In the name of God

Shiraz E-Medical Journal
Vol. 10, No. 3, July 2009

http://semj.sums.ac.ir/vol10/jul2009/87038.htm

The Male Contraception Supermarket.

Badiei Sh*, Bahasadri Sh**.

* Medical student, St George's Medical School, University of London, London, United Kingdom ** Assistant Professor, Department of Obstetrics and Gynecology, Iran University of Medical Sciences, Tehran, Iran.

Correspondence: Dr. Sh. Bahasadri, Akbarabadi Hospital, Tehran, Iran, Telephone: +98 (912)323-0491, Fax: +98(21) 2243-6758, Email: sh_sadri@yahoo.com

Received for Publication: October 27, 2008, Accepted for Publication: February 11, 2009.

Abstract:

Contraception has emerged as an important health issue as the world's population continues to rise. New male contraceptive methods are likely to become a valuable tool in addition to other resources available for family planning. Having access to a wider range of contraceptive methods will improve population control efforts worldwide. For this review, Medline, PubMed, and EMBASE searches were performed using the terms "male contraception, male contraceptive advances, and contraception for men" in key word searches. Hits were restricted to resources written in [what languages?] and published between the years 1966-2007.

Keywords: male, contraception

Introduction:

Contraceptive technologies that are currently on the market are far from ideal, despite the recent introduction of three new hormonal methods for women: the contraceptive patch, the contraceptive ring and the Mirena IUS (intrauterine system). It was hoped that these new methods would appeal to women and result in lower rates of unwanted pregnancies. However, in the developed world teenage pregnancy rates are high and there is still a significant need for abortion in cases of unwanted pregnancy. In underdeveloped and developing countries the situation is more extreme; every minute at least one woman dies from complications resulting from pregnancy and child birth,[1] and only 5-10% of women use modern contraception.[1] For them, lack of adequate contraception is often a life or death matter. Though politics, war, tradition, and economics all play a role in perpetuating this condition, a cheap, effective, and user friendly option would make substantial improvements in the lives of these women.

In contrast, the male contraceptive supermarket offers only three options: withdrawal, the condom, and vasectomy. The first two methods have unacceptable user failure rates and vasectomy is not readily reversible.[2] However, the male reproductive system offers a range of potential targets for new contraceptives. Various processes in reproductive physiology serve as targets for male contraception, including processes involved in the testicular production of spermatozoa, processes involved in the maturation of spermatozoa, its transport within the testis and epididymis, and its passage to and interaction with female germ cells. Androgens have been demonstrated to induce reversible infertility, particularly in combination with certain progestins and GnRH antagonists.[3]

Scientists have taken three main approaches to male contraception:

1) A hormonal approach, which is being studied for men in the form of implants and shots.[4]

2) A non-systemic approach, which targets the sperm directly without impacting the rest of the body.[5]

3) A non-hormonal but systemic approach, which is taken orally and affects the whole body.[6]

We will examine each of these targets in turn and will discuss the current state of research.

Hormonal male contraception:

Over the past few decades, research on male contraception focused primarily on the inhibition of spermatogenesis through negative feedback mechanisms induced by testosterone.[7, 8] Alternative androgens and testosterone regimens including different formulations of testosterone, testosterone in combination with progestins, anti androgens, and GnRH analogs have been tested.[9, 10] Among the different hormonal male contraceptive regimens being studied, a combination of testosterone and desogestrel/etonogestrel is the closest to being introduced into the market. However, there are still challenges for using hormone combinations,

such as determining the most appropriate dosage of each hormone, and which delivery systems would effectively deliver each component. Other challenges have been documented, and include: [11-13]

1. Choosing the most effective method of delivery (e.g. IM injections, implants, or patches).

2. Most methods require at least 1 ½ - 2 ½ months to achieve complete infertility.

3. Reversal of infertility can take up to 3 ½ -5 months.

4. Potential side effects on lipid profile, prostate gland, lean muscle weight, mood, and acne.

5. Some men (5-20%) do not respond to this method.

All other factors being equal, it would be preferable to choose a targeted method that is highly, if not entirely targeted to contraceptive processes and which has little impact on other systems in the body. Fortunately, several promising methods meet this criterion.

Non-hormonal Non-systemic approaches:

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-Hormonal but Systemic Methods of Male Contraception

i. Gossypol:

Gossypol is a polyphenol (C30H30O8) derived from the cottonseed plant. The effect of gossypol on human male fertility has been known in China for many years. In 1929, a study of couples who used crude cottonseed oil for cooking showed that they had smaller than average families.[24] These researchers showed that the oil specifically affected male fertility. Eventually, researchers isolated the contraceptive compound gossypol from cotton seed oil, and are developing it for use on the market.

This discovery of gossypol as a male contraceptive in China during the 1970s led to large scale testing for its use as a male contraceptive. These studies enlisted 10, 000 men who were monitored over a decade.[25] The researchers found that men taking a daily gossypol pill had low conception rates and no complaints about change in libido. However, the studies revealed two serious concerns; disruption of potassium uptake and incomplete reversibility (almost 40% of men did not regain fertility). Though gossypol has been abandoned by the World Health Organization, it continues to be studied for its effectiveness at lower doses. Some researchers propose taking advantage of gossypol's lack of reversibility because it still has the advantage of being a non-surgical alternative to vasectomy.[26, 27]

ii. Nifedipine:

Nifedipine is a well known medication for antihypertension and migraines, and belongs to a class of drugs known as calcium channel blockers (CCBs). 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.[28, 29] 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.[30]

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.[31]

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.[32] Miglustat does not affect the genetic integrity of the sperm, allaying concerns about birth defects in cases of failed contraception.[33]

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 com-

plete. Prematurely released sperm are molecularly incomplete and therefore incapable of fertilizing an egg.[24, 34]

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.35 While grinding the compound (micronization) improved oral uptake slightly, injecting the compound into muscle tissue did not make a difference.[36]

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.[35]

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.[37] Drs. Amobi and Smith also observed these effects when similar drugs were used to examine the vasa deferentia,[38, 39] 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,[41] and thioridizine's side effects were found to be so severe that the manufacturer discontinued its production in 2005.[40] 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 dif-

ferent 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.[42]

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.[43] 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.[44-47] 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.[48-50] Simple wet heat in the form of hot water, which is inexpensive and available to everyone, was the first contraceptive heat method discovered by the scientific community. In 1946, Dr. M. Voegeli reported on this method after more than ten years of experimentation with nine male volunteers. Although time-consuming, this method was perfectly effective and resulted in normal offspring after cessation. The simple wet heat method in use today is not substantially different from what Voegeli developed in 1921. Although various combinations of temperature, time, and heat source have been studied (artificial cryptorchidism, polyester suspensories, and ultrasound), more research needs to be done in this area.

Conclusion:

Without substantial advancements in contraceptive development, more couples will continue to have unwanted children or abortions due to condom failure, more children will be born into permanent poverty, more women in developing countries will die due to complications arising in childbirth, more women around the world will become intimately familiar with hormonal side effects, and parents will become economically responsible for a life they may not have the means to support.

Developing the male contraceptive supermarket is well within our ability, as the technical challenges are not complex. We bear in mind that the best methods also happen to be the least profitable. Therefore, public and government support is needed in order to make such products accessible to those who need them.

References:

1. Save the Children. State of the World's Mothers, 2005 and Complete Mothers' Index, 2005.

2. Hargreave TB: Towards reversible vasectomy. Int J Androl 1992; 15 (6): 455-459.

3. Wang C, Swerdloff RS: Male hormonal contraception. AJOG 2004; 190 (4): S60-S68.

4. Hoesl CE, Saad F, Poppel M, Altwein JE: Reversible, non-barrier male contraception: status and prospects. Eur Urol 2005; 48 (5): 712-723.

5. Goodwin LO, Leeds NB, Jacob A, Hurley IR, Benoff, S: Splicing Variants of the Human Testis-Specific Voltage-Dependent Calcium (Ca) Channel (VDCC): Potential Contribution to Human Male Infertility and Target for Contraceptive Development. Fertil and Steril 1997; 68 (1): S30-S31.

6. Robaire B: Advancing towards a male contraceptive: a novel approach from an unexpected direction. Trends Pharmocol Sci 2003; 24 (7): 326-328.

7. Lye RJ, Sipila P, Vernet P, Wagenfeld A: Male contraception—a topic with many facets. Mol cell Endocrinol 2004; 216 (1, 2): 75-82.

8. Wang C, Swerdloff RS: Male contraception. Best Practice & Research Clinical Obstetrics & Gynaecology 2002; 16 (2): 193-203.

9. Nieschlag E, Zitzmann M, Kamischke A: Use of progestins in male contraception. Steroids 2003; 68 (10-13): 965-72.

10. Amory JK, Bremner WJ: Male hormonal contraception: the future of male contraception? Medicine 2006; 34 (1): 25-26.

11. Wu FC: Hormonal approaches to male contraception: Approaching reality. Mol Cell Endocrin 2006; 250 (1-2): 2-7.

12. Amory JK, Bremner WJ: Newer Agents for Hormonal Contraception in the Male. Trends Endcrinol Metab 2000; 11 (2): 61-66.

13. Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C: Lancet 2006; 367 (9520):1412-1420.

14. Sethi N, Srivastava RK, Nath D, Singh RK: Preclinical toxicity study of a male injectable antifertility agent (styrene maleic anhydride) in rhesus monkeys, Macaca mulatta. J Med Primatol 1991; 20 (2): 89-93.

15. Chaudhury K, Bhattacharyya AK, Guha SK: Studies on the membrane integrity of human sperm treated with a new injectable male contraceptive. Hum Reprod 2004; 19 (8): 1826-1830.

16. Barone MA, Nazerali H, Cortes M, Chen-Mok M, Pollack AE, Sokal D: A prospective study of time and number of ejaculations to azoospermia after vasectomy by ligation and excision. J Urol 2003; 170 (3): 892-896.

17. Santos NC, Figueira-Coelho J, Martins-Silva J, Saldanha C: Multidisciplinary utilization of dimethyl sulfoxide: pharmacological, cellular, and molecular aspects. Biochem Pharmacol, 2003; 5 (7): 1035-1041.

18.Ali BH: Dimethyl sulfoxide: recent pharmacological and toxicological research. Vet Hum Toxicol 2001; 43 (4): 228-231.

19. Misro M, Guha SK, Singh H, Mahajan S, Ray AR: Vasudevan PInjectable non-occlusive chemical contraception in the male-I. Contraception 1979; 20 (5): 467-473.

20. Lohiya NK, Manivannan B, Mishra PK, Sriram S, Bhande SS, Panneerdoss S: Preclinical evaluation for noninvasive reversal following long-term vas occlusion with styrene maleic anhydride in langur monkeys. Contraception 2005; 71 (3): 214-226.

21. Manivannan B, Bhande SS, Panneerdoss S, Sriram S, Lohiya NK: Safety evaluation of long-term vas occlusion with styrene maleic anhydride and its non-invasive reversal on accessory reproductive organs in langurs. Asian J Androl 2005; 7 (2): 195-204.

22. Burton J, Sievert C, Socha J, Stahele B, Stice J, Townsend G, et al: Development and evaluation of the Intra Vas Device (IVD)--Poster. Paper presented at The Future of Male Contraception, Seattle, WA 2004.

23. Zaneveld LJ, Burns JW, Beyler S, Depel W, Shapiro S: Development of a potentially reversible vas deferens occlusion device and evaluation in primates. Fertil Steril 1988; 49 (3): 527-53.

24. Anderson RA, Baird DT: Male contraception. Endocr Rev 2002; 23 (6): 735-762.

25. Meng GD, Zhu JC, Chen ZW, Wong LT, Zhang GY, Hu YZ, et al: Follow-up of men in the recovery period immediately after the cessation of gossypol treatment. Contraception 1988; 37 (2): 119-28.

26. Coutinho E: Gossypol: a contraceptive for men. Contraception 2002; 59: 259-63.

27. Gu ZP, Mao B, Wang X, Zhang RA, Tan YZ, Chen ZX, et al: Low dose gossypol for male contraception. Asian Journal of Andrology 2002; 2 (4): 283-7.

28. Benoff S, Cooper GW, Hurley I, Mandel FS, Rosenfeld DL, Scholl G.M, et al: The effect of calcium ion channel blockers on sperm fertilization potential. Fertil Steril 1994; 62 (3): 606-617.

29. Opie LH, Yusuf S, Kubler W: Current status of safety and efficacy of calcium channel blockers in cardiovascular diseases: a critical analysis based on 100 studies. Prog Cardiovasc Dis 2000; 43 (2), 171-196.

30. Saha L, Bhargava VK, Garg SK, Majumdar S: Effect of nimodipine on male reproductive functions in rats. Indian J Physiol Pharmacol 2000; 44 (4), 449-455.

31. Actelion Ltd Zavesca (r) Capsules Available for Prescription in the U.S. 2004.

32. van der Spoel AC, Jeyakumar M, Butters TD, Charlton HM, Moore HD, Dwek RA, et al: Reversible infertility in male mice after oral administration of alkylated imino sugars: a nonhormonal approach to male contraception. Proc Natl Acad Sci U S A 2000; 99 (26), 17173-17178.

33. Suganuma R, Walden CM, Butters TD, Platt FM, Dwek RA, Yanagimachi R, et al: Alkylated imino sugars, reversible male infertility-inducing agents, do not affect the genetic integrity of male mouse germ cells during short-term treatment despite induction of sperm deformities. Biol Reprod 2005; 72 (4), 805-813.

34. Population Council. Probing Studies in Male Contraception. 2005. Online at www.popcouncil.org/biomed/Probing.html.

35. Mruk D, Wong CH, Silvestrini B, Cheng CY: A male contraceptive targeting germ cell adhesion. Nature, 2006; Medicine advance online publication.

36. Cheng CY, Mruk D, Silvestrini B, Bonanomi M, Wong CH, Siu MK, et al: AF-2364 [1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide] is a potential male contraceptive: a review of recent data. Contraception 2005; 72 (4): 251-61.

37. Amobi NI, Guillebaud J, Kaisary A, Lloyd-Davies RW, Turner E, Smith IC: Contractile actions of imidazoline alpha-adrenoceptor agonists and effects of noncompetitive alpha1-adrenoceptor antagonists in human vas deferens. European Journal of Pharmacology 2003; 462 (1-3): 169-77.

38. Amobi NI, Guillebaud J, Kaisary A, Turner E, Smith IC: Discrimination by SZL49 between contractions evoked by noradrenaline in longitudinal and circular muscle of human vas deferens. British Journal of Pharmacology 2002; 136 (1):127-35.

39. Amobi NI, Chung IP, Smith IC: Attenuation of contractility in rat epididymal vas deferens by Rho kinase inhibitors. Autonomic & Autacoid Pharmacology 2006 26 (2): 169-81.

40. World Health Organization. Thioridazine – Withdrawn due to poor benefit/risk profile." WHO Pharmaceuticals Newsletter 2005 1: 2.

41. Mayo Clinic. Drugs & Supplements: Phenoxybenzamine (Systemic). Accessed online at http://www.mayoclinic.com/health/drug-information/DR202458, 1998.

42. Carlson AE, Westenbroek RE, Quill T, Ren D, Clapham DE, Hille B, et al: CatSper1 required for evoked Ca2+ entry and control of flagellar function in sperm. Proc Natl Acad Sci USA 2003; 100 (25), 14864-14868.

43. Hippocrates & Adams F: The genuine works of Hippocrates. Baltimore: Williams & Wilkins: 1939.

44. Fukui N: On a hitherto unknown action of heat ray on testicles. Japan Medical World 1923; 3, 27-28.

45. Moore CR, Oslund R: Experiments on the sheep testis- Cryptorchidism, vasectomy and scrotal insulation. American Journal of Physiology 1923; 67: 595-607.

46. Robinson D, Rock J: Intrascrotal hyperthermia induced by scrotal insulation: effect on spermatogenesis. Obstet Gynecol 1967; 29 (2), 217-223.

47. Watanabe A: The effect of heat on the human spermatogenesis. Kyushu Journal of Medical Science 1959; 10: 101-117.

48. Sarge KD: Male germ cell-specific alteration in temperature set point of the cellular stress response. J Biol Chem 1959; 270 (32): 18745-18748.

49. Sarge KD, Bray AE, Goodson ML: Altered stress response in testis. Nature 1995; 374 (6518): 126.

50. Sarge KD, Cullen KE: Regulation of hsp expression during rodent spermatogenesis. Cell Mol Life Sci 1997; 53 (2): 191-197.