Perspectives of contraceptive choices for men

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Apart from condoms and vasectomy, which have several limitations of their own, no other methods of contraception are available to men. Various chemical, hormonal, vas based and herbal contraceptives have been examined and few of them have reached the stage of clinical testing. Promising leads have been obtained from testosterone buciclatelundecanoate, alone or in combination with levonorgestrel butanoate or cyproterone acetate, RISUG, an injectable intra vasal contraceptive and a few herbal products, particularly the seed products of Carica papaya. It is feasible that an ideal male contraceptive, that meets out all the essential criteria will be made available to the community in the near future.

Keywords: Carica papaya, Herbal methods, Hormonal methods, Male contraception, RISUG, Vas based methods

In the new millennium, India has crossed the one billion mark, sharing 16% of the world population on 2.4% of the global land area. More than 18 million people are added every year, which is almost the entire population of Australia. With the current trend, it is projected that India may overtake China in the year 2045 to become the most populous country in the world, the distinction which no Indian would be proud of. Although India was the first to launch National Family Planning Programme as early as 1952 in order to curtail the population menace, 16% of currently married women in the country have an unmet need for family planning: 8% women want child spacing without contraceptive use, while the other 8% do not want any more child but without the use of contraceptive1. As per the National Family Planning Survey (1998-1999), 25% of total family planning programme had an unmet need, and the contraceptive prevalence rate in the country is only a moderate 48.2%, with female sterilization accounting for 34.2% and the currently available male methods accounting negligible.

Currently men’s involvement in regulating family size is negligible, as there is an argument that they do not have sufficient contraceptive choices to adopt, compared to their female counterparts. For regulation of male fertility, the various steps in reproduction that lead from sperm production in the testis to sperm egg interactions and fertilization in the female genital tract need to be considered. Accordingly, the biomedical options available in control of male fertility are limited to (1) inhibition of spermatogenesis at the level of testis, (2) inhibition of sperm maturation at the level of epididymis, (3) inhibition of sperm transport at the level of vas deferens, (4) inhibition of sperm deposition in the female genitalia, and (5) inhibition of sperm egg interaction at the level of female reproductive tract. The options available to men are limited to condoms, periodic abstinence, withdrawal and male sterilization. Survey among married men in developing countries indicate that only 4% of men use condoms, 4% undergo vasectomy, 3% use periodic abstinence and 4% use withdrawal in which periodic abstinence and withdrawal have higher failure rates and are often practiced with other contraceptive measures.

Current Trials

It is speculated that men’s participation in family planning would increase, if there are wider choices of contraception available to them, which should be safe, effective, and economical and that it should provide long term and completely reversible contraception, preferably free of surgery with greater acceptability rate. One of the main problems encountered in development of a male contraceptive is the fact that it is necessary to achieve azoospermia or make all the sperm nonfunctional, since it is believed that even a single functional spermatozoon is adequate for fertilization. Azoospermia could be easily achieved by
interfering with production of testosterone which is indispensable for spermatogenesis, but the same could interfere with libido which is unacceptable.

A number of approaches including the use of hormones or non-hormones involving androgens, antiandrogens or GnRH analogs with sites of action in the testis and epididymis, and non occlusive devices that have either a chemical or mechanical effect on spermatozoa as they pass along the vas deferens, are being investigated; these approaches may interfere with sperm function either in the testis, epididymis or in other parts of the male reproductive tract, and are intended mainly to affect sperm production directly or render the spermatozoa infertile without affecting the circulating testosterone level. Most of these approaches have reached the stage of clinical testing, but none of them has so far reached the stage of acceptability or commercialization for public utility.

Hormonal methods

The hormonal approach to male contraception is based on the suppression of gonadotrophin secretion with secondary suppression of spermatogenesis to achieve azoospermia, the ultimate goal in male contraceptive studies. Androgen alone in the form of testosterone esters, testosterone enantate, testosterone buciclate, testosterone undecanoate, alpha methyl 19 nor testosterone [MENT] and testosterone buciclate or testosterone buciclate alone and androgen in combination with progestogen i.e., depot-medroxy progesterone acetate and testosterone enantate, medroxy progesterone and testosterone enantate, levonorgestrel and testosterone undecanoate, levonorgestrel and testosterone enantate/testosterone buciclate, desogestrel and testosterone, and androgen in combination with progestogenic antiandrogens viz., cyproterone acetate and testosterone enantate, cyproterone acetate and testosterone buciclate, norethisterone enanthate and testosterone undecanoate and norethisterone enanthate and testosterone enantate have been investigated up to clinical trial for many years but without identifying a suitable regimen which would result in suppression of spermatogenesis to achieve contraception, without adverse metabolic effects.

The WHO consultative meeting on "Setting the Agenda for Fertility Regulation Technology Research in Reproductive Health for the Next Decade" (held at Geneva, Switzerland, 1996) identified two leads in the field of male contraception viz., (i) a tri-monthly injectable levonorgestrel butanoate plus testosterone buciclate or testosterone buciclate alone and (ii) non-surgical vas occlusion. The latter is considered more advantageous because it causes minimal hormonal and systemic side-effects and offers a better scope for reversal. Currently, testosterone undecanoate alone or in combination with depotmedroxy progesterone acetate or norethisterone enanthate are also under clinical trial to identify more priority leads for male contraception.

Vas based methods

Vasectomy is a simple, safe, effective and an inexpensive method of male contraception; the operation can be easily performed in 10-15 min on an out-patient basis with minimal training for most surgeons. It is perceived in some cultures that vasectomy reduces physical strength and has been claimed by some men who had undergone the operation and also by their partners that it reduces sexual potency. In addition, vasectomy is considered as a permanent method and even if reanastomosis of the vas is successful, the resulting fertility is poor.

An ideal intravasal device for male contraception should be easy to insert, and be flexible; it should prevent sperm passage and be capable of being easily removed for restoration of vas patency and return of fertility. Initial attempts have been made to solve the problems associated with the reversal of vasectomy. Several mini biomedical devices, viz., intravasal thread, copper wire, biogalvanic cells, and tantalum clips have been tried, but they failed to meet out the ideal requirements. Injectable plugs, employing percutaneous injection of polyurethane elastomer to form plugs and non injectable silicon plugs, called the 'shug' have also been tried up to the level of clinical trial in over 10,000 men. However, the surgical intervention for implantation of devices into the vas deferens and their reversal limits further consideration in use of intravasal devices for mass family planning programme. Hence, from the delivery point of view, injection of a polymer into the vas lumen, by a minimal invasive procedure that provides a safe and effective contraception and offers reversal, would appear to be more advantageous, convenient and globally acceptable.

Styrene maleic anhydride (SMA), currently renamed as RISUG, is a co-polymer of styrene and maleic anhydride and offers fertility control through multiple modes viz., it blocks the vas deferens and prevents forward flow of sperm, induces pH lowering effect and causes charge disturbances to the membrane of the spermatozoa, resulting into the
acrosome damage. Further, SMA has no teratogenic effect and is toxicologically safe in animal models. Clinical trials at Phase I and Phase II levels have shown contraceptive efficacy and safety of SMA in humans. It has also been demonstrated in Phase II clinical trials that SMA could be delivered into the vas lumen by "No Scalpel injection" method with minimal invasion. However, in order to make this procedure widely acceptable as a better alternative to vasectomy, its contraceptive efficacy should last longer, with the possibility of reversal at desire.

Preliminary investigations have been carried out in langur monkeys to ensure reversal by a non-invasive method, following a short term vas occlusion with SMA @ 60 mg in 120 µl of DMSO in each vas deferens for 150 days. The procedure leads to uniform azoospermia in 90 days. Non-invasive reversal procedure, following three consecutive azoospermia extended for 150 days, by palpation, per-cutaneous electrical stimulation, supra-pubic percussion, and per-rectal digital massage in successive steps resulted into reversal of azoospermia with severe oligospermia on the same day of reversal manipulations, which gradually improved and normospermia, comparable to that of the pretreatment levels, could be achieved within 30 days of reversal manipulations. Ultrastructure of spermatoxoa and vas morphology, which showed deleterious changes after vas occlusion, also returned to normalcy after 90 days of reversal. Sperm function tests, i.e., hypo-osmotic swelling test to demonstrate membrane integrity, acrosomal intactness test to demonstrate the status of acrosome and the sperm mitochondrial activity index test to demonstrate flageller mitochondria and motility disorders, also indicated regain of fertility following 30 days of reversal. Repeat vas occlusion and reversal have also been successfully demonstrated in langur monkeys, with a possibility of using the technique as spacing method. Currently, this procedure appears to be one of the most promising among the vas based contraceptive approaches with the feasibility of reversal at desire.

Herbal methods

The ayurvedic and unani texts mention the use of a number of plant preparations for fertility regulation. The Asian countries, particularly India and China, have contributed the most and have identified the novel drug prototypes found in plants, which have been reported to possess fertility regulating properties. The compounds that are being sought in particular are those which are orally effective, non-steroidal, non-estrogenic, safe and effective in inhibition of spermatogenesis or interfere with sperm maturation in men.

To date, several hundred plants have been reported to possess significant antifertility properties. In all these plants, studies were restricted only to the level of spermatogenesis through histology and fertility tests in rats and mice. The roots of Aristolochia indica and Plumbago zeylanica, the leaves of Azadirachta indica, Catheranthus roseus, Vinca rocea and Ocimum sanctum, the flowers of Hibiscus rosa-sinensis and Malvaviscus czonati, the seeds of Carica papaya and Vitex negundo, and the fruits of Momordica charantia, have been identified as lead plants for male fertility regulation.

The gossypol isolated from the seeds of cotton plant and the glycosides of Tripterygium wilfordii have been studied extensively up to the stage of clinical trials. Although, gossypol was found to be more effective with 99% efficacy assessed by semen examination in human trials, further studies were abandoned due to its major side effects such as hypokalemia, low therapeutic index and uncertain recovery upon withdrawal of the drug. The glycosides of Tripterygium wilfordii have shown reversible impairment of motility in human. However, preliminary toxic evaluation indicated that these compounds are immunosuppressive at high dose regimens. Further success of this plant as a male contraceptive warrants special attention to prove deeply to their precise dose/immuno effect relationship.

Extensive animal studies carried out with the seed extracts of Carica papaya indicated that this product could be identified as a potent testicular/post testicular orally effective contraceptive in the near future. Chloroform extract, benzene chromatographic fraction of the chloroform extract and its methanol and ethyl acetate sub-fractions of the benzene chromatographic fraction and the isolated compounds from the sub-fractions have shown promising results in rats, rabbits and langur monkeys. Chloroform extract showed total motility inhibitory action after 60 days in rat, and severe oligospermia by 90 days and uniform azoospermia by 120 days in rabbit. With benzene chromatographic fraction total sperm motility inhibitory action was achieved within 60 days after treatment in rats and uniform azoospermia was achieved after 15 days in rabbits. Similar results
were achieved with methanol and ethyl acetate sub-fractions of the benzene chromatographic fraction in rat and rabbit. The effects were free of toxicity up to 180 days study period and completely reversible following withdrawal of treatment. Fertility test indicated 100% antifertility effect. Pre-clinical investigations carried out in langur monkeys revealed uniform azoospermia after 90 days of treatment with chloroform extract which continued until one year study period, while benzene chromatographic fraction and its sub-fractions showed total sperm motility inhibitory action after 60-90 days of treatment. The effects were free of toxicity and reversible.

The major limitation associated with the herbal contraceptive is that in many cases it is becoming increasingly difficult to get a useful lead from the published results. The results vary within the same plant and a herbal contraceptive being used by human based on folklore medicaments may be effective in human but ineffective in animal models. Such a plant should not be rejected based on experiments on rats and mice, when the same plant is being used by people for centuries. Therefore, potential contraceptives from herbal sources should be explored based on established route of administration, appropriate animal toxicological studies and phased clinical trials in order to increase the acceptability of these products for human use.

**Conclusion**

Available evidences indicate that among the various procedures being developed for male contraception, hormonal contraception, either androgen alone or in combination with progestogen or antiantrogen is being viewed at low profile because of their insufficiency in inducing suppression of spermatogenesis and further steroids related long term complications. Research is still being continued with several combination regimens to alleviate these complications. Vas occlusion by SMA at the therapeutic dose level i.e. 60 mg in 120 μl DMSO provides instant contraception that can be conveniently delivered possibly by no scalpel injection in human. It offers long term contraception with no adverse side effects. Successful reversal is possible by a non invasive procedure. The results also suggest the feasibility of a male spacing method by repeat vas occlusion through no scalpel injection and non-invasive reversal. The seed products of Carica papaya also provide sufficient evidence that they can meet out the essential criteria of an ideal male contraceptive.

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