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Digest

Promising results in development of male contraception

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ABSTRACT

Nowadays, conscious planning of the family is very important for many people. The possibility of using protective measures against unplanned pregnancy is a great comfort. Most forms of contraceptives are intended for women, although their use can be ruled out in various health conditions. Scientists have been trying to develop a different type of method for men for many years. More and more research is being done and there have been promising results. It is hoped that soon both genders will have a similar range of contraceptive options to enable responsible family planning.

Introduction

For many years, contraception has allowed men and women to consciously plan families and decide about the possibility of having a child. Making decisions about your own body is a basic human right. The history of contraception began in ancient times, where women placed various substances of a slightly acidic nature, or physical barriers, into the vagina to prevent sperm from entering the uterus. As time progressed, newer and more advanced methods of contraception for women appeared. In 1838, the first reports of a barrier method appeared, which consisted of applying a cap to the cervix. In 1881, the first surgery for female sterilization was described. As science progressed, work continued on hormonal methods of preventing pregnancy, and in 1957, the results of a clinical study conducted on oral contraception were published, and in 1959, a product appearing on the market.[1] Many more female contraceptive methods have been developed since then, with the most popular being female sterilization and intrauterine devices, and the pill and injection agents being slightly less so. In 2015, nearly 64% of women were using some method of contraception. Fig. 1 is presenting estimates of contraceptive prevalence by method among married or in-union women aged 15 to 49 (percentage) from 2015.[2]

The history of male contraception is much shorter. The oldest method of contraception currently used by men is the condom. There are reports that the first versions were being used in ancient Egypt[3]; however, the first documented reports about condoms come from 1564 published by Gabriello Fallopio, in which they were described as a method of preventing syphilis infection. Until 1844, condoms were made from the intestines of animals such as sheep or goats. They had some disadvantages, one of which was their high price. However, production costs were reduced by the use of rubber, following the discovery of vulcanisation in 1844, and the condom gained popularity in the 1870s.[4] Production switched to latex after 1930s[3]; however, this is not an ideal substance, as approximately 4.3% of men and women may be allergic to latex.[5] Two types of allergic reactions can occur: type I - anaphylaxis and type IV - hypersensitivity. Symptoms may include itching, coughing, chest tightness, shortness of breath and wheezing. However, later discoveries led to the use of plastic and polyurethane in condom production.[3]

Another well-known method of controlling male fertility is vasectomy. There are two types of this procedure: irreversible and reversible vasectomy. All vasectomy procedures aim to close the vas deferens.[6] Although the first vasectomy was performed to cause prostate atrophy, it was later acknowledged as a full-fledged contraception method during the Second World War.[7] One of the newest, and most effective, methods is no-scalpel vasectomy.[8] However, there are continual efforts to identify possible improvements to this procedure.

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Between 2011 and 2015 in the US, 60% of unmarried men aged 15 to 44 in the US surveyed reported having used a male form of contraception during their last sexual intercourse, the most common being a condom.[9] On the other hand, in a 2004 study, 55% of the surveyed men from 4 different continents expressed their willingness to use new methods of contraception for men. Interestingly, most of them showed the greatest interest in the drug in the form of a once-a-day orally taken pill (only in Indonesia was the once-a-month injection more popular). Fig. 2 is presenting percentage of men interested in using a new method of male contraception from 2004.[10]

Another study providing valuable data is the satisfaction with the use of male contraception in the form of a transdermal gel (with testosterone and nestorone). It was shown that out of 79 respondents, 44 were satisfied with this form of the drug and as many as 26 would use it as the main method of preventing unwanted pregnancy.[11] So we can see an upward trend in men's interest in a new form of contraception for them.

In the period 2010–2014, about 44% of pregnancies were unintended[12] which could mean that contraception was not used, or that it did not fulfil its role. Nevertheless, as the responsibility for pregnancy arguably lies with both women and men. Both sexes should have access to a similar range of contraceptive options. Despite this, male contraception methods remain the minority constituting only 21% of all used contraception methods in 2015.[2] However, there are implications that new male contraceptives may be of great significance in preventing unwanted pregnancy. This is particularly important in countries where the percentage of contraceptive use is low (40%); in Africa, only 33% of women of reproductive age use some form of contraception, and the introduction of new methods may encourage their wider use.[2,13] This may well result in a decrease in the number of unwanted pregnancies, thus potentially improving quality of life and wellbeing: the unintended birth rate decreased by 27% in developing countries between 1990–94 and 2010–14.[12] Hence, a great deal of research is currently underway on possible male hormonal or non-hormonal method of contraception.

In spermatogenesis, haploid spermatozoa are formed as a result of meiotic division from spermatogonia. The process is governed by gonadotropins, more specifically FSH (follicle stimulating hormone) and LH (luteinizing hormone, which causes Leydig cells to produce testosterone, which is needed for the proper course of spermatogenesis), these being peptide hormones produced by the pituitary gland following stimulation by gonadoliberin produced by the hypothalamus. They also affect the development of sexual characteristics and fertility.[14] The current paper reviews possible forms of male contraception and the results of the latest research on this subject.

Hormonal contraception

Currently, many types of male contraception are being worked on, one group of options being oral formulations. Dimethandrolone (7α, 11β-dimethyl-19-nortestosterone) undecanoate (DMAU) is a compound which offers great promise. It is administered to the patients in the form of an ester and is then metabolised in the body to DMA (Dimethandrolone). After 28 days of oral administration, a decrease in plasma LH (luteinizing hormone), responsible for the proper functioning of the interstitial cells of the testes in which testosterone is produced, FSH (follicle-stimulating hormone), responsible for stimulating sperm production and increasing the production of androgen-binding protein (ABP), and testosterone levels was noticed, which affected male fertility. Participants receiving 400 mg DMA in powder and 400 mg with castor oil/benzyl benzoate per day demonstrated lower concentrations of LH and FSH (<1.0 IU/L) and serum T level (<50 ng/dL). After seven days of taking DMAU, a significant decrease in the levels of gonadotropic hormones and testosterone (median < 24 ng/dL) produced in the body were found to fall. DMA binds to receptors for progesterone and androgens located in the pituitary and hypothalamus, thus inhibiting the secretion of pituitary hormones that affect testicular hormonal activity, i.e. the hypothalamus from secreting GnRH and the pituitary from secreting LH and TSH, via negative feedback.[15]

An analysis of the form of DMA administration found all delivery methods to be effective; however, increased conversion of dimethandrolone undecanoate to dimethandrolone was noticed for castor oil and the self-emulsifying drug delivery system. Their effectiveness as potential contraceptives for men can be improved by increasing ester hydrolysis. In addition, its metabolism is also dependent on the fat content taken with meals: taking this compound on a diet high in fat (50% calories as fatty substances) increases ester hydrolysis, making it a more effective treatment. Moreover, only administration of DMAU (7α,11β-dimethyl–19-nortestosterone undecanoate) by the self-emulsifying drug delivery system was found to be reasonably effective under fasting conditions.[16]

11β-Methyl-19-Nortestosterone17β-dodecylcarbonate (11β-MNTDC) is another substance tested for use as oral male contraception. It is a prodrug in the form of an ester that is converted in vivo into the active substance: 11β-methyl-19-nortestosterone. Like DMA, it inhibits the secretion of androgens by binding to androgen and progesterone

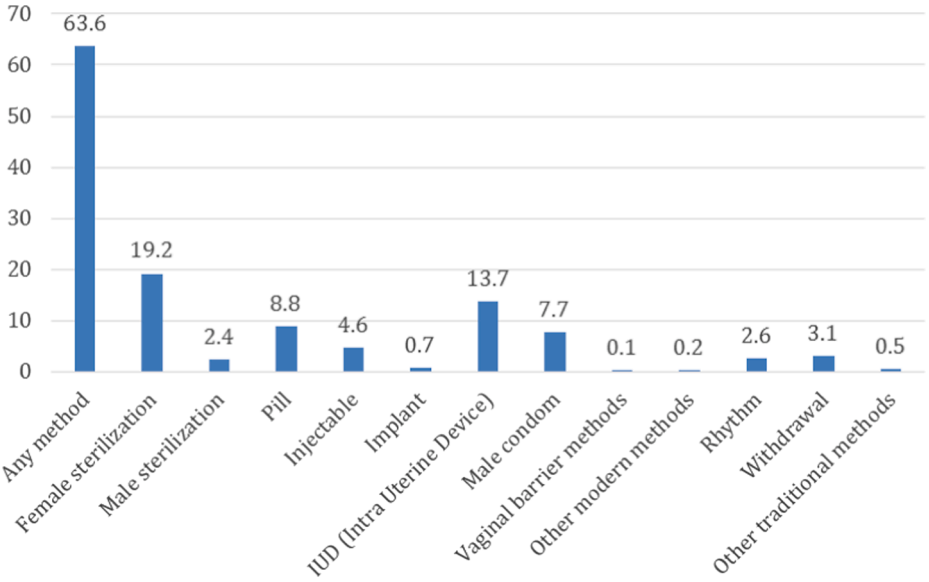

Fig. 1. Estimates of contraceptive prevalence by method among married or in-union women aged 15 to 49 (percentage), 2015. [2]

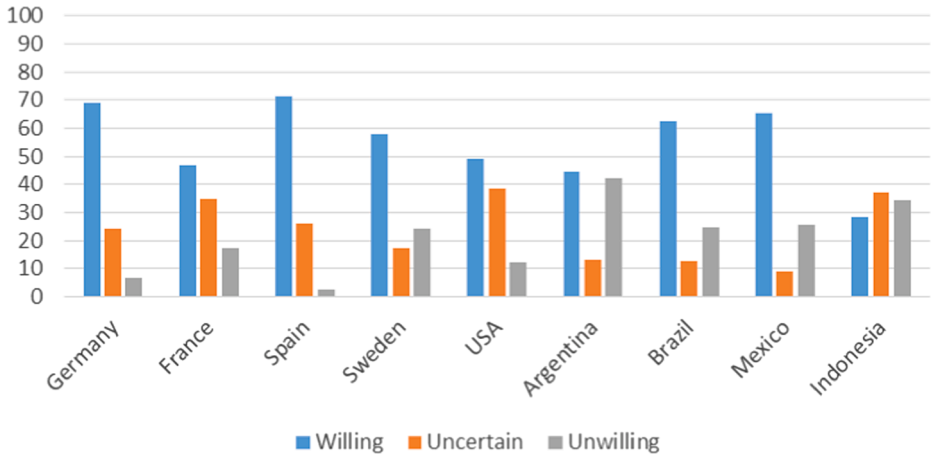

Fig. 2. Percentage of men interested in using a new method of male contraception (2004).[10]

receptors. Taking this substance with food was found to significantly increase its serum concentration. Doses of 200, 400 and 800 mg effectively reduced sex hormone levels. No reduction in FSH concentration was observed, and significant suppression of luteinizing hormone was observed only at the 200 mg dose. Interestingly, already after a single intake of 11b-MNTDC with food, a decrease in plasma testosterone was noticed.[17] However side effect of long-term oral 11β-MNTDC use is decreased libido and erectile dysfunction in patients. Out of 42 respondents, five reported a decrease in sex drive, and three reported problems with erection and ejaculation. What's more, the decrease in libido was more common in men taking 11β-MTDC in a dose of 200 mg than 400 mg. It is also worth noting that the use of 11β-MNTDC has the undesirable effect of a decrease in HDL-C concentration and an increase in LDL-C concentration in the body, most with the oral use of a dose of 400 mg. With parenteral administration, this disorder is less noticeable. Researchers suspect that this is due to the "first pass effect", that is, in large part, the drug is excreted via metabolic pathway in liver before it enters the systemic circulation, especially when taken orally. However, in order to accurately determine the risk of developing cardiovascular diseases, we still need further research on this effect of 11β-Methyl-19-Nortestosterone17β-dodecylcarbonate.[18]

An alternative form of using hormonal contraception are injections of norethisterone enanthate (200 mg) and testosterone undecanoate (1000 mg). After 24 weeks (one dose every eight weeks) participants demonstrated a decrease in sperm concentration to $\leq$ 1 million/ml, and a significant decrease in serum level LH and FSH, compared to the results obtained before treatment initiation. Fifty-two weeks after injection, sperm concentration returned to $\geq$ 15 million/ml. Which indicates the potential reversibility of this method. Moreover, 75% of participants were satisfied with this method. Unfortunately, side effects have also been reported,including: mood disorders, increased libido, and acne.[19]

Another study examining the effectiveness of the combination of testosterone and progesterone derivatives compared four different substances (levonorgestrel, cyproterone acetate, norethisterone acetate all taken orally and Nestorone®- progestin taken through the skin) with a combination of transdermal exogenous testosterone. The greatest suppression of FSH and LH production occurred in patients who were taking cyproterone acetate and levonorgestrel together with testosterone administered via skin. Significantly, the reduction of gonadotropic hormone concentration by progesterone is exacerbated by the transdermal application testosterone (LH $<$ 0.5 IU/L and FSH $<$ 0.5 IU/L). The authors note that such research is needed to determine the minimum effective dose of progesterone derivatives in order to reduce adverse reactions. [20]

The use of these testosterone and LH-lowering preparations in teenage boys is a problematic issue, as the reduced levels of the above-mentioned hormones in adolescents can cause serious side effects such as sexual development problems, decreased testicular weight, gynecomastia, and disturbed body proportions in favour of body fat and disadvantage of muscle tissue. [21]

Summarizing, the benefits of male hormonal contraception include among others its reversibility and a variety of forms of administration. Unfortunately, this is not an ideal method of preventing undesirable pregnancy, because apart from side effects such as a negative effect on the lipid metabolism, decreased libido, mood disorders, acne, adolescents should not take them due to potential sexual development disorders.

Mechanical methods

Male fertility can not only be controlled by hormonal drugs. Mechanical methods which offer the advantage of not influencing the hormonal balance can also be used. One of the most promising drugs may be RISUG ® (Reversible inhibition of sperm under guidance). This styrene and maleic anhydride copolymer[22] injected into the vas deferens lowers the pH level and creates a positive charge, thus preventing the proper transport of male reproductive cells through the female reproductive tract.[23] In albino rats, zero animal fertility was observed 90 days after RISUG injection. Interestingly, this method is reversible, by injecting solvents such as DMSO (dimethyl sulphoxide) or $NaHCO_3$. Restoration of fertility varied depending on the solvent used: satisfactory fertility after 45 days for DMSO, and after 30 days for $NaHCO_3$. No serious tissue changes (testis cells of Rattus norvegicus) were observed after use for less than a year; however, focal degeneration was noticed in the group in which occlusion of the vas lasted for 360 days without DMSO or $NaHCO_3$ reversal. More research is needed to confirm the safety of this procedure.[22] This preparation was also found to be effective in rabbits with no serious side effects. A complete absence of sperm in the ejaculate was noted after 30–60 days. Sperm concentration returned to normal 135–150 days after DMSO or $NaHCO_3$ treatment.[24]

VasalGel™ a styrene-*alt*-maleic acid (SMA) polymer with a high molecular (360 kDa) weight can also be injected. It acts as a barrier through which spermatozoa cannot pass through. It can be removed by DMSO. This preparation has already been tested on rabbits and rhesus monkeys. Studies show that this method is also very effective but more research is needed to determine its absolute safety. [23]

It has also been proposed that ultrasound with frequency range of 8 Hz to 22 kHz may serve as a means of contraception for men by reducing the mobility and viability of sperm cells, and slowing their movement into the epididymis. [25] This appears to be a cheap and reversible method.

Chemical contraception

Many preliminary but promising studies exist on potential chemical contraceptives. It has been found that the number of spermatozoa may be reduced by disrupting the synthesis of retinoic acid. This can be achieved by inhibiting the ALDH1A2 enzyme in human germ cells, which is a catalyst for the conversion of retinaldehyde to retinoic acid. Currently, this method has been tested on zebrafish, using WIN 18,446, i.e. bis-(dichloroacetyl)-diamine as an inhibitor – Fig. 3.

However, further research and the discovery of more possible ALDH1A2 inhibitors are needed. [26]

Another target may also be the pan-retinoic acid receptor α isoform. By inhibiting this receptor, scientists achieved inhibition of spermatogenesis in mice, and this effect was reversible, but requires further research to determine its potential use in humans. [27]

Other studies have examined the effect of glycogen synthase kinase-3-α (GSK3α), found inter alia in sperm cells, and calcineurin. The former is known to be responsible for the regulation of transcription factors and sperm protein phosphatase. Spermatozoa without the GSK3α exhibit impaired motility and are unable to enter the state hyperactivation that is needed for conception. Mice lacking sperm-specific calcineurin (PP2B-protein phosphatase 2, type B) demonstrate impaired sperm maturation and mobility. A noticeable correlation between the quality of sperm and the amount of these enzymes may be key to discovering a new path for male contraception. [28]

BrdT protein is a potential target for non-hormonal male contraception. These are the domains involved in the recognition of transcriptional regulatory proteins among others in spermatogenesis because they are specific for the testes. The search for inhibitors specifically targeting this protein may have a significant impact on the development of research work on effective male contraception. [29]

CatSper channels are sperm-specific. They regulate the concentration of calcium ions in the intracellular space, thus influencing sperm motility, making them a promising target for a new male contraception. Researchers found that RU-1968F1 (steroid structure –Fig. 3) is an inhibitor of these channels and is not sperm-toxic. Promising results indicate the possible use of this compound in a non-hormonal new male pregnancy preventive measure. [30]

The α-4 subunit of Na, K-ATPase is a potential grip site for non-hormonal contraceptives. The sodium–potassium pump is a protein responsible for the transport of sodium ions outside the cell and potassium into the cell interior using energy from ATP hydrolysis. It is composed of 4 α subunits and 3 β subunits. The alpha-4 subunit is a potential target of male contraception as it is present in the testes and expressed in spermatids and spermatocytes. Animal studies have shown

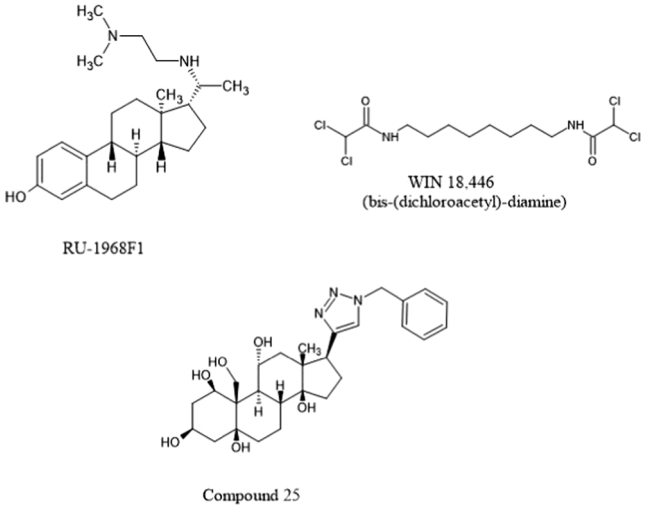

Fig. 3. Chemical structures the most important compounds.

that administration by oral gavage of ouabain derivatives (including compound 25 – Fig. 3) to rats resulted in, inter alia, reduced sperm motility and hyperactivated motility that is necessary to fertilize the ovum. [31]

Another promising method of male contraception is the use of epinn inhibitors. It is a protein found on the surface of sperm. When ejaculation occurs, the protein binds to semogelin1 (SEMG1), which leads to the inability of sperm motility. This is temporary, however, as this binding is hydrolyzed by the protein-specific antigen (PSA), leading to regaining motility by male reproductive cells. Compounds against Eppin are being developed to prevent it from binding to SEMG1. One of them is EP055, which has shown very promising results in animals during research. After administration as an infusion (at a dose of 75–80 mg / kg), a significant decrease in sperm motility was observed and this effect was reversible.[32,33]

As science progresses, the number of potential targets for male contraception grows that does not focus on the effects on the hormonal balance of patients. Among them there are:

- Serine protease 55 (Prss55), which is testis-specific and in the absence of it, the infertility of the tested animals was demonstrated [34]
- Calcium- and integrin-binding protein 4 (CIB4), highly expressed in the testes, which plays a significant role in shaping the upper region of the sperm head. During the studies, it was shown that mice lacking this protein were sterile. [35]
- Transmembrane serine protease 12 (Tmprss12), strongly expressed in the testes, contributes to the possibility of sperm migration in the woman's reproductive tract. It has been proven that the inactivity of this protein results in infertility. [36]
- Testis-specific serine kinase (TSSK) is a group of proteins that are expressed in sperm and are strongly associated with the differentiation of male reproductive cells. Animals lacking these proteins were confirmed to be infertile. [37,38]
- Kallikrein-related peptidases (KLKs) are enzymes responsible for liquefying (via SEMG hydrolysis) of the ejaculate after ejaculation-the sperm becomes mobile enough to fertilize the egg. Reversible sterility can be achieved by inhibiting these proteins. [39]

Clinical trials

Currently, four preparations with potential use in male contraception are under evaluation in clinical trials. In one study (NCT00161447), a group of men aged 18 to 55 years were given three drugs: Testim, Depo-Medroxyprogesterone and Acyline. Two study groups were formed; the first was given only Testim and Depo-Medroxyprogesterone, while the second was administered all three drugs. This combination was aimed at inhibiting the production of gonadotropic hormones and thus spermatogenesis. An important point of the study was the addition of the gonadoliberin antagonist, which accelerated and intensified the whole process. These studies reached phase II. Sperm concentration was found to drop significantly over the course of administration among the men who were given testosterone and medroxyprogesterone acetate: sperm counts were 72 ± 29 million per ml at the beginning of the study, while 57% had<100,000 sperm per ml. after 12 weeks, and 86% in 24 week . However, in patients receiving all three drugs, the mean sperm count was 68 ± 46 million per ml at the beginning of the study, and 65% of the group had<100,000 sperm per ml after 12 weeks, and 76% after 24 weeks. The two groups demonstrated similar times to reach the original concentration of sperm following treatment. In addition, there were very few side effects in the study group. This offers promise as a potential male contraceptive. [40]

In another clinical trial (NCT01382069), patients were administered dimethandrolone undecanoate (DMAU). In the first part of the study, the doses were increased to determine the degree of safety and oral dose tolerance for healthy men. Volunteer recruitment is currently underway for the second part of the study. The study is still in phase I.[15,16]

Study (NCT03298373) have also been conducted in Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Torrance, California, United States) and University of Washington Medical Center & Health Sciences (Seattle, Washington, United States) to determine the safety and tolerability parameters of 11-β Methyl Nortestosterone Dodecylcarbonate for healthy men. Similarly, in phase I, increasing doses of the preparation will be administered for 28 days to determine whether 11β-MNTDC is a safe form of contraception.

Recruitment is still ongoing (in Phase IIb), for international clinical trial (NCT03452111) in which Nestorone® and Testosterone Combination Gel will be administered to patients via the transdermal route. It is planned to administer the drug daily for 12 months and examine the sperm concentration to see if it has fallen enough to prevent conception during sexual intercourse. Interestingly, pairs will be recruited, and consultations will be conducted every month with the man, and every third with the woman to more identify possible side effects.

Finally, another study (NCT02927210) in Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (Torrance, California, United States) and University of Washington Medical Center & Health Sciences (Seattle, Washington, United States) is examining the potential of Dimethandrolone Undecanoate given as injection. The study is currently in the recruitment phase and is expected to be completed in October 2020. This is the first phase of the study and, as in the previous case, the safety and degree of tolerance, pharmacokinetics and pharmacodynamics of the DMAU will be examined.

Conclusions

Many methods of male contraception are under investigation, but their results are promising. A number options are being considered to improve patient comfort and effectiveness. The search for new potential non-hormonal grip points for male contraceptives is a very important direction in which we should follow due to the lack of drug interference with the hormonal balance of the human body. Continued research has already yielded positive results, and these offer hope that varied contraceptive methods for men will soon be widely available.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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