Review Article

Male contraception

Vivek Mathew, Ganapathi Bantwal

Department of Endocrinology, St. Johns Medical College, Bangalore, India

ABSTRACT

Contraception is an accepted route for the control of population explosion in the world. Traditionally hormonal contraceptive methods have focused on women. Male contraception by means of hormonal and non hormonal methods is an attractive alternative. Hormonal methods of contraception using testosterone have shown good results. Non hormonal reversible methods of male contraception like reversible inhibition of sperm under guidanceare very promising. In this article we have reviewed the current available options for male contraception.

Key words: Gonadotropin-releasing hormone agonists, hormonal contraception, male contraception, non hormonal contraception, reversible inhibition of sperm under guidance

A birth control pill for men, that's fair. It makes more sense to take the bullets out of the gun than to wear a bulletproof vest.

-Anonymous

INTRODUCTION

The World's population has risen to an alarming level, which in turn leaves its nations bulging at the seams in terms of population density. At the same time the paradox is that the financial and material resources cannot match the population growth that has occurred. A second paradox is the uneven population growth. While some nations are experiencing a population explosion, others show a negative growth. The future population growth rate is highly dependent on the fertility rate. Fertility levels have shown a decrease in the recent decades. If this trend in fertility decline continues, the world population may reach 9.3 billion in 2050 and 10.1 billion in 2100.[1] Hence, the concept of contraception as a method for population control is of paramount importance.

Human race has been innovative and imaginative regarding contraceptive techniques throughout the history. In all probability, the earliest contraceptive method known to man is coitus interruptus (genesis 38) which is in fact withdrawal of penis before ejaculation. Prolonged lactation was known to have contraceptive qualities from early historic times. Egyptian writings from as early as 3500 BC reveal the use of lemon and honey as spermicides.[2] Barrier contraceptives made their mark in history with the introduction of condoms made of animal skin. However, when one looks at the contraceptive choices available in the market, the balance is tilted in favor of women. Condoms and vasectomy are the two methods of contraception easily available for men at present. In this article, we have tried to review the hormonal and non-hormonal methods of contraception that are available or likely to be available for men.

PROSPECTS OF MALE CONTRACEPTION

An ideal contraceptive for men should be easily available, cheap, easy to use, without side effects, not affect libido, and easily reversible [Table 1]. The concept of male contraceptive is relatively well received across the world. Multi cultural studies have shown a relatively good acceptance for male contraception among men with more than three-fourths of men expressing intent to use a contraceptive if available.[3] Most men and women in various studies found the idea of male contraceptive use agreeable.[4] However, there are multiple religious, educational, economic and cultural barriers standing in the way of male contraception. When

Corresponding Author: Vivek Mathew, Department of Endocrinology, St Johns Medical College, Bangalore, India. E-mail: vmat78@gmail.com

Table 1: Characteristics of an ideal male contraceptive
Acceptable to both partners
Does not interfere with libido and sexual activity
No short term or long term side effects
Relatively inexpensive
Easily available
Rapidly effective
Easy to use
Rapidly and easily reversible

the clinical trials done on contraception are examined, it is seen that the bulk of them have concentrated on female contraceptive methods. A few trials on male contraceptives have actually been withdrawn. However, the concept of hormonal and non-hormonal male contraceptive methods are highly alluring given the acceptability and potential marketing prospects if such a drug comes in to existence.

WHAT CONTRACEPTIVE METHODS DO WE HAVE NOW?

Condoms
Various forms of condoms including those made from animal skin and intestines have been in use. Rubber condoms made their appearance in the 20th century and they have a dual purpose of preventing sexually transmitted diseases and acting as a contraceptive.[2] At present, latex condoms and polyurethane condoms are available in the market. However, contraception rates when using condoms are unacceptably high (pearl index = 12).[5] Long term compliance of patients with condom use is known to be generally poor. Condom failure may also occur secondary to condom breakage, slippage and incorrect use.[6] Latex allergies[7] are known to occur with condoms and some users also describe a decrease in sexual pleasure with condom use.[8]

Vasectomy
Vasectomy is a simple surgery performed under local anesthesia wherein the vas deferens is isolated and brought out from the scrotum through an incision followed by division and ligation. It is a safe outpatient procedure used all over the world as a male contraceptive option. Many modified techniques of vasectomy are in use. In the 'no scalpel technique', a simple scrotal puncture is made for the identification of vas which is in turn divided and occluded.[9] The advantages of no scalpel technique include minimal blood loss and low rates of infection.[10] The rate of unwanted pregnancies after vasectomy is generally less than 1%.[5] However, there is delay in the development of azoospermia and effective contraception after the surgery which necessitates the use of an alternate contraceptive like condoms during this period. Another disadvantage of vasectomy is that the reversibility of procedure is not always successful.

As the time elapsed from the procedure increases, the reversibility rate comes down.[11] In fact, many patients may also develop anti sperm antibodies which may also bring down the fertility rate.[12] Irrespective of the surgical method used, the surgical experience may be an important player in the success rate of vasectomy and its reversal. In experienced hands, complications like blood loss and infections are minimal. However, a significant number of men complain of testicular discomfort post vasectomy.[11]

OTHER NON-HORMONAL METHODS OF CONTRACEPTION

Non-hormonal targets of contraception include sperm production at the testicular level, sperm maturation at the level of epididymis and sperm motility. Obviously, the selectivity, specificity and lesser side effects compared to hormonal methods make these approaches attractive. However, many of these are experimental and in different phases of development.

Testicular level targets
Local application of heat
Testes, due to their extra abdominal position in the scrotum are at a lower temperature. In fact, occupational exposure of high temperature to the scrotum and testes has been shown to decrease sperm count and produce infertility.[13] Scrotal exposure to hot water bath in combination with testosterone in a clinical study decreased sperm count and motility.[14] Tight scrotal support in a clinical study also showed a reversible decrease in sperm count.[15]

Gosssypol
Gosssypol is an interesting plant extract derived from the cotton plant. It was shown to affect both spermatogenesis and sperm motility. The studies with gossypol have been done mainly on Chinese men. Most users were able to adequately suppress the sperm concentration to levels required for contraception.[16,17] However, in at least one-fifth of the patients, the effect was irreversible.[18] Other significant dose-dependent side effects included hypokalemia and periodic paralysis.[19]

Triptolide
Triptolide is a Chinese herbal extract from *Trypterigium wilfordii,* which was shown to reduce sperm motility and density. However, in animal experiments, the effects were irreversible and the compound was also found to have immunosuppressive properties.[20]

Indenopyridines
Indenopyridines are experimental compounds in development which can affect the sertoli cells and germ

cells. Studies with l-CDB-4022 an indenopyridine have shown that it activates the ERK/MAPK (mitogen-activated protien kinase) pathway, reduces expression of prosurvival factors, alters expression of Sertoli-germ cell adherens junction proteins, disrupts sertoli cell microtubule structure, and induces the proapoptotic factor, Fas, which in turn, in the end, may result in germ cell loss.[21] When it was used in combination with a gonadotropin-releasing hormone (GnRH) antagonist, it induced reversible infertility in male rats.[22] Gonadotropin and sex steroid concentrations were unaffected and there were no overt toxicities when the drug was administered in monkeys.[23]

Adjudin

Adjudin is a derivative of lonidamine which was developed as an anticancer drug. Adjudin was shown to disturb the adhesion between sertoli cells and germ cells. The effect was quite rapid and round spermatids and spermatocytes got detached within 3-6 days of treatment.[24] Other significant changes included retraction of the Sertoli cell cytoplasm, formation of large vacuoles and presence of multinucleated germ cells, and relocation of Sertoli cell nuclei to a higher position within the seminiferous epithelium.[25] Skeletal muscle atrophy and liver inflammation were seen in the male rats treated with adjudin. To bypass these effects, an effort was made to conjugate adjudin with recombinant mutant follicle stimulating hormone (FSH) protein so that a testes-specific delivery could be made.[26] While over all drug exposure was reduced, infertility induction was relatively good.

Epididymis-based targets

Spermatozoa undergo maturation in the epididymis. HE-6, a G protein-coupled receptor in epididymis regulates fluid resorption in the efferent epididymal ductules. HE-6 deficient mice have fluid accumulation in the testis with stasis of spermatozoa and are infertile.[27] CRISP-1, a member of the Cystiene-Rich Secretory Protein Family, possibly prevents precocious initiation of capacitation during sperm transit and storage.[28] Beta defensins belong to a large family of antimicrobial peptides. They are expressed in the male reproductive tract, particularly in the testes and epididymis. They are known to have roles in sperm maturation, sperm motility and cervical mucus penetration.[29] Human carbonyl reductase P34H is expressed in the epididymis and accumulates in the acrosomal region. It has a role in zona pellucida binding and P34H loss is associated with male infertility.[30]

Epididymis has many proteinase families in which the disintegrin and metalloprotease (ADAM) gene family is prominent. Knock out studies of ADAM genes show that they have an important role in fertility and these genes have roles in sperm migration and oocyte binding.[31]

There are several protease inhibitor families expressed in the epididymis including cystatin, Kunitz, Kazal and Serpin families which also play a role in sperm maturation and are potential targets for contraception.[32] Though there are multiple potential epididymal targets, a major difficulty in delivering the drugs to epididymis presents in the form of blood–epididymis barrier. One solution to this challenge is to identify molecules that can pass through the barrier. Other ways include use of endogenous transport systems including glucose, amino acid carriers, and receptor-mediated transcytosis.

Sperm based targets

Inhibiting sperm motility or increased beating of flagella (hyperactivation) are interesting targets for contraception. These types of drugs have two important advantages. First is of course, rapid onset of action, and it may be possible to use the drug immediately before intercourse. Also, many of these drugs may bypass the problem of passage through blood–testes barrier.

Miglustat

Miglustat (N-butyldeoxynojirimycin) is an inhibitor of glycosphingolipid synthesis. Miglustat produces reversible infertility reducing sperm motility and modifying acrosome morphology in mice.[33] In contrast to these findings, administration of miglustat in men failed to reproduce similar effects.[34]

Reversible inhibition of sperm under guidance

Reversible inhibition of sperm under guidance (RISUG) was developed by Guha and is under research for last two decades in India.[35] RISUG is composed of a polymer of styrene maleic anhydride complexed with the solvent dimethylsulfoxide and is injected in to the vas using a no scalpel technique.[36] It is being developed as an alternative to vasectomy. Within a few minutes of injection, RISUG solidifies and anchors itself onto the microscopic folds of the inner walls of the vas deferens producing a blockade to sperm transport. Once sperm comes into contact with the polymer, the combination of positive and negative charges on the polymer surface puts the sperm membrane under ionic stress, which in turn bursts the sperm membranes.[37] The advantages of RISUG over vasectomy are a faster onset of action and absence of autoimmune effects or granuloma formation.[38] The technique has shown good effectiveness but a few patients undergoing the procedure had reversible swelling of testes.[39] Primate studies have shown that RISUG is reversible,[40] as the polymer can be flushed out using sodium bicarbonate or dimethyl sufoxide. Although there are studies showing the reversibility of RISUG, more evidence is required.[41,42] At present, RISUG is undergoing clinical trials in the United States under the name of Vasalgel.

Soluble adenylate cyclase

Another interesting target for inhibiting sperm motility is "soluble" adenylate cyclase (sAC) in the sperm. sAC produces cAMP in the cytoplasm of the sperm which is required for the capacitation of sperm and possibly hyperactivation. In fact, mice lacking sAC are infertile, and their sperms are found to be immotile.[43] Inhibitors of sAC have also shown to be effective in preventing sperm capacitation and motility. Sodium-hydrogen exchanger (sNHE) found in sperm is required for the expression of sAC which makes it a potential target for contraception.[44]

Channel and ion-based targets

Transmembrane proteins called CatSpers have been identified which can form a tetramer with another transmembrane protein CatSperbeta.[45] This complex helps in calcium entry into the sperm tail through a bicarbonate-activated, voltage-sensitive channel and the rise in intracellular calcium in turn increases sperm hyperactivation. CatSperdeficient mice have been shown to be infertile.[46]

Sperm motility requires maintenance of sperm volume and potassium chloride. Co transporters and ion-specific channels play an important role here which makes them attractive targets for contraception.[47] Another target that has caught attention is sperm flagellar energy carrier (SFEC) which transports Adenosine Tri phosphate(ATP) into the principal piece of sperm and hence causes flagellar activation.[48]

A VACCINE FOR CONTRACEPTION

Throughout the history, vaccines have provided solutions for infectious and non-infectious diseases. So, it is not surprising that antigens have been targeted for a male contraceptive vaccine. One of those antigens that have been targeted is Eppin, a testes-epididymal-specific protease inhibitor found on spermatozoa which may play a role in sperm-semenogelin interaction in the coagulum of human ejaculate.[49] In fact, studies in monkeys have shown that the vaccination resulted in reversible contraception.[50] The downside of this vaccine includes inconsistent reversibility, requirement of booster doses and also varied efficacy. Other potential targets for vaccination include GnRH and FSH.[51]

A HORMONAL APPROACH TO MALE CONTRACEPTION

Hormonal targets for contraception are under development for the last four decades. Male hormonal contraception aims to bring a suppression of spermatogenesis using hormonal supplementation. The infertility produced this way should be reversible. To achieve a target oligospermia or azoospermia, intratesticular testosterone levels should be reduced in addition to suppressed FSH. Such reductions in intratesticular testosterone levels can produce symptoms of hypogonadism which may require external testosterone replacement. The suppression of pituitary gonadotropins and cessation of spermatogenesis can be achieved by testosterone injections alone. However, the issue here is that adequate suppression of spermatogenesis may not be seen in one-third of the patients in whom an additional agent may be required.[5,51] Since the last 5 decades, clinical trials are being done in the field of male hormonal contraception. However, many studies had their own limitations. The 10th summit on male hormonal contraception suggested that the following criteria should be fulfilled in the clinical trials for the regulatory approval for male hormonal contraception:[52]

1. In Phase II dose-finding studies, the suppression of spermatogenesis can be used as the main parameter. As the surrogate parameter, sperm concentrations, measured according to World Health Organization-recommended methods can be used, and the goal should be ≤1 million/ml.

2. After cessation of treatment, each participant should be followed-up until reversibility of sperm production to criteria that are compatible with normal fertility has been shown. Usually, return to sperm concentrations of at least 20 million/ml provides sufficient evidence of fertility. These figures could be revised, probably downward, as new data on fertility parameters emerge.

3. Currently, only men with sperm concentrations ≥20 million/ml should be included. This threshold could be revised, probably downward, in the future as new data on fertility parameters emerge. Participants with known or suspected infertility should not be enrolled in clinical efficacy studies.

4. Open-label, non-comparative contraceptive efficacy studies are acceptable if the primary endpoint is not susceptible to bias.

5. For contraceptive efficacy, 2 independent Phase III trials for 1 year beginning when the male volunteer has suppressed to ≤1 million sperm/ml should be completed by 200 men or couples per trial.

6. For safety assurance of a new chemical entity, trials are required to involve at least 300-600 men for 6 months at the intended combination and dose, 100 men exposed for 1 year, and a total of 1500 men in Phase I-III studies at the minimum.

7. Long-term safety will be monitored by postmarketing surveillance.

8. The necessary laboratory investigations, especially semen analysis, need to be made under strict quality control.

Male hormonal contraceptive efficacy trials have shown that, when sperm count was suppressed below 1–5 million

sperm/ml, the overall efficacy was approximately 95%.[51] A sperm concentration at or below 1 million sperm/ml of ejaculate was associated with a risk of pregnancy of approximately 1%. In the following sections, we will review the major clinical studies using hormonal contraception.

Testosterone Enanthate

In an efficacy trial[53] conducted by World Health Organization (WHO), 200 mg of testosterone enanthate (TE) was given IM weekly to healthy men for a period of 6 months. The study group included both Asian and Caucasian men. About 65% of the men became azoospermic after a mean period of four months. The study revealed a pregnancy rate of 0.8 pregnancies per 100 person-years and an efficacy rate of over 99%. However, a true efficacy of the regimen could not be assessed as only men who became azoospermic entered the efficacy phase. After seeing the short comings of the initial study, WHO designed another multicentric study.[54] In this study, fertility was reduced to 8.1 pregnancies per 100 person-years in those men whose sperm concentration was suppressed to less than 3-5 million/ml. There were no pregnancies with the men who were azoospermic.

Though these trials showed fairly good efficacy there were also a few drawbacks. One was of course the requirement of weekly intramuscular injections. There was also a reversible reduction in testicular volume, a 6% increase in hemoglobin and a 10-15% reduction in HDL cholesterol level. Also, there was a delay in full contraceptive action by 3-4 months. However, the quality of life and sexual function were well maintained.

Testosterone undecanoate

Testosterone undecanoate is available in oral and injectable preparations. Initial study using testosterone undecanoate injection was done in Chinese men using monthly injections of 500 or 1000 mg.[55] Not only all people in the 1000 mg group become azoospermic, but they also did it more quickly than the 500 mg group. However, the kind of efficacy seen in the Asian population was not reproduced in the Caucasian population.[56]

Another Chinese study tried a different protocol with monthly injections of 500 mg of testosterone undecanoate following a loading dose of 1000 mg.[57] Only 3% of the men failed to suppress sperm concentrations below 3 million sperm/ml. The contraceptive efficacy was 96.7%. However, sperm rebound occurred in 6 men during efficacy phase. A recent study performed once again in Chinese people using testosterone undecanoate showed that the pregnancy rate is as low as 1.1 / 100 person years.[58]

Testosterone gel

A study with testosterone gel in combination with depotmedroxyprogesterone acetate (DMPA) also showed that a good number of patients attained oligospermia and azoospermia.[59] They can achieve higher serum testosterone levels and have less skin irritation compared to testosterone patches.

Testosterone progesterone combination therapy

Testosterone progestin combination regimen was shown to be superior to testosterone alone therapy in suppressing spermatogenesis. This is attributed to the fact that progestins can inhibit gonadotropin secretion from the pituitary.[51] Initial trials of combination therapy concentrated on whether the combination is superior to testosterone alone. An RCT of levonorgestrel TE combination vs. TE alone showed that the combination was superior to TE alone in achieving azoospermia.[60] Norethisterone and testosterone undecanoate combination also have not been shown to induce high rates of azoospermia.[61] DMPA in combination with testosterone has shown good results in Chinese and Australian studies.[62,63] Increasing number of injections is a downside of this therapy. Testosterone undecanoate and 19-norethisterone enanthate can be dissolved in castor oil and can possibly be given as a single injection. However, the results of a study looking at this combination are still to be published (www.conrad.org/news-pressreleases-63.html). A major worry about any testosterone progesterone combination is a greater decrease in HDL cholesterol and an increase in weight. Hence, attention was directed to reducing these side effects.

Use of etonogestrel implants combined with testosterone pellets subcutaneously in patients showed that high rates of azoospermia can be achieved with this combination.[64] It was interesting to note that when the route and type of progestin was changed, there was less reduction of HDL cholesterol. Another study used 750-1000 mg testosterone undecanoate every 10-12 weeks with etonogestrel. Spermatogenesis was suppressed to ≤1 million/ml in 90% of the patients.[65] A potential side effect of all androgen-based therapies is an increase in benign prostatic hypertrophy or prostate cancer which requires further exploration in randomized, controlled trials.

Gonadotropin-releasing hormone-based contraceptive therapy

One of the key roles of FSH and testosterone is to maintain spermatogenic homeostasis by inhibiting death signals for the germ cells.[66] GnRH antagonists, when added to androgen therapy as an adjuvant have been tried in male contraception.[51,67] In a trial that used Nal-Glu in combination with TE, azoospermia was induced at 12 weeks which was then maintained by TE alone for 20

additional weeks demonstrating a role in induction of azoospermia.[68] When GnRH antagonist cetrorelix was used in combination with 19-nortestosterone, azoospermia developed in all subjects, but was not maintained after cetrorelix was discontinued.[69] It is possible that as a non-aromatizable androgen was used, the feed back suppression of estrogen on pituitary was not present, and hence the failure to suppress spermatogenesis.

In a combination study, acyline combined with DMPA and testosterone gel did not show any significant difference in sperm suppression and rapidity of sperm suppression compared with testosterone and DMPA alone.[59] There is a need for further studies to delineate the effects on contraception before GnRH antagonists are put in to clinical use. GnRH agonists are generally not used as they may allow continued production of FSH even after chronic administration.

Other potential hormone-based approaches

From the trials conducted in different populations, it was seen that there was a differential response to hormonal contraception among men from different ethnic groups.[70] Asians responded favorably to hormonal contraception compared to Caucasians. Caucasian men may suppress sperm output faster initially but ultimately to a lesser degree than Asians.[71] Chinese men were shown to have lower endogenous testosterone production and higher sensitivity to negative testosterone feedback.[72,73] Hence, Chinese men may be more sensitive to fixed doses of exogenous testosterone. Genetic polymorphisms in androgen receptor (AR) like increased number of CAG repeats are associated with decreased androgen action. However, there are conflicting reports as to whether these polymorphisms influence the degree of spermatogenesis suppression.[74,75] In a study[76] in Chinese men higher baseline serum Leutinizing hormone (LH) level and relatively higher serum LH and FSH level during the suppression phase with testosterone undecanoate was found in partial suppressors. Logistic regression analysis in the study showed that larger testis volume, higher serum FSH concentrations alone, or interaction of serum LH, FSH, testosterone and sperm concentrations were associated with the degree of sperm suppression. An integrated analysis[71] of the determinants of spermatogenic suppression showed that progestin coadministration increased both the rate and extent of suppression. Younger age and lower initial blood testosterone or sperm concentration were also associated with a faster suppression of sperm output. But the distribution of polymorphisms of AR or FSH receptor genes did not differ between partial and complete suppressors. These findings suggest the requirement of dose optimization in individuals. An alternate hypothesis explaining differential response in spermatogenesis suppression to testosterone is that a persistent intratesticular Dihydro Testosterone (DHT) levels may promote spermatogenesis. However, clinical trials using 5 alpha reductase inhibitors did not show any additional contraceptive benefits.[77]

In order to bypass the prostatic side effects of androgens, prostate-sparing selective androgen receptor modulators (SARMs) were developed. 7α-methyl-19-nortestosterone (MENT), a SARM has been tested in the contraceptive field as an implant and 73% of patients who used the SARM developed azoospermia.[78] However, the combination trial of MENT with etonorgestrel did not show promising results.[79] (S)-N-(4-cyano-3-trifluoromethyl-phenyl)-3-(3-fluoro, 4-chlorophenoxy)-2-hydroxy-2-methyl-propanamide (S-23) a new SARM developed was tested in male rats in combination with estradiol benzoate (EB).[80] The study showed that a selective AR modulator combined with EB is an effective and reversible regimen for hormonal male contraception in rats. Oral testosterone supplements and the new small molecule SARMs in development raise the potential for a new male pill for contraception.

CONCLUSION

Contraception is considered to be the key answer to population control. Though there are quite a few researches in male contraceptive methods, the actual pharmacological marketing of the products have not materialized in a promising way. This has led to lacunae in contraceptive choices available to men at present. Most men choose vasectomy and condoms as a contraceptive option now. Combinations of testosterone with progestins and newer SARMs have shown good results. Other non-hormonal approaches based on sperm and epididymal targets have exciting possibilities.

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