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## Methods of contraception for men

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## **Abstract**

Many pregnancies in the world are unintentional and some of them end in abortion, hence there is a great need and amount of research on contraceptives. There are many methods of pregnancy prevention for women. However, men also want to be responsible for their reproductive health. Currently, there are few methods of contraception for men (male condoms, vasectomy, withdrawal) and they have their drawbacks, so research on new contraceptives for men is ongoing. Hormonal methods under research include testosterone, nesterone, and DMAU. On the other hand, adjudin, WIN 18.446, BMS-189453 and RISUG are promising methods of non-hormonal male contraception. These substances can be a discovery and a breakthrough in male contraception, they will allow men to better control their fertility and reproductive health, and can also be a suitable solution for couples in which there are contraindications for women to use contraception.

**Key words:** fertility; reproductive health; male contraception.

## **Introduction**

Contraception is a collection of methods or measures that are used to prevent pregnancy. According to studies [1] in 2010-2014, about 44% of pregnancies were unintentional. In developed countries, the ratio of unintentional pregnancies was 64 per 1000 women in 1990-1994 and decreased by 30% in 2010-2014 to 45 per 1000 women. Along with its decline, a decrease in the abortion rate was observed. In developed countries, in 2010-2014, 59% of unintended pregnancies ended in abortion. In contrast, in developing countries, the rate of unintended pregnancies decreased by 16% from 77 per 1000 women to 65 per 1000 women in the abovementioned years. His decline was associated with a decrease in unintended births. Hence the need for services in the field of sexual and reproductive health, as well as a large amount of research on contraception.

According to WHO [2], contraceptive methods used by women include: combined oral contraceptives, progestogen-only pills, implants, monthly injectables or combined injectable contraceptives, combined contraceptive patch/vaginal ring, intrauterine device containing copper/levonorgestrel, female condoms, female sterilization, lactational amenorrhea method, Standard Days Method, Basal Body Temperature Method, TwoDay Method, Sympto-thermal Method, emergency contraception pills, calendar method or rhythm method. By contrast, methods of contraception for men include: male condoms, male sterilization (vasectomy) and withdrawal (coitus interruptus). Male condoms have the effectiveness of 2 pregnancies per 100 women per year with consistent and correct use and 13 pregnancies per 100 women per year as commonly used [2], moreover, for some men they are difficult to use or reduce sexual pleasure. Condoms made of latex can cause allergic reactions in both women and men, and in rare cases lead to anaphylaxis [3]. Vasectomy [4] should be considered a permanent form of contraception because vasectomy reversal or sperm collection with in vitro fertilization are expensive (so not everyone can benefit from them) and may not be effective.

In contrast, withdrawal (which involves trying to keep the sperm out of the woman's body, preventing fertilization) is not the most effective form of contraception, and the effectiveness is 4 pregnancies per 100 women per year with consistent and correct use and 20 pregnancies per 100 women per year as commonly used [2]. Studies [5] show that as many as 78% of men say that responsibility for contraception should be shared, not just on the side of one sex. That is why research on new and better methods of contraception for men is so important and necessary. Men do not experience health problems related to unintended pregnancy, such as postpartum depression [6], hence safety is a key factor in obtaining acceptance of male contraception.

### **Hormonal male contraceptives**

Normal sperm concentration is above 15 million sperm per milliliter of ejaculate. In contrast, oligospermia of less than 1 million spermatozoa per milliliter of ejaculate as a contraceptive method results in a failure rate of 1% [7], which is comparable to the effectiveness of hormonal contraceptives for women. Testosterone by negative feedback inhibits the secretion of LH and FSH from the pituitary gland, which leads to a decrease in their concentration and, consequently, to the lack of signals necessary in spermatogenesis. This results in a reduction in sperm count in most men after 3-4 months of testosterone administration. Sperm counts repeat 3-6 months after stopping testosterone [3]. Two WHO studies [8,9] involving weekly intramuscular injections of testosterone enanthate (TE) have confirmed that this is an effective method of contraception. However, not all men achieved the required amount of sperm in the ejaculate and remained prolific, some of the subjects gave up because of their unwillingness to inject, and high doses of TE can lead to the development of atherosclerosis. Nestorone is a synthetic derivative of 19-norprogesterone and has no binding activity on the estrogen and receptor [10]. In studies [11] involving the use of testosterone and nestorone in the form of transdermal gels, it was found that 88.5% of men correctly using treatment daily for 20 weeks had a sperm count of 1 million per milliliter of ejaculate or less. It was a much higher result than in the case of a gel with testosterone alone, in the case of which only 23% of respondents achieved such a result.

DMAU is a substance with androgenic and progestagenic effects. A study [12] on men taking this medicine for 28 days orally did not show any serious side effects, treatment was well tolerated. Doses > 200mg significantly inhibited serum testosterone, LH and FSH. Possible forms of administration, i.e. the form of powder administered with food, in castor oil and in self-emulsifying drug delivery systems (SEDDs) were also compared [13]. All three formulas were well tolerated and effective, but only oil and SEDDs increase the conversion of DMAU to DMA. In addition, SEDDs showed some efficacy after fasting.

### **Non-hormonal male contraceptives**

Animal studies [14] have shown that adjudin works by interfering with the adhesion of germ cells, in particular sperm, to Sertoli cells, thereby releasing immature sperm from the epithelium, resulting in infertility. However, after discontinuing use, the cells gradually renew and differentiate, resulting in a return of fertility. In addition, further research [15] suggests that in addition to anti-spermatogenic activity, this substance has anti-cancer, anti-inflammatory, anti-neurodegeneration, and anti-ototoxicity effects.

In rats, the bioavailability of adjuvin is low due to the blood-testis barrier. It has been shown [16] that overexpression of F5 peptide, which is an endogenously produced reversible modifier of this barrier, in combination with low and self-ineffective doses of adjuvin causes male infertility.

Vitamin A and its metabolite, which is retinoic acid, are necessary for the proper production of sperm in mammals [17]. Studies suggest that bisdichloroacetyldiamine WIN 18.446 reversibly inhibits the synthesis of retinoic acid from vitamin A in the testes by inhibiting the enzyme aldehyde dehydrogenase 1a2. This resulted in a decrease in intravascular retinoic acid after just 4 weeks of treatment and preceded the decrease in sperm count and loss of mature germ cells in tissue samples. Fertility returned after stopping treatment [18]. BMS-189453 is a pan-retinoic acid receptor antagonist.

In low-dose studies [19] (in high-dose studies > 240mg / kg there were overt signs of toxicity and deaths [17]), disturbances in spermatogenesis in mice were observed. Induced sterility was reversible and no abnormalities were noted, except for changes in the testicles. EPPIN is an epididymal protease inhibitor located on the surface of sperm and binds to semenogelin-1 plasma protein, which causes loss of semen function [20]. The Catsper channel is a semen-specific channel, permeable to Ca<sup>2+</sup>, and plays a key role in male fertility. In studies with IgG cells against the Catsper 1 transmembrane domain, a decrease in sperm motility was observed. Subsequently, studies on two B-cell epitopes of the extracellular part of the transmembrane domains and the Catsper1 pore region showed significant decreases in fertility without visible systemic diseases or abnormal mating behavior [21].

RISUG is an injectable medicine consisting of a copolymer of maleic anhydride styrene chemically reacted with dimethyl sulfoxide. In studies [22] on 139 men who were given 120 µl of RISUG as bilateral vas intraluminal injection. Six men had a procedure error and did not achieve azoospermia, while the remaining 133 had severe oligospermia or azoospermia. In 82.7% it was maintained for a month, while in the remaining 17.3% from 3 to 6 months. Most had scrotum enlargement, scrotal or inguinal pain without dysfunction that resolved within a month.

Research on male contraception is extremely important and needed, most men want to be responsible for their fertility and reproduction. The available methods, such as condoms or withdrawal are not fully effective and vasectomy may be irreversible. In addition, women may have contraindications to the use of certain methods of female contraception, e.g. combined oral hormonal contraception and venous thrombosis. Test substances are promising and may be a breakthrough in male contraception. However, further research is needed into the long-term effects of treatment and possible side effects, the exact efficacy in various populations, and what effects these agents have on men with initially abnormal sperm results.

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