

Review Article

## Innovation and Challenges in Male Contraception

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Received : 19 October 2022  
Accepted : 13 June 2023  
Published : 20 November 2023

DOI  
10.25259/GJMPBU\_113\_2022

Quick Response Code:



### ABSTRACT

The unwanted cases of pregnancy have increased resulting in improper family planning and cases of depression or stillbirth. The decision regarding reproduction is shared equivalently by men and women. Although the contraception methods result in effectiveness, they have more complications than effective results. Hormonal disbalance and endometriosis are a few such examples. Contraception for males is limited, yet has more effective results and fewer complications. The development of male contraception is vastly researched over the past few decades. Various hormonal and non-hormonal methods are being developed to provide better contraception with minimum or no disadvantage. The basic advantage of developing a male contraceptive includes its availability, low cost, no side effects, and ease of use.

**Keywords:** Experimental male contraception, Hormonal, Vas-occlusion methods

### INTRODUCTION

One of the crucial concerns addressed as a Public Global Health Issue is unintended/unwanted pregnancies. According to an estimate, countries that are developing or underdeveloped, have around 74 million unwanted pregnancies annually, out of which 25 million are aborted and 47,000 result in maternal death every year.<sup>[1]</sup> In India, with a rate of 70.1 pregnancies occurring per 1000 women aged 15–49, nearly half of them have unplanned pregnancies and one-third of them have an abortion.<sup>[1]</sup> One of the reasons for unplanned pregnancies is the failure of the method of contraception used, so this demands the use of better methods of contraception.

Contraception, in simple words, means birth control designed to prevent pregnancy. It is axiomatic that after reaching the age of puberty, men are fertile their entire age whereas women, after reaching puberty are fertile for only 3–4 days in a month/36–48 days in a year, approximately 1600 days in their entire fertile years until menopause occurs. While numerous options for contraception exist for women, methods for male contraception are limited to condoms and vasectomy. Furthermore, with the options available in women's contraceptives, the drawbacks are more and get intense with time causing hormonal disbalance, heavy periods, and endometriosis. This evaluation gives rise to developing male contraception with better access and acceptability. Since the last few decades, extensive research has been undertaken to improve and advance the female contraceptives, yet the need for the development of male contraceptives arises more, as their availability could provide the male partner a stable relationship with an opportunity to share the family planning responsibility and give men in general the opportunity to regain control over their fertility.

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To develop an ideal male contraceptive, the basic needs to be achieved are availability, accessibility, and few/no side effects from its use and budget-friendliness. With the approaches taken for ongoing research on male contraceptives, hormonal methods are potentially closest to a possible clinical application.<sup>[2]</sup> With the object of developing a hormonal contraceptive long-lasting delivery system, intramuscular (IM) injections of testosterone undecanoate and transdermal patches and gels containing androgens, a combination of testosterone, and nesterone are on the verge of being developed.<sup>[3]</sup> Non-hormonal methods such as vas-occlusion device Vasalgel, a solution of styrene maleic anhydride is injected into both vas deferens leading to blockage of the deferens, and preventing the passage of sperm are also close to being approved.<sup>[3]</sup>

## BACKGROUND LITERATURE

### Contraceptive mechanisms

The mechanism of contraceptives is either hormonal or non-hormonal. The mechanism of action of female hormonal contraception includes: Suppression of luteinizing hormone (LH) which leads to inhibition of ovulation, eventual thickening of cervical mucus, hindering the transport of sperm, and no development of endometrium.<sup>[4]</sup> Usually, hormonal contraceptives are primarily the combination of hormones, progestins, estrogen, or either of those.<sup>[5,6]</sup> Progestins primarily suppress LH and ovulation as a mechanism cursor of contraceptives.<sup>[7,8]</sup> They find their way in oral pills, transdermal patches, implants, etc. In oral contraceptives, they are derived from 19 nor-testosterone and include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, desogestrel, norgestimate, and gestodene.<sup>[7,9]</sup> The primary function of estrogen in a contraceptive is to regulate bleeding, along with inhibiting another ovarian hormone, that is, follicle-stimulating hormone (FSH), and preventing the formation of the dominant follicle.<sup>[10]</sup> In contrast to the long list of progestin formulations, only a few estrogenic compounds are used in hormonal contraceptives: Ethinyl estradiol, mestranol, and estradiol valerate.<sup>[11]</sup>

Non-hormonal contraceptives do not involve the use of any hormones. Instead, they block the invasion of sperm, their motility, or the fusion with ovum.<sup>[12,13]</sup> Various methods include condoms for both, males and females, intrauterine devices, spermicide, surgical methods for both men and women and withdrawal.<sup>[14]</sup>

The methods available for the contraception of females are described in [Table 1].

### Available male contraceptive

Condoms and vasectomy are the only two methods of contraception available for use by men.

### Condoms

Condoms are the oldest method used to date, which is reliably reversible. They serve as an exterior barrier blocking fertilization.<sup>[15]</sup> Although an overall estimate of 9.5% of men in India use condoms, the vast difference lies in urban and rural parts of India. Only 7.6% of men in rural India use condoms, and the percentage rises to 13.6% when urban parts of India are considered, showing better knowledge and awareness of contraceptives in the urban parts of India.<sup>[16]</sup>

Since condoms provide an exterior barrier; they perform the dual function of protecting against sexually transmitted diseases and preventing pregnancies without interfering with hormonal parts of the body. Yet, the failure rates of its typical use are very high, that is, 18% raising a concern about its use.<sup>[17]</sup>

### Vasectomy

Widely accepted by both developed and developing countries, the no-scalpel technique developed by China uses a single midline puncture in the scrotal raphe using scissors.<sup>[18-20]</sup> Vasectomy, with advancement in medical technique and tools, can be easily performed surgically and mainly involves ligation of the vas deferens through a small scrotal incision.<sup>[21]</sup>

Although the method is widely accepted, its drawback has awoken concern for its use. The main and major drawback lies in its delay in the onset of azoospermia, which means a complete absence of sperm from the semen. This delay lowers its efficacy, as the sperm still appears in the ejaculate even after surgery for 3–4 months.<sup>[19]</sup> After going through vasectomy, 10–15% of men experience chronic testicular discomfort.<sup>[8]</sup>

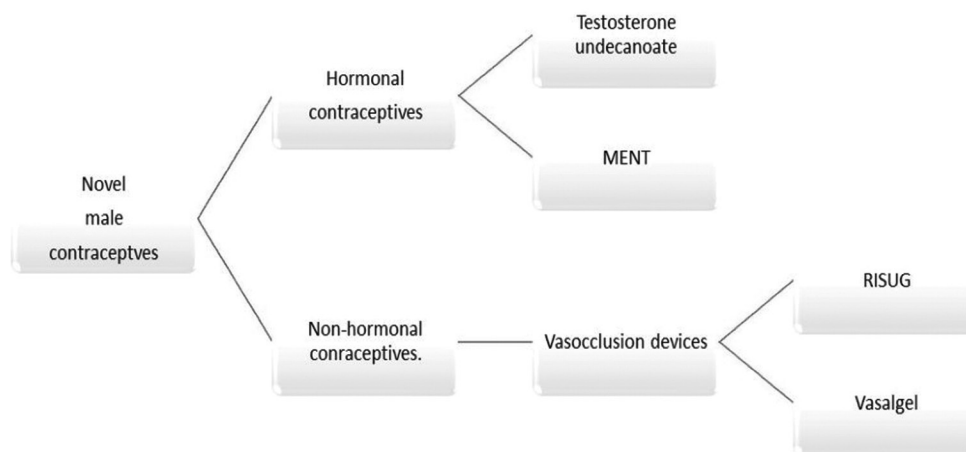
Previously, the method was considered irreversible, though, now it is considered reversible as the surgical procedure called vasovasostomy can re-join the ligated deferens. Unfortunately, the rates of pregnancy after vasovasostomy vary from 50% to 75% in previously fertile men.<sup>[19]</sup> Although there are many advantages, the major disadvantage of both procedures is the time. The earlier the surgery done, the lesser is the chance of reversal.<sup>[22,23]</sup>

Over the world, Asia accounts for approximately three-fourths of 32 million couples going through vasectomy, out of which India and China account for 20 million vasectomy users.<sup>[24]</sup> Only a 2% prevalence of vasectomy is seen in Latin America and the Caribbean.<sup>[24]</sup> Puerto Rico, with a prevalence of 5.3%, has the highest rate in the region. In sub-Saharan Africa, less than one-tenth of 1% of married women rely on a partner's vasectomy for contraception.<sup>[25]</sup> Vasectomy is a highly effective method of male contraception. It has a failure rate of <1% with few or no serious complications.<sup>[26]</sup>

**Table 1:** Available contraceptives for women, their mechanism, and failure rates.

Contraceptives	Mechanism	Failure %	Reference
<b>Hormonal contraceptives</b>			
Oral contraceptive	They are combinations of progestins and estrogen or consist either of those, preventing pregnancy by preventing ovulation.	9	[41]
Hormonal implants	A thin, tiny rod, and size similar to matchstick's size is implanted in the arm releases hormones to prevent pregnancy.	0.05	[42]
Depo-Provera contraceptive injection	It is a shot of hormone consisting progestin, given once in every 3 months, prevents pregnancy by thickening of cervical mucus.	6	[43]
Ortho-Evra patch	A transdermal patch, releases combination of hormones, progestin, and estrogen to prevent pregnancy.	9	[44]
Hormonal IUDs	A small piece of flexible plastic shaped like T, which releases a tiny amount of progestin in body, preventing pregnancy by making mucus of the cervix thick, and blocking the entry of sperm.	0.1–0.4	[45]
<b>Non hormonal</b>			
Condom (female)	A latex rubber sheath placed in the vagina to block the sperm's passage	21	[15]
Cervical cap	A rubber soft barrier that blocks the cervix to prevent sperm from entering into the mucus.	12	[46]
IUDs-Copper IUDs	The IU is a T-shaped device inserted into the uterus to alter the movement of sperm cells and to prevent them from fertilizing an egg.	0.2–0.8	[45]
Diaphragm	A dome-shaped barrier, which covers the cervix hindering the sperm passage.	12	[47,48]
Spermicide (only)	Spermicide contains chemicals that prevent sperm from fertilizing an egg when put in the vagina before sex.	28	[47]
Sponge	Contraceptive sponge uses spermicidal and barrier methods to prevent pregnancy	20–40	[49]
Vaginal ring	A small flexible ring placed in the vagina, once a month, prevents conception.	9	[50]

IUDs: Intrauterine device

**Figure 1:** Experimental novel male contraceptives ongoing research.

### Need for male contraception

Although the population is increasing the contraceptives of a male are limited to only two methods, condoms, and vasectomy. Condoms and vasectomy, although they provide a huge success rate, come with complications.<sup>[13,27]</sup> The former hinders the sexual pleasure and has a high failure rate, whereas, the latter even with low failure rates, irreversibility is itself a huge complication, along with other risks that

include bleeding, infection, chronic orchialgia, granuloma formation, and recanalization.<sup>[13]</sup> The need to develop a male contraceptive should focus on overcoming the drawbacks of available methods of male conception: The limited efficacy and compliance problems associated with condoms, and the irreversibility of male vasectomy need to be addressed. There are various ongoing researches as in figure 1 on both hormonal and non-hormonal methods of male contraceptives.

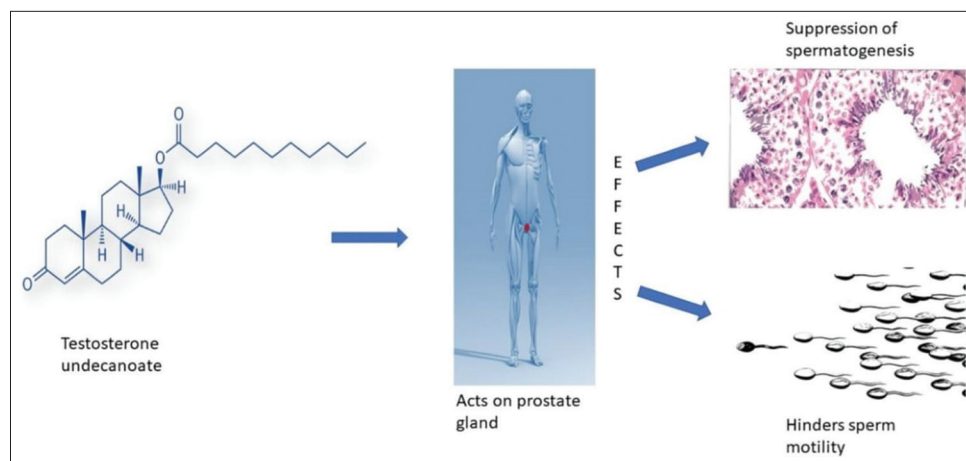


Figure 2: Action of testosterone undecanoate.

## Experimental male contraceptives

### Hormonal

The main aim of the ongoing research on hormonal contraceptives for males is to improve the suppression of sperm and reduce the side effects occurring in androgens.<sup>[28]</sup> The mechanism of action of hormonal contraceptives is similar to that of female hormonal contraceptives. It is based on the suppression of gonadotrophins, that is, LH and FSH secretion and release from the pituitary.<sup>[8]</sup> The suppression of gonadotrophins from exogenous sex steroids or gonadotrophin-releasing hormone results in (1) suppression of production of sperms from immature male sperm cells, that is, spermatogenesis and (2) decrease in intratesticular testosterone.<sup>[8]</sup> This profound suppression of sperm output inhibits fertility in men providing an effective male-directed contraceptive method.<sup>[20,28,29]</sup> Various regimens studies include the use of testosterone enanthate and androgen-progestin combinations that suppress the gonadotrophins (pituitary hormones) which block sperm production.<sup>[28]</sup>

### Testosterone ethanoate

For the replacement of testosterone in hypogonadal men, new researches are being done on the testosterone delivery system as shown in figure 2.<sup>[30]</sup> One such research found testosterone undecanoate, given as IM injection was found potentially long-lasting hormonal male contraceptive agent.<sup>[31,32]</sup>

In one such study, 308 men volunteered for the research trial. During the suppression phase, nine out of 308 men showed a decrease in sperm concentration which was <3 million/mL and 296 men entered the efficacy of 6 months. No pregnancy was observed when men had azoospermia or severe oligo-zoospermia.<sup>[32]</sup> In 2.3% of men, sperm rebound to levels, above the threshold during treatment, and also

one pregnancy occurred during the same.<sup>[32]</sup> Based on these results, phase 3 trials were done across ten centers in China, volunteered by 1045 men given the dosage of 500 mg testosterone undecanoate injection. The result showed 1% and 1.1% failure rate at the end of 12–24 months.<sup>[29]</sup> Thus, the study showed that it can be a formulation that is safe and effective, along with the property of reversibility as a contraception formulation for men.<sup>[29]</sup>

The common side effects are acne, weight gain, oiliness of the skin, increase in hematocrit and hemoglobin decrease in high-density lipoprotein cholesterol, and sleep-related breathing disorders.<sup>[32]</sup> These adverse effects may be dependent on the dose and methods of testosterone administration.<sup>[29,31]</sup>

### Gossypol

Shanghai Pharmaceutical Company (Shanghai, China) prepared a yellow pigment extracted from seeds of *Gossypium barbadense* known as Gossypol. The gossypol was studied as a drug that can be used as a constituent for male contraceptive pills as it showcased some qualities similar to contraceptives.<sup>[33,34]</sup> During the 1970s and 1980s, China did an extreme study, in which gossypol suppressed sperm production along with sperm motility. Along with these, it slightly changed the morphology of the sperm, of which the mechanism is still unknown.<sup>[19]</sup> The study was done in two large phases that enrolled over 8000.<sup>[19,20]</sup>

Development of azoospermia was seen in the majority of men after prolonged treatment. Although 90% efficiency was shown for gossypol in preventing pregnancy, approximately 1% of men developed hypokalemia and almost 20% did not regain fertility after treatment.<sup>[19]</sup>

Another research done by Coutinho *et al.* concluded and showed the potential of developing gossypol into a useful contraceptive pill for men. In this study, the dose regimens

**Table 2:** The ongoing experimental novel male contraceptives and their trials done with their complications.

Contraceptives	Successful models	Complications	Reference
Testosterone undecanoate	Human males	Decrease in HDL polymer. Increased hematocrit and hemoglobin.	[29,31]
Gossypol	Human males	Fertility did not return after the treatment.	[19]
MENT (implants)	Rats and human males	Decrease in HDL polymer. Increased hematocrit and hemoglobin. Pain and bruising at removal. One in five men showed impotency.	[32,51]
RISUG	Non-human primates (rhesus and langur monkeys), rats, rabbits and human males.	No such complications were observed	[19,52]
Vasalgel	Non-human primates, and human males	Granulomas developed	[29]

MENT: Alpha-methyl-19nortestosterone, RISUG: Reversible inhibition of sperm under guidance, HDL: High-density lipoprotein

used showed efficacy achieved by 60% of men.<sup>[33]</sup> On the positive part, this study showed no side effects, and in 51% of men, reversibility occurred within 1 year of stopping the treatment.<sup>[33]</sup> However, in 19% of men azoospermia persisted.<sup>[33]</sup> The research potential shows that it would give men an additional alternative to vasectomy and barrier methods.<sup>[33,34]</sup>

### 7-Alpha-methyl-19nortestosterone (MENT)

The development focus of male contraceptives as mentioned earlier has been on developing a contraceptive that is more potent than testosterone and suppresses gonadotrophins with no or fewer side effects.<sup>[29,32]</sup> MENT is one such compound that cannot be reduced to dihydrotestosterone like steroids and has fewer stimulating effects on the prostate gland.<sup>[29]</sup>

In a study performed in rats, MENT showed 10 times more potent action than the testosterone present in muscles, 4 times more potent in the prostate gland but has lesser effects on the prostate gland, which was confirmed in a study with monkeys.<sup>[29]</sup> MENT was initially developed as an implant. When the study was done in men, it effectively showed suppression of spermatogenesis given the condition of four implants that were used and released a total of 1600 mcg/day. The MENT implants are under development and being optimized to 1-year implant.<sup>[32]</sup>

### Non-hormonal: Vas-occlusion method

#### Reversible inhibition of sperm under guidance (RISUG)

Along with hormonal methods of male contraceptives, non-hormonal methods have also been a part of research since the 1970s. Researchers in India and China have been working to develop a method that could temporarily block the vas deferens.<sup>[19]</sup> A vas-occlusion method should be removable at a later stage for reversibility.<sup>[19]</sup>

India develops a vas-occlusion method known as RISUG. It uses styrene maleic anhydride (SMA) product that lines the

vas deferens, administered through intra-vas injection.<sup>[35]</sup> The RISUG, when present in the vas, creates a pH level that generates a positive charge, which results in the disruption of the acrosomal membrane and obstructs normal sperm transport through the female reproductive tract.<sup>[36]</sup> The study of RISUG done on non-human primates was found to be an effective contraceptive. It also showed reversibility in primates with vibratory massage, hence returning fertility.<sup>[19]</sup> For over a tenure of 1 year, the study has shown successful and effective contraceptive efficiency.<sup>[19]</sup> Although various compositions of RISUG have been studied in India for several decades, no product has yet been launched in the market.<sup>[19]</sup>

#### Vasalgel

The United States is now developing another vas-occlusion product for men which is an intra-vas injection like Vasalgel.<sup>[37]</sup> This intra-vas injection consists of a high molecular weight polymer, that is, SMA polymer dissolved in dimethyl sulfoxide (DMSO).<sup>[38,39]</sup> Unlike RISUG, Vasalgel does not claim any pharmaceutical effect and is understood to work by occluding the vasa differentia. When injected into the vas deferens, the hydrogel formed by SMA acid acts as tissue adherent, which forms the mechanical barrier by filling the lumen and blocking the passage of sperm.<sup>[37]</sup> Studies done on rabbits for 12 months of treatment proved Vasalgel to be reliable, showing azoospermia.<sup>[3]</sup> Furthermore, reversibility was achieved in the rabbits.<sup>[3]</sup>

Another research was done by Colagross-Schouten *et al.*, in which 16 adult male rhesus monkeys were given intra-vas injections of Vasalgel consisting of 25% styrene-maleic acid in DMSO.<sup>[40]</sup> After 1 week of recovery, the males were returned to outdoor group housing, which included at least 3 and up to 9 intact, breeding females with a successful history.<sup>[40]</sup>

Results: After Vasalgel was administered in the males, they were housed with intact females,; the treated males had no conception. All 16 male rhesus monkeys were housed with

intact females for at least one breeding season and showed no conception and out of 16 males, nine were continually housed with females for 2 years.<sup>[40]</sup>

Complication: Minor complications were observed:

- Incorrect placement of Vasalgel into the vas-deferens
- Development of granuloma
- Three unilateral vasectomies were performed. One was for the correction of placement and the other two were elective.<sup>[32]</sup>

The conclusion of the study found Vasalgel to be an effective method in adult male rhesus macaques.<sup>[29]</sup> The Vasalgel was well tolerated and showed minimal complication. Furthermore, flushing out Vasalgel is warranted.<sup>[40]</sup>

Experiments of the novel methods of male contraceptives that are being developed have been successfully performed in their chosen models and their details are shown in [Table 2].

## CONCLUSION

Conventionally, women have been burdened with the cause of reproduction, hence, contraceptives for females have been a focused area of research. However, for reproduction decisions and outcomes both men and women now agree to share the responsibility equally. To prevent an unwanted pregnancy, contraception is the best tool available. Acknowledging the fact that male contraceptives are limited to only two options, that is, condoms and vasectomy, the need to develop a male contraceptive that is easier to use, accessible, efficient, and produces no side effects is very crucial. The developing methods of novel male contraceptives will have an important impact on the interaction between men and women in the community/society. Various hormonal and non-hormonal approaches have been developed for decades; yet, there is no promising product ready for use. Despite this delay, the novel non-hormonal devices developed for males have shown better results than hormonal ones in their preclinical trials. Furthermore, for advancement and better knowledge of contraceptives that are available and are to be released, changes that should be made to improve reproductive health services are the healthcare system, schools, and communities. Public policies should be improved to broaden the range of reproductive health clinics that reach deeper into the communities. To remove the negative stereotypes regarding male reproductive health and to motivate them to use contraceptives, targeted community-led programs should be implemented to make men aware that they should share the responsibility of reproduction equally with female partners.

## Declaration of patient consent

Patient's consent not required as there are no patients in this study.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Sahu A, Sharma H, Nema RK, Sahu GK. Innovation and challenges in male contraception. *Glob J Med Pharm Biomed Update* 2023;18:30.