Devendra Singh Thakur et al, /J. Pharm. Sci. & Res. Vol.2 (7), 2010, 384-393

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Contribution of Male Contraception in World Population

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Abstract:
This review focuses on the challenges and opportunities in the development of new forms of male-based contraceptives. Further these review concentrate on those recent advances in science and technology that offer possible inroads for shifting the paradigm for male-based contraception. The development of an effective, reversible and safe male contraceptive has been the focus of research around the world for more than 30 years. There are numerous challenges in the development of a male contraceptive. Unlike women, who produce one functional gamete per month, men produce near about 100 million sperm every day. Based on animal studies and clinical results from treating hypogonadotropic hypogonadal men, a contraceptive agent that would functionally suppress either the formation or maturation of spermatozoa with a 90% efficacy would probably have little or no effect on fertility. Several non-hormonal avenues for male contraception are being developed, and a recent study provides an exciting novel approach to male contraception by administration of a drug that modifies the biosynthesis of glycosphingolipids.

Key Words: *Male contraception, Androgen, Antifertility vaccines, Gossypol*

Introduction:

There is a global need to support individuals in family-planning due to the increasing growth rate of the world's population with its negative impact on environment, economic growth and poverty reduction in underdeveloped countries. Aware of this responsibility, health organizations and pharmaceutical companies continue to financially support or actively pursue research towards new contraceptive approaches. The numerous steps required for male reproductive competence present, at first sight, many potentially attractive targets for functional disruption in order to achieve fertility regulation in men. Despite these possibilities, however, there are relatively few realistic approaches currently being pursued. Those that are include (a) the suppression of sperm production, (b) disruption of sperm maturation and/or function, and (c) interruption of sperm transport.

Male contraception

There are several approaches to the control of spermatogenesis via either hormonal methods or non-hormonal methods directed at sperm function and maturation. Most of the studies conducted so far in human volunteers have used hormonal combinations [1, 2]. The objective of these studies has been to induce azoospermia by suppressing the follicle-stimulating hormone (FSH). Traditionally, the only male contraceptive method available aside from prophylactics devices (particularly condoms) was to undergo a vasectomy which involved blocking the vas deferens (by way of tying or clamping). This minor surgical procedure is very effective with a failure rate as low as 0.2% [3]. However it remains problematic due to post operation pain [4] and the undesirability of surgery.

Male fertility, in particular spermatogenesis, can be manipulated through a variety of mechanisms some of which are fully reversible.

- Castration is the term given to the removal of the scrotum and testis, with the penis included in rare cases. With the removal of the testis, spermatogenesis is unable to occur and subsequently the patient becomes infertile. Currently, once the testis are removed it is impossible for infertility to be reversed however there is research to suggest that grafting testicular tissue can result in gamete and sperm production [5] .
- Ethane Dimethane Sulfonate (EDS) treatment results in the loss of Leydig cells on a temporary basis which subsequently

leads to a decrease in the concentration of testosterone in the reproductive system. Furthermore, Germ cells production which is essential for spermatogenesis, is found to be inhibited which leads to a temporary period of reduced fertility [6,7].Unlike castration, EDS treatment is reversible once treatment ceases and may be hastened with the assistance of androgen treatment.

- Cryptorchid treatment involves relocating the testis from the scrotum to the peritoneal cavity. It has been noted in studies that undescended testis can lead to a reduction in testicular weight, germ cell apoptosis and in some cases infertility [8]. This is caused by the adverse effect of increased testicular temperature [9, 10] which the body cannot reduce.
- Androgen therapy involves treating patients with excess concentrations of Androgens, in the Males case this consists of Testosterone. Studies show that excessive Testosterone can reduce the concentration of Spermatozoa and inhibit Spermatogenesis all together.

APPROACHES

I. Inhibition of Hypothalamic-Pituitary Function

A. Counteraction of GnRH Activity by:

1. GnRH agonist or antagonist
2. GnRH agonist/antagonist Plus Androgen
3. Anti-GnRH vaccine Plus Androgen

B. Suppression of Pituitary Gondotropins by:

1. Androgens
2. Progestogens
3. Antiandrogenic Progestins - CPA (Cyproterone acetate) and DNG (Dienogest)
4 Progestogens Plus Androgens
5 CPA Plus Androgens
6. DNG Plus Androgens

C. Inhibition of FSH Secretion/Action by:

1. Inhibin
2. Anti-FSH Vaccine

II. Direct Inhibition of Spermatogenic Cells in Testis by:

a. Colchicine
b. Nitrofurans
c. Bis-dichloroacetyl diamines
d. Gossypol
e. Mild testicular heating

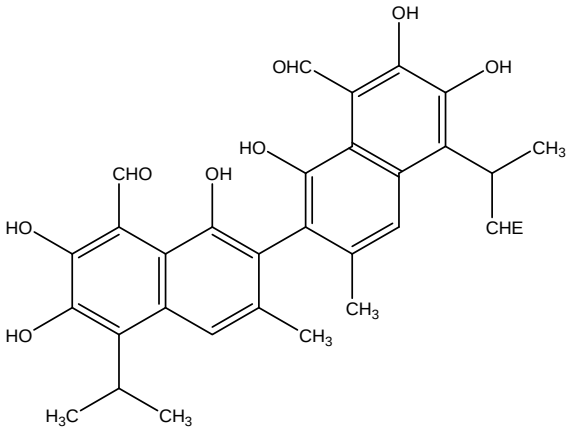
III. Post-Testicular Actions

1. Inhibition of Epididymal Sperm Maturation by:
a. Cyproterone acetate
b. α - Chlorohydrine
c. 6-Halo-6 deoxy sugars
d. Selective inhibition of 5α - reductase activity in epididymis
2. Anti-Sperm-Antigen Vaccine
3. Reversible Intra-vasal Devices:
a. Silastic/silicon plugs
b. Styrene Maleic Anhydride (SMA)
c. Intravasal copper

Non-Hormonal male contraception:

A large number of chemical agents have been described [11] but all tend to lead to total spermatogenic arrest and, ultimately, to irreversible sterility. Gossypol was one of the more attractive drugs in this category. It was identified as an antifertility agent by Chinese scientists and clinical studies on more than 8,000 men were conducted. Because of the high incidence of irreversibility and potentially serious side effects such as hypokalaemia ,gossypol has not been widely used outside China. Physical agents such as irradiation, ultrasound and high temperature also lead to spermatogenic arrest when applied at appropriate dose levels. Their limitations lie in the equipment needed and the careful monitoring of the dosage required to avoid irreversible damage. Recent clinical studies have shown that long-term mild elevation (1-20C) of temperature by the simple expedient of close apposition of the testes to the abdominal cavity during waking hours

can lead to azoospermia or severe oligozoospermia [12] .The safe reversibility, contraceptive efficacy and potential acceptability of this simple and inexpensive procedure need to be established.



Gossypol

Sperm maturation inhibitor:

A reversible, post-testicular drug action on the normal function of sperm stored in the epididymis would be rapid in onset and, on withdrawal of the drug, normal sperm would return quickly in the ejaculate. There would be no disruption of normal endocrine function and the long latent period required to suppress spermatogenesis would be avoided. Since sperm spend only a relatively short time in the epididymis (3-10 days in the human), any interference with their competence at this stage would be more likely to involve their motility, capacitation and acrosome reaction, events specific to sperm. Many chemical compounds with reversible effects on sperm stored in the epididymis have been described but all have been discarded for their toxicity. Alpha-chlorohydrin and the 6-chloro-6-deoxy sugars were amongst the best explored [13]. They at least established that the principle was attainable and, at antifertility doses, demonstrated the ideal characteristics of a post-testicular drug. Other compounds and their analogues are currently under investigation by various agencies e.g. sulphasalazines, imidazoles, pyrimethamine. Chinese investigators showed that a multiglycoside extract of the plant *Tripterygium Wilfordii*, long used in Chinese traditional medicine for the treatment of psoriasis, caused reductions in sperm motility and concentration in male patients .A collaborative programme has been established to isolate, identify and screen pure compounds extracted from the plant for their antifertility action.

New Vas Deferens-Based methods of male contraception

Since vasectomy is generally permanent, researchers have spent many years studying reversible alternatives to vasectomy. Some of the most promising prospects are discussed below.

i) Reversible Inhibition of Sperm Under Guidance (RISUG):

In this method, a gel composed of powdered styrene maleic anhydride combined with dimethyl sulfoxide (DMSO) is injected into the vas deferens, coating its walls and partially blocking the lumen. RISUG can be injected either percutaneously or by exposing the vas using the common no-scalpel method [14]. Within minutes of insertion, the gel solidifies and anchors itself to the microscopic folds of the inner walls of the vas deferens. As sperm comes into contact with the polymer, the combination of positive and negative charges on the polymer surface causes the membranes of the sperm to burst [15] .The sperm thus become immotile (unable to travel) and are unable to fertilize an egg. This chemical effect has another advantage; unlike vasectomies, which can take up to three months to achieve infertility, RISUG is effective almost immediately [16] Because it does not always completely block the vas,

RISUG may cause less back-pressure than vasectomy. In addition, RISUG may reduce the production of anti-sperm antibodies, and prevent the development of sperm granulomas, thus eliminating the painful nodules that a small percentage of men experience after vasectomy. Finally, the inner surface of the vas deferens also returns to normal upon removing RISUG. The reversal procedure can be performed whenever required, whether after days, weeks, or years of use. Since the polymer remains primarily whole, it can be flushed out by dissolving it with an injection of DMSO, a compound that is used in the medical treatment of many conditions, [17] and which is biodegradable in small quantities [18] The advantage of this method is that fertility can be inhibited by one injection and restored by another [19] "Noninvasive" reversal is also possible [20] Researchers have completed preliminary trials in humans, and 140 men are currently enrolled in a larger trial. RISUG has proved to be safe and effective in 25 years of animal and human trials [19-21]

ii) IVD: "Intra Vas Device"

This contraceptive is delivered through soft, hollow silicone plugs that are implanted in each vas deferens, two on each side. Each plug is anchored to the vas wall by a tiny suture (thread) [22] The IVD can be inserted by the "no-scalpel" vasectomy method. In addition, the double plug design offers an extra layer of protection in the event that sperm gets past the first plug. In primate studies, researchers found azoospermia in the entire cohort by the fourth ejaculation, and upon removal of the plugs, normal sperm counts returned by the fourth ejaculation [23] Based on these successful primate studies, researchers expect IVD reversal to be much simpler technically than vasectomy reversal efforts, however, getting the plugs out is not necessarily the same as restoring fertility. Since the plugs block the vas, questions remain about whether back-pressure will cause epididymal ruptures over time. This would mean that, much like vasectomies, the potential for pregnancy could drop dramatically with each year of use. In the meantime, Shepherd Medical announced FDA approval of a clinical trial designed to determine the effectiveness of the new IVD design; an 18-month effectiveness trial was started in 90 men in 2006.

Non Horonal but systemic methods of male contraception

Nifedipine:

Dr. Benoff was the first to recognize nifedipine's contraceptive effect, whilst working at one of New York University's hospital infertility clinics in 1992. Scientists have observed that sperm samples taken from men taking nifedipine exhibit low levels of mannose lectin in the sperm cell membranes, which is critical for binding with an egg's zona pellucida. Nifedipine treatment may physically prevent mannose lectins from moving to the surface of the cell membrane by stiffening the membrane with excess cholesterol [24, 25] Despite these advantages, its effective dose remains unknown and clinical trials have not yet demonstrated its effectiveness as a contraceptive.

There are now several groups of scientists using various methodologies to develop a better understanding of sperm calcium channels and the processes leading to sperm-egg fusion. The work of these different groups may eventually lead to new approaches that can be used for drug development [26]

iii. Miglustat (NB-DNJ, trade name Zavesca®)

The compound N-butyldeoxynojirimycin (NB-DNJ), trade name Zavesca®, uses a similar approach to nifedipine, but may be

more sperm-specific in its action. Miglustat is particularly exciting because it has passed safety tests and has recently been approved in both the United States and the European Union for treatment of Gaucher disease, a rare genetic disorder [27]

Studies on mice at the University of Oxford demonstrated that a low dose of miglustat effectively interferes with sperm development, and that the effects of this method are reversible. Miglustat impairs sperm motility by causing irregular mitochondrial sheaths, poor attachment of tails, and deviant head shapes. In addition, these deviant head shapes, along with absent or malformed acrosomes prevent fertilization in the event that sperm is able to get the egg. These effects were shown to be reversible within three weeks of drug cessation [28] Miglustat does not affect the genetic integrity of the sperm, allaying concerns about birth defects in cases of failed contraception.

iv. Adjudin

Adjudin is a relatively new prospect for male contraception, and is an analogue of an existing drug known as Lonidamine. Lonidamine is an anti-cancer medication which was found to have contraceptive effects in clinical studies conducted in the 1980s. Lonidamine was later abandoned when it was discovered that high doses have the potential to cause kidney damage. A group of researchers at New York's Population Council identified several nontoxic compounds similar to Lonidamine, and one of these compounds – AF-2364, or Adjudin – is moving toward clinical trials in humans.

Spermatids must undergo a series of cellular changes in order to become functional sperm. These changes include packing down the sperm's DNA, shaping the cell for improved motility, and preparing the cell's membrane to recognize and fuse with an egg. When rats were treated with Adjudin, the bridges between Sertoli cells and spermatids broke before maturation processes were complete. Prematurely released sperm are molecularly incomplete and therefore incapable of fertilizing an egg.

Effective delivery has been one of adjudin's major development obstacles. The compound has extremely low bioavailability, with less than 0.035% of an oral dose reaching the targeted tissues.While grinding the compound (micronization) improved oral uptake slightly, injecting the compound into muscle tissue did not make a difference.

To overcome this obstacle, a targeted delivery system was devised by Population Council scientists, who found a way to improve the delivery of adjudin by attaching it to a modified FSH molecule. Because FSH receptors on sertoli cells cannot differentiate between adjudin and its modified counterpart, adjundin can effectively be delivered to target cells in much smaller doses. Furthermore, no side effects were observed in trials performed on rats. In these studies, hormones, body weight, and testes weight all remained normal. Rats treated with a single dose of adjudin failed to produce offspring four to six weeks after the injection, despite reported mating activities. Although long term side effects have not yet been tested extensively, all of the treated animals regained full fertility within 5 months and had normal pups.

V. 'Dry orgasm' pill

Dr. Nnaemeka Amobi and Dr. Christopher Smith from King's College London announced that after about ten years of work they have discovered how two drugs – phenoxybenzamine, a high blood pressure medication, and thioridazine, a discontinued schizophrenia medication – each act effectively as male contraceptives, and

achieve this function through similar mechanisms. Drs. Amobi and Smith found that the two medications disrupted the transport of sperm by changing the way the smooth muscles of the vasa deferentia behaved during an orgasm. The vasa deferentia has two different types of smooth muscle: longitudinal muscle fibers and circular muscle fibers. Normally, the two muscle types work together to move sperm toward the urethra, however this effect was inhibited when segments of vasa deferentia were exposed to either phenoxybenzamine or thioridazine in the lab, preventing the longitudinal smooth muscle fibers from contracting,. The circular smooth muscles did contract, however, causing the vas to clamp shut. Drs. Amobi and Smith also observed these effects when similar drugs were used to examine the vasa deferentia, and have successfully identified other drugs which have a similar contraceptive effect, but with the reduced occurrence of side effects. This is fortunate, because the common side effects of phenoxybenzamine range from dizziness, increased heartbeat, and sinus congestion,and thioridizine's side effects were found to be so severe that the manufacturer discontinued its production in 2005 [29] Although alternatives to phenoxybenzamine and thioridazine have not yet hit the markets, early clinical trials suggest the drug should be effective within 2-3 hours of ingestion and last for approximately 24 hours.

There are half a dozen of other potential male contraceptive drugs with very different contraceptive mechanisms. There are several other plant based compounds, such as Triptergyium Wilfoerdii, Neem oil and Pappaya seed extract which merit further study. Other drugs such as an immunocontraceptive or an enzyme inhibitor pill are still in the conceptual stages of development. Another new development is the discovery of CatSper genes, which encode a series of calcium ion exchange channels specific to the male reproductive tract. The study of these genes will help us understand the contraceptive potential of calcium channel blocker drugs, and might suggest new mechanisms for treatment paths [30]

In addition to these prospective technologies, there is another method that is well known and readily used, the **"**heat method of male contraception". The deleterious effect of heat on male fertility has been known since ancient times and is mentioned in Hippocratic writings from the fifth century B.C.[31] These methods derive their effectiveness from the simple fact that the testes must be several degrees cooler than normal body temperature in order to maintain proper spermatogenesis Heat's action on fertility is not completely understood, but at least part of the effect seems to be due to a heat shock factor (HSF) that initiates cell death in sperm above about 95 degrees Fahrenheit (35˚ Celsius), whereas in the rest of the body, temperatures of about 108˚ Fahrenheit (42˚ C) are required to disable cells.

Newer Horonal male contraceptive

- *Newer Androgens*

Newer methods of sustained delivery for T suitable for use in a contraceptive regimen are being pursued. Testosterone buciclate, a synthetic ester given by depot injection, maintains physiological androgen levels for up to three months in hypogonadal men [32]. Testosterone undecanoate (TU) is a long-chain ester that is absorbed via the lymphatics. Therefore, when given orally, TU escapes first-pass hepatic metabolism [33]. It can be given orally two to four times a day, or by injection, where it maintains serum T levels for at least six weeks in hypogonadal men [34]. Interestingly, the concentration of the androgen and the type

of oil vehicle might be of importance in maximizing the effect of injected TU. A recent study of TU in a concentrated castor oil preparation showed a longer duration of effect when compared with TU in a less concentrated tea-seed oil [35]. This longer half-life may make the concentrated TU–castor oil preparation an even stronger candidate for future trials in male contraception. Recently, a trial of injectable TU (in tea-seed oil) as a hormonal male contraceptive was conducted in China [36]. Other esters such as 19-nortestos- terone (19-NT) have been evaluated as potential substitutes for TE. In addition to its potent androgenic effects, 19-NT has ten times the progestational activity of testosterone and, therefore, inhibits FSH and LH production to a greater degree than TE [37]. 19-NT has been used in contraceptive trials in conjunction with a progestin and was shown to be as effective in suppressing sperm counts as TE [38]. A derivative of 19-NT, 7a-methyl-19-nortestosterone (MENT), is of considerable interest. Transdermal T patches for the treatment of male hypogonadism has been in use for the past few years, but have only recently been tested for male contraception. Recently, non-steroidal androgenic compounds have been described [39]. These compounds are safe when administered orally to rats and, if safe in humans.

Novel Male contraceptive agents

- Eppin (epididymal protease inhibitor) is a member of the whey acidic protein (WAP)-type four-disulfide core (WFDC) gene family. Various studies provide updated information on Eppin and the Eppin-like genes within the Eppin cluster on human chromosome 20. A virtual structural model of the Eppin protein demonstrates that the C-terminal half of Eppin is structurally homologous to the Kunitz-type trypsin inhibitor. The Eppin N-terminal may have structural similarities to defensin-type molecules, rather than to that of the WAP consensus sequence. Human spermatozoa have a receptor for Eppin.When recombinant semenogelin (Sg) is digestedwith PSAmany lowmolecularweight fragments are produced. However, when Eppin is bound to Sg, digestion by PSA is modulated. Addition of antibodies to the C-terminal of Eppin resulted in blocking PSA activity modulation. Eppin, encoded by a single-copy gene, is a protease with antibacterial activity that is claimed to be expressed solely in the testis, the epididymis, and on sperm [40]. Eppin thus appears to be a valid target for contraception. High anti-body titres in serum and semen were achieved, yet the mechanism of action remains unclear. Immunological neutralisation of eppin could lead to local infection and inflammation, and consequently to infertility, which would be undesirable. Immunisation against a body constituent such as eppin could also lead to local reactions, and to the formation of immune complexes and autoimmune disease. When rhesus monkeys were immunized against the luteinising hormone β-subunit, granular deposits, indicating immunoglobulin penetration, were observed in pituitary cells of one animal [41] and monkeys immunised with ovine luteinising hormone developed alopecia. Immunisation against eppin (or other antigens from the male reproductive tract) could lead to immune orchitis and epididymitis, causing irreversible infertility. In O'Rand and colleagues' study, only five of seven monkeys regained fertility [42].
- Recently in 2008, Sadeghi et al., observed the contraceptive effects of Ruta graveolens L.,which has beenmentioned formale contraceptive in Iranian traditional

Table 1: Summery of antifertility vaccines.

Antigen	Species	Vaccine formulation	Refs
PZP	Horse	PZP from pig ovaries, without additional carrier, incorporated into biodegradable lactide–glycolide microspheres. Complete Freund's adjuvant and Carbopol 934	[48]
PZP	African Elephant	PZP from pig ovaries, without additional carrier. Trehalose dicorynomycolate in Drakeol mineral oil as adjuvant	[49]
PZP	Cynomolgus Monkey	Recombinant rabbit homolog of ZPB, with staphylococcal protein A as a carrier. Muramyl dipeptide as an adjuvant	[49]
Rabbit homolog of ZPB and ZPB	Baboon	Recombinant bonnet monkey ZPB, with diphtheria toxoid as a carrier. Squalene and Arlacel A as adjuvants	[50,51]

Abbreviations: PZP, pig zona pellucida; ZPB, zona pellucida glycoprotein B.

folkmedicine,was experimented on human sperm [43].

- In a recent study, Platt's group [44] proposed a novel approach to male contraception. Oral administration of an alkylated imino sugar, N-butyldeoxynojirimycin (NB-DNJ), resulted in a reversible suppression of fertility in mice. Both the onset and reversal of drug action occurred by the third week of treatment. At doses that resulted in a complete inhibition of fertility. NB-DNJ is an inhibitor of ceramide-specific glucosyl transferase, thefirst enzyme inthebiosyntheticpathway for glucosylating sphingolipids, and has been reported to be effective in treating disorders of glycosphingolipid storage [45]. The sulfoglycolipid seminolipid (sulfogalactosylalkyla-cylglycerol) is a well-recognized component of the plasma membrane of spermatozoa and has been shown to be essential for spermatogenesis [46] and play a significant role in the recognition of the zona pellucida (the membrane surrounding amammalianoocyte) by sperm [47].Therefore, an agent that alters

the biosynthesis of glycosphingolipids would be expected to affect the formation of the cell membrane. The extensive damage observed in the nucleus, mitochondrial sheath and acrosome of sperm following treatment with NB-DNJ might also be linked to altered glycosphingolipids associatedwiththese organelles,but this remains to be established. Itwill be interesting to determine whether, at doses used to induce infertility, NB-DNJ also causes significant changes in other tissues, suchas thebrain, that are rich in sulfoglucolipids.

- Antifertility vaccines: The example of antifertility vaccines are cited in following Table 1
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Conclusion:

The road to male contraception appears to be long and winding. Often researchers and the public are frustrated by lack of progress and inflated promises. Admittedly, the need for male contraception is not as urgent as before the advent of female oral contraceptives, male contraceptive research is driven more by intellect and less by emotion. A bit more emotion and a few prominent proponents would hasten progress in male contraception. The development of new generations of male-based contraceptives has lagged woefully behind developments in female-based contraception owing to several factors, including societal acceptance, trust by the female and a poor understanding of basic male reproductive function. Although there appears to be an ongoing shift in philosophy regarding the overall acceptability of male contraception in several different societies, many pharmaceutical companies are at a crossroads in acknowledging male contraception as a profitable market in an ever tightened and constrained industry.

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