterone suppresses the production of GnRH, luteinising hormone, and FSH, causing a reversible inhibition on endogenous testosterone production and spermatogenesis.

Non-hormonal contraceptive agents aim at disrupting spermatogenesis or the sperm-egg interactions by interfering with sperm motility or processes involved in fertilisation. The theoretical advantages of non-hormonal contraception include target specificity, which could minimise the systemic side-effects that may be associated with the hormonally based agents, and the possibility of having a more rapid onset of action.

In this review, we first summarise recent advances in male contraception, with emphasis on newer regimens that may be introduced into clinical practice in the near future.

Male hormonal contraceptive methods

The goal of male hormonal contraception is the sufficient inhibition of spermatogenesis to result in azoospermia; however, early studies of male hormonal contraception showed that a sperm concentration less than 1 million/ml, classified as ‘severe oligospermia’ is associated with a low pregnancy rate (about 1% per year), an efficacy similar to that of the female hormonal contraceptives [5]. Therefore, severe oligospermia is considered a standard for a male hormonal contraceptive, and is currently used as an end point in clinical development of these methods. An interval of 2–3 months is required for male hormonal contraceptives to reach their full effect, similar to the time required for vasectomy to become fully effective.

Hormonal contraceptive agents lead to the suppression of endogenous testosterone production via negative feedback on the hypothalamus and the pituitary gland. Therefore, it is important to replace peripheral testosterone with sufficient androgen administration to prevent the development of symptoms related to androgen deficiency, such as low libido, erectile dysfunction, changes in mood and behaviours, and disturbance of certain metabolic processes. On the contrary, supraphysiological dosing of testosterone may be associated with unwanted side-effects, such as acne, an increase in haemoglobin concentrations, and a decrease in high-density lipoprotein (HDL) cholesterol. Therefore, it is prudent for hormonal regimens to aim to maintain serum testosterone levels, and, by extension, androgen action at target tissues, within the normal, physiologic range.

Testosterone alone as a male hormonal contraceptive

Testosterone enanthate

After many years of development studies, The World Health Organization (WHO) conducted two large, multicentre, male hormonal contraceptive efficacy trials between the late 1980s and early 1990s,