

Current Status of Male Contraception

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ABSTRACT

Rapid Population growth has caused a serious problem in economic growth and human development in the developing countries like India. The control of human fertility, in the sense of its limitation is the most important and urgent one, amongst all bio-social and actuarial problems, confronting mankind today. Methods and intentions, typically termed for birth control are generally considered a pivotal ingredient to family planning. Male Contraception is one of the promising answers to the above problems perhaps. The development of male contraceptive is relatively newer concept, researched or reviewed so far. Mechanism of male contraception, different methods and different intelligent drug delivery systems and possible novel drug delivery system (NDDS) are reviewed in this article.

Keywords: Male contraception, Mechanisms, Advanced drug delivery systems, Herbal microcapsules.

INTRODUCTION

The developments of male contraceptives represent relatively novel method of contraception. Male involvement in the field of contraception has been low. The limited work on male contraception may be due to cultural background, social and economic condition, indifference and poor understanding of factors controlling male fertility. The only method available to men is still those that were available during the first half of the century, namely Condom, Vasectomy, Withdrawal etc. While prophylactic condoms provide good barrier protection from unwanted pregnancies but they are not as effective as

oral contraceptives for women. Likewise, vasectomies are very effective but few men are willing to undergo the surgery.¹

Human sperm is optimally produced at a temperature that is a few degrees below body temperature. Infertility is induced if the temperature of the testes is elevated. For this reason, men trying to conceive are often encouraged to avoid wearing snugly-fitting undergarments. The thermal suspensory method of male contraception utilizes specially designed suspensory briefs to use natural body heat or externally applied heat to suppress spermatogenesis. Such briefs hold the testes close to the body during the

day, ideally near the inguinal canal where local body heat is optimum. Sometimes this method is also called artificial cryptorchidism, as it simulates the infertility in men with undescended testicles.²

Drug therapy is also being evaluated as a potential form of male contraception. Many drugs have been investigated in male contraception. One such drug, Nifedipine, is thought to induce sterility by blocking calcium channels of sperm cell membranes which results in cholesterol deposition and membrane instability of the sperm, rendering them incapable of fertilization.

Herbal preparations have also been used as male contraceptives. Gossypol, a constituent of cottonseed oil, was found to be an effective and reliable male contraceptive in very large-scale experiments conducted in China. Most recently, a form of sugar that sperm interact with in the fertilization process has been isolated from the outer coating of human eggs.

Perhaps one of the most researched methods of male contraception using drugs involves the use of hormones. Like female contraceptive pills, Male Hormone Contraceptives (MHCs) seek to stop the production of sperm by stopping the production of hormones that direct the development of sperm.³

MECHANISM OF ACTIONS OF MALE CONTRACEPTIVES⁴

Current researches in India to develop a male contraceptive are directed mainly towards:

- (I) development of antispermatogenic agents to suppress sperm production,
- (ii) prevention of sperm maturation,
- (iii) prevention of sperm transport through vas deferens (or rendering these sperm infertile) and

- (iv) prevention of sperm deposition.

(i) Agents for Suppression of Spermatogenesis

The ability of an androgen-alone modality to induce and maintain azoospermia was evaluated in a multicentre contraceptive efficacy study carried out by WHO, using weekly injections of 200 mg of testosterone enanthate (TE), as a prototype androgen. The results showed that the cumulative life table to achieve azoospermia was only 64.5%.⁵ The inability of an androgen-alone regimen to induce and maintain uniform azoospermia was evident even when testosterone buciclate (TB) was used.⁶ TB, when administered to short-term castrated rhesus monkeys exhibited a pharmacokinetic profile, which was superior to that induced by TE. These studies clearly indicated the need for caution in using relatively short-acting androgens like TE for male contraception.⁷

(ii) Combination Regimens

In progestogen – androgen combination regimes, smaller doses of androgens are needed, compared to androgen-only modality, since androgen potentiates the antispermatogenic activity of the progestogen, which acts as the primary antispermatogenic agent in the regimen. Effective suppression of spermatogenesis could be achieved only by use of a potent and long-acting progestogen like depot medroxyprogesterone acetate. It would be worthwhile to initiate studies in Indian men, since this would make available a viable contraceptive option for use in family planning programmes in India.⁸

(iii) Follicle-Stimulating Hormone Suppression

While a role for follicle-stimulating hormone (FSH) in the maintenance of spermatogenesis was well known, details of its site of action were shown. These studies

carried out at the Indian Institute of Science, Bangalore showed that FSH deprivation by immunoneutralization significantly reduced the proliferation of spermatogonial cells and a marked inhibition in the transformation of spermatogonia to primary spermatocytes.⁹ Another study showed that immunizing bonnet monkeys with recombinant FSH receptor protein affected testicular function and fertility.

(iv) Inhibition of Sperm Maturation

With the development of new andrology techniques like subzonal insemination of sperm and intracytoplasmic sperm injection, the relevance of the epididymis in sperm maturation has come under increasing doubt. A role for epididymis in sperm maturation was established in nonhuman primates and in humans at the All India Institute of Medical Sciences. These studies evaluated changes in sperm motility and its hormonal dependence, changes in sperm ultrastructure and reorganization of lipid bilayer and changes in lectin binding to sperm.¹⁰ As an extension of the above studies, sperm surface proteins undergoing maturational changes were identified. These studies clearly showed the occurrence of modification in sperm surface epididymal glycoproteins during maturation.

(iv) Prevention of Sperm Transport

This is essentially a vas deferens based approach. Vasectomy has been in use since many decades as a terminal method to prevent sperm transport; intra- and extra-vasal non-occlusive methods have been developed in India. Two major approaches have been attempted in India to prevent sperm transport through the vas deferens. These are use of intravasal copper by Kapur and colleagues at the All India Institute of Medical Sciences, and injection of a non-sclerosing agent, styrene maleic anhydride (SMA) into the vas

by Guha and colleagues at the Indian Institute of Technology.¹¹

(v) Prevention of Sperm Deposition¹²

Barrier methods like use of condoms have dual effectiveness, viz. prevention of sperm deposition in the female tract and prevention of transmission of STDs and HIV. The contraceptive prevalence of condom in India is an insignificant 31% (NFHS 1998–99). Recently, scientists and experts agreed that to increase use of condoms four major issues needed to be addressed:

- changing norms about sexual behavior and condom use,
- assuring effective use,
- providing greater access to condoms,
- changing restrictive policies concerning condoms.

DIFFERENT METHODS OF MALE CONTRACEPTION

Emerging approaches to male contraception can be broadly classified into two groups. One direction does not directly affect spermatozoa production and early stages of development, but subsequently, during passage in the epididymis and the vas deferens, the functional character is altered and the number passing on the ejaculatory duct reduced. There is thus the possibility of localized intervention with virtually no systemic effect. The second class of method aims to suppress spermatozoa production generally by manipulating the hormonal status. Moreover, there is a requirement of regular intake of drugs orally or by injection. Different methods of male contraception are shown in Fig.1.

(i) Natural Method

Withdrawal method (coitus interruptus) and periodical abstinence particularly in mid-cycle are the only two natural methods of contraception for males.

Although discouraged and rightly so, by westerners because of high failure rates, these methods have a good place in India and other developing countries as they need no special training.

(ii) Physical Methods¹³

a) Barrier Methods

Barrier methods place a physical impediment to the movement of sperm into the female reproductive tract. The most popular barrier method is the *male condom*, a latex or polyurethane sheath placed over the penis. There are about 50 million condoms used world wide. Effectiveness can be improved with proper and consistent use and the use of spermicides. The condom has traveled a long way from what it was to the colored and flavored forms, which exist as of date. Condoms are now available at an optimal thickness and in a variety of sizes, shapes, widths, and lengths. The ever-increasing rate of sexually transmitted diseases, more specifically AIDS, and the rising figures of teenage pregnancy have restored the condom its previous importance.

b) Vas occlusion

Newer "vas occlusive" methods offer alternatives to vasectomy with completely reversible effects. Vas occlusive devices block the flow of or render dysfunctional the sperm in the vas deferens. The most recent form of vas occlusive male contraception, called Reversible Inhibition of Sperm Under Guidance (RISUG), involves the use of a styrene that is combined with the chemical DMSO (dimethyl sulfoxide). The complex is injected into the vas deferens. The complex then partially occludes passage of sperm and also causes disruption of sperm cell membranes.

(iii) Hormonal Methods

a) Androgen Only Regimen¹⁴

In the first large scale efficacy trial of male contraception, it was demonstrated that 200mg injections of testosterone given i.m. weekly rendered 65% of the 399 volunteers azoospermia. Complete azoospermia or oligospermia was seen within six months. Recovery was seen within 4-8 weeks of cessation. A single injection of 1200mg testosterone buciclate when given i.m. produced azoospermia in 3 of 8 volunteers in week 10 after administration and persisted upto 18 weeks by average. A dose of 25mg testosterone propionate given daily i.m. was studied for a period of 6 weeks on rats and was found to produce sperm suppression.

b) Androgen / Progestin Combination Regimen

The addition of progestin to an "androgen only regimen," has induced long term azoospermia with fewer side effects, due to synergistic actions of androgen and progestin. The dose combination of testosterone enanthate (TE) and oral desogestrel suppressed sperm production significantly by week 8 and all subjects became azoospermic after 20 weeks of treatment.¹⁵ Preliminary results from a study using 6-month depot medroxy progesterone acetate and implanted T pellets indicated effective sperm suppression. Although there were no major side effects.¹⁶

c) Synthetic Androgen¹⁷

In a clinical trial to study the effect of MENT (7 α -methyl-19-nor testosterone) implants, two subdermal implants each containing 112mg MENT acetate in polyethylene vinyl acetate polymer were administered for 4 weeks. MENT acetate rapidly hydrolyzed to MENT *in vivo*. The implants produced a reversible, nontoxic decrease in fertility, and

MENT is also being studied as a long acting contraceptive.

d) Gonadotropin Releasing Hormone (GRH) agonist analogs¹⁸

The paradoxical antigonadotropic effects of highly potent GRH agonist analogs have provided a new tool for contraception. Treatment with high doses of these analogs inhibits human testicular androgen production. The unavoidable side effects accompanying decrease in testosterone are eliminated by simultaneous exogenous testosterone treatment, but antispermatogenic effects remains due to persistent decrease in FSH secretion.

(iv) Non Hormonal Methods

a) Immunocontraceptive Mechanism Targeting Sperm Protein

Novel surface constituents called differentiation antigen get inserted on the surface of the sperm during various stages of development and maturation, which play a role in the process of fertilization. Lactate dehydrogenase C4 (LDH – C4) has been identified as a sperm specific antigen.

b) Epididymal Enzyme Targeted Approach¹⁹

N- acetyl- β -D-hexosaminidase enzyme (NAH) is secreted in the epididymis and enters the sperm cells after they leave the testis. The enzyme has two variant forms A & B. Sperm cells contain only the B type. The B form gives the sperm cells the ability to recognize , bind with and penetrate the egg resulting in fertilization. By inhibiting the B variant , the sperm can no longer recognize the egg, but the A variant is available for performing the necessary physiological function of NAH in the rest of the body. The analogue was tested on male mice, inhibiting 90% of enzyme activity *in vivo* and *in vitro*.

It was found that plasma serum derived Protein C Inhibitor (PCI) and a synthetic peptide derived from its sequence inhibited both binding and penetration of zona- free hamster oocytes by human sperm. PCI retards sperm activity by inhibiting enzymes that are involved in sperm motility or by inhibiting sperm-zona penetration or by inhibiting, binding and penetration to the plasma membrane of the egg. PCI therefore, has the potential to be developed as a contraceptive.

(v) Plant Product

The Chinese plant *Tripterygium wilfordii* and its botanical cousins contain several orally active compounds that provide male contraception. Pills made from *Tripterygium* have been used in traditional Chinese medicine for over 1000 years. Researchers are isolating the compounds with contraceptive effects for further research.²⁰

When extracts from the seeds of papaya fruits (*Carica papaya*) were fed to monkeys, the monkeys had no sperm in their ejaculate. Researchers are trying to determine whether papaya seed extracts are safe for use in additional studies.²¹

The neem tree (*Azadirachta indica*), common in India, has many medicinal uses. Very small quantities of neem oil have been successfully tested as an alternative to surgical vasectomy. Fresh neem leaves caused reversible contraception in male rats, and there are anecdotal claims of the use of neem leaf extracts as effective male contraception.²²

Pills made from Gossypol, a compound found in cotton seeds, have been abandoned as a potential male contraceptive because of unreliable reversibility in clinical trials. Researchers have suggested that gossypol might make a good non-invasive alternative to surgical vasectomy.²³

The leaf extract of Beal (*Aegle marmelos*) result a significant diminution in

the activities of key testicular steroidogenic enzyme along with low levels of plasma testosterone and relative wet weights of sex organs in respect to control without any significant alteration in general body growth. Germ cells numbers in different generation at stage VII of seminiferous epithelial cell cycle were diminished significantly after the treatment of the above extract without any toxicity in liver and kidney.²⁴

(vi) Miscellaneous²⁵

Lonidamine is an anticancer drug that showed antispermatogenic activity however it caused renal damage. Oral Ornidazole, 400 micrograms / kg daily for 2 to 3 weeks induced rapid infertility after 6 days. After withdrawal of the drug, fertility returned within 7 days. Nifedipine, an hypertensive drug produced antispermatogenic activity by slowing the movement of the calcium through cell membrane, which was essential for sperm to function. The effect was reversible and the drug was found to be safe in the regimen that was followed.

A new male contraception method is undergoing clinical trials in India. The goal of this research is to achieve a method which restricts its effects to the region of the vas deferens. First, the belief that there was a strong peristaltic movement in the vas during ejaculation had to be examined. It was found that only the ampula part of the vas is given a tight squeeze to release the stored sperm into the semen. Therefore, a device to manipulate sperm could safely be inserted into the vas. Using the fact that the acrosomal membrane of the sperm is disturbed when sperm are subjected to electrical currents.

NOVEL CONTROLLED RELEASE MALE CONTRACEPTIVES

For the convenience of consumer, controlled release contraceptive preparations are very useful. The prolonged release character of a controlled release drug delivery system is to minimize the need for frequent drug intake and assure better compliance. Very few male contraceptives are available today, hence the area of male contraceptive NDDS can be maneuvered intelligently, as suggested in fig. 2.

Biodegradable Pellets²⁶

In this system, crystalline testosterone is fused into a pellet formation and six 200-mg pellets are implanted in the abdominal wall. The pellets are biodegradable and the release of drug suppresses sperm output for about 6 months. The release kinetics have been shown to approach zero order.

Long Acting Contraceptive Preparations²⁷

The injectable LH-RH-containing poly (DL-Lactide-co-glycolide) PLGA spheres is act as a contraceptive agent in males. Developments are being made for an injectable system much like Depo-Provera, in which testosterone enanthate would be administered along with depot medroxyprogesterone acetate(DMPA). Synthetic testosterone, 7 α -methyl-19-nortestosterone(MENT) for use in subdermal contraceptive implants in men. In conjunction with an LH-RH analogue, this potent steroid could be used in a system designed for 1 year of contraceptive use.

Transdermal Devices²⁸

A further development is the novel administration of testosterone via a transdermal device. The device is designed to administer testosterone for 1 month or longer, and initial testing shows a zero order release both *in vitro* and *in vivo* testing on

rhesus monkeys. The system is a disk shaped bandage-type device that contains microspheres of hormone suspended in liquid and immobilized in a crossed linked polymer.

Implantable Controlled Release Preparations²⁹

Cylindrical capsules of PLGA have also been investigated for their use in delivering buserelin acetate. Buserelin is a Gonadotropin-releasing hormone (GnRH) agonist. A GnRH agonist inhibits FSH and LH secretion from the pituitary, thus decreasing testosterone secretion and suppressing spermatogenesis. Preliminary testing of the device as a contraceptive has been inconclusive as the delivery of GnRH agonists must be carefully combined with the administration of androgens so as to inhibit only spermatogenesis and avoid adversely affecting other androgen supported functions in the body.

Herbal Microencapsulation

Research can be possible for encapsulation of active and potent compound, isolated from herbal resource utilizing different synthetic and natural polymer by different techniques. In the point of view the herbal microencapsulation which have anti fertility effect can be claim some what novel work, for avoiding the complication of the conventional herbal dosage form and drug to be released at controlled fashion.

CONCLUSION

The review is aimed at a new male contraceptive technique likely to be reversible and also useful for spacing birth. A high rate of acceptability of male contraception was seen among the urban population. A number

of public opinion surveys throughout the world have reported that 60-80% of men would use new contraceptive techniques, if made available.³⁰ In view of efficacy and safety of different male contraceptives demonstrated in animal trials the Drug Controller of India gave permission for phase-I Clinical Trial. Development of novel contraceptive devices will be very useful for population. Further there is a potential need for research and development of male contraceptive NDDS and ofcourse colloidal particulate carriers are promising in this perspective.

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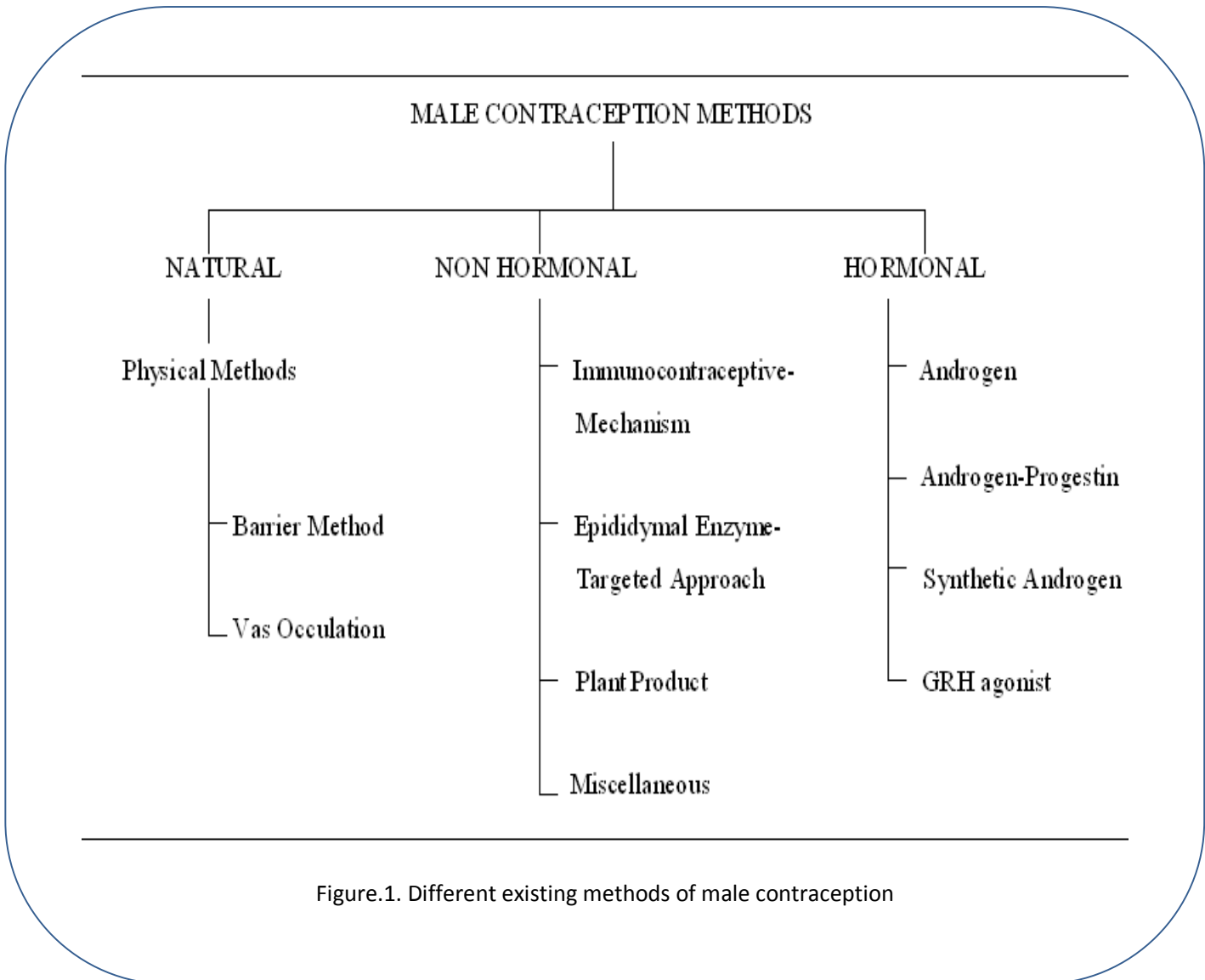


Figure.1. Different existing methods of male contraception

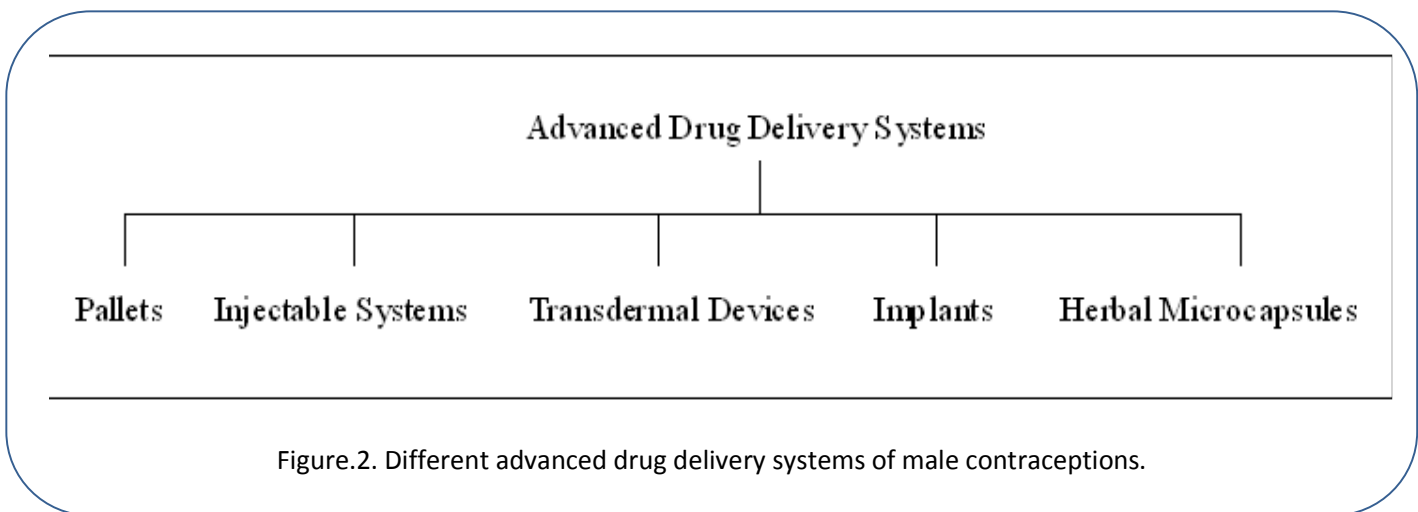


Figure.2. Different advanced drug delivery systems of male contraceptions.