

Male Contraception

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LEARNING OBJECTIVES

The goal of the lecture is to provide each student with knowledge, understanding and appreciation of:

- The rationale for increasing contraceptive choice by developing improved and new methods for use by men;
- Research approaches towards male contraceptive development;
- The current status of male contraceptive trials;
- The need for and importance of acceptability and behavioural studies related to use of male contraceptive methods.

INTRODUCTION

Very few options for men to initiate fertility control are currently available. Due to the potential public health impact of a novel method of contraception for men in the developed and developing world, a number of organizations are conducting or supporting studies which focus on the male contraceptive aspect of reproductive health. These include bilateral and multilateral donors, national governments and Ministries of Health, research institutions, universities, non-governmental organizations (NGOs), and the private sector.

A comprehensive research agenda in male contraception would address the following topics:

- New and improved condoms;
- Vasectomy/vas occlusion;
- Male hormonal contraception;
- Long-term safety of existing and new methods;
- Immunocontraception;
- Reproductive physiology research in males geared towards identification of new leads for fertility regulation, especially those with local, specific modes of action;
- Assessment of acceptability and sexual behaviour related to male contraceptive methods.

While no individual organization can support such a broad range of activities, there is a great deal of collaboration between these agencies, and their research portfolios are complementary.

In conducting research on and development of methods for men, investigators need to keep in mind the need for these products to be as effective as comparable female methods and acceptable to both partners. The products need to be safe and, ideally, reversible. Such methods will provide for expanded choices available to couples to regulate their fertility in that they will:

- Address an unmet reproductive health need;
- Respond to the diverse individual contraceptive needs of couples; and
- Provide a valuable and welcome alternative to the limited options of the condom, vasectomy and withdrawal, that are currently available to men.

NEED FOR MALE CONTRACEPTION

For individual couples, the goal of practising contraception varies from postponing childbearing, spacing births and limiting family size to absolute freedom from childbearing. Contraceptive needs of couples vary according to their type of relationship, purpose of contraception and age. Currently available methods of fertility regulation for men and women do not adequately meet the varied and changing personal needs of couples in their reproductive lives and in the widely different geographical, cultural, religious and service delivery settings around the world. While increasing the choice available to either partner will ensure the wider availability of safe and effective means for fertility regulation, the shortcomings of currently available male methods are a major barrier to the greater involvement of men in family planning. To address the disparity between need and available technologies, The 1994 International Conference on Population and Development (ICPD) called for the development and promotion of male methods of contraception alongside those technologies that would provide for the prevention of sexually transmitted infections (STIs), including HIV/AIDS as well as unplanned pregnancy. As a result of increased understanding of gender issues and roles required for improved reproductive health, there is more recognition for the need for shared contraceptive responsibility¹. The availability and use of acceptable male contraceptive methods could reduce the burden traditionally placed almost exclusively on the female partner.

MALE CONTRACEPTIVE OPTIONS – Methods and related biomedical research

Improved male condoms

Male latex condoms offer very effective prevention from unplanned pregnancy *and* HIV/AIDS infection. They are therefore considered a “dual protection” method. When used correctly and consistently for each sex act, condoms are 97% effective in preventing pregnancy. They offer very effective protection against transmission of HIV as well, as determined by retrospective analyses and prospective studies in discordant couples. Research is ongoing to determine the effectiveness of the condom in preventing the transmission of other sexually transmitted infections (STIs) in women and men.

Because protection from HIV and other STIs is a critical health concern, and condoms are the only widely available products that offer dual protection, several condom manufacturers, as well as the public sector, are investigating new materials and designs for male condoms. Improvements in the technology of male condoms could address and overcome many of the acceptability issues that hinder expanded use of these products. Minor changes in condoms, such as the material from which they are made or their size or shape, could lead to greater acceptability and thus greater use of this important and low-cost method.

Improved methods of vasectomy; non-surgical vas occlusion

Male sterilization, or vasectomy, is the most effective of male methods of contraception currently available. World-wide, more than 40 million couples use vasectomy as their method of fertility regulation; however this method is popular in only a few countries. Expanding use of vasectomy as a safe and effective method requires overcoming several obstacles, namely socio-cultural and political barriers, provider bias, myths and misperceptions surrounding vasectomy, and inadequate information and communication.

Vasectomy is considered one of the safest and most reliable family planning methods currently available; pregnancy rates in the first year following vasectomy are between 0 and 2%. Multiple studies and analyses have not indicated any association between vasectomy and cardiovascular disease, prostate cancer, or testicular cancer². Currently, research needs are related to increasing information about the safety and efficacy of the procedure, dispelling myths, and increasing male acceptance of sterilization.

Greater acceptance of vasectomy is affected by two main factors: (i) the need for a surgical intervention; and (ii) the fact that the procedure needs to be considered permanent, as the success rate of reversal is low. Thus an approach is sought which makes vas occlusion easier to perform and more predictably reversible. Targeting the vas deferens as a site to block sperm transport is an attractive option, as infertility could be achieved rapidly and could, hypothetically, be fully reversible. A variety of methods have been investigated, each with advantages and disadvantages with respect to efficacy, local toxicity, reversibility, rapidity of onset of infertility, and ease of administration³.

In perhaps the only prospective trial comparing methods of male sterilization/vas occlusion, a ten-centre study in China investigated the effectiveness, reversibility and safety of three methods: i) no scalpel vasectomy, ii) chemical vas occlusion, iii) and polyurethane plug vas occlusion. Twenty-four months following the procedure; no-scalpel vasectomy had the highest rate of contraceptive efficacy, as determined by the rate of sperm disappearance in the ejaculate. Following an optional reversal procedure, those men who had received the no-scalpel vasectomy demonstrated more rapid and higher rate of successful reversal, as defined by a subsequent pregnancy. Plans are being developed to follow-up the vasectomy volunteers to establish long-term (10 year) efficacy of these various procedures.

To date, there is no method of vas occlusion that has proven to be more efficacious with greater success of reversal than vasectomy, though research continues.

Hormonal Male Contraception

Finding an effective, safe, acceptable, reversible and preferably long-acting, hormonal contraceptive method for men is a research priority for WHO and other organizations. Although there are currently no systemic methods of contraception for use by men, the development of a male-use equivalent of oral, injectable and implantable female steroid hormone methods of contraception has been the subject of research for the past 30 years or more. Such a method is the most feasible of all new leads and it is now within grasp. This would provide a valuable addition to the currently limited options of male initiated methods.

The goal of such a method is to alter the endogenous hormonal system such that sperm production is completely arrested. A number of studies in animals and men have shown that the administration of androgens alone, androgen and progestin combinations, and combinations of androgens with gonadotrophin-releasing hormone receptor ligands can suppress gonadotrophin secretion and thereby reduce spermatogenesis either completely to azoospermia (zero sperm) or to a sufficiently low level

of oligozoospermia (reduced sperm counts) to render men infertile. Fertility is correlated with sperm counts higher than 1 million/ml of ejaculate, with increasing sperm concentrations resulting in increased risk of fertility⁴.

Androgens alone

Results from a landmark ten-centre WHO study, as reported in 1990⁵, demonstrated the physiological effects of a weekly injectable testosterone ester (200 mg of testosterone enanthate - TE). The administration of this androgen inhibited pituitary gonadotrophin - luteinizing hormone (LH) and follicle stimulating hormone (FSH) - secretion, suppressed sperm counts dramatically, and maintained peripheral testosterone at levels high enough to preserve libido and potency. While the regimen demonstrated proof of concept, it required weekly intramuscular injections and was not effective enough to reliably suppress sperm counts in non-Asian men.

A more detailed follow-on study established that the spermatogenic suppression to azoospermia or severe oligozoospermia induced by weekly TE resulted in sustained but reversible contraception with pregnancy rates of 0/230 person-years and 4/50 person-years, respectively⁴. Sperm counts were suppressed more slowly in the Asian than in the non-Asian men in the first two months of injections, although by 6 months high levels of suppression were achieved⁶. In this clinical trial, the regimen was reported to be acceptable by both the users and their partners, in spite of the need for weekly injections. However, many of the men indicated that a longer-acting preparation, which could be given at less frequent intervals, would be more attractive.

Testosterone undecanoate (TU) is a unique testosterone ester which, in its injectable formulation, has a pharmacokinetic profile⁷ more favorable than that of TE. It offers the promise of a one-monthly or two-monthly injectable product for use alone or in combination with a progestin. A WHO-supported multicenter trial in China evaluated the contraceptive efficacy of an initial dose of 1000 mg TU, followed by 500 mg maintenance (treatment) doses given either every four or six weeks. Of the 308 men who participated in the study, 290 became and remained azoospermic or severely oligozoospermic; no pregnancies were caused by any of these men in the 6 month efficacy phase of the study. An acceptability study involving the trial participants and their wives was conducted concurrently with the efficacy study; the results indicate that men and women were generally supportive of the concept of male contraception. Most participants reported "no change" in their overall well-being as a result of participation in the study; side effects such as pain at the injection site and inconvenience due to the frequency of injections were cited as the main complaints.

This regimen is now being tested in a phase III contraceptive efficacy trial in 1000 Chinese volunteers. It is expected that the data collected during this study will inform policy makers and family planning service providers before any introduction of male hormonal contraception in China is initiated.

Based on the need for longer acting androgens and improved delivery systems – to reduce the burden on men and the service delivery systems - WHO, in collaboration with the United States National Institutes of Health, has worked to develop and test several novel forms of testosterone. One of these, testosterone buciclate (TB), has a very favorable pharmacokinetic profile, superior to that of TE and TU. Following an injection, circulating levels of TB are expected to remain at effective levels for approximately 3 months. Preliminary clinical research has indicated the potential use of this androgen in contraceptive applications^{8,9}. Toxicology studies would be required before clinical studies could begin. Other androgens being tested for contraceptive applications include 19-Nortestosterone, testosterone biodegradable pellets, and a novel androgen 7 α -methyl-19-nortestosterone (MENT).

Androgen and progestin combinations

Following the presentation of evidence that androgens alone provided some promise as contraceptive agents, a series of studies demonstrated that the combination of an androgen with a progestin was more effective in suppressing spermatogenesis than an androgen alone^{10,11}. A progestin can act synergistically with an androgen to suppress gonadotrophin synthesis and release¹²; there is also some evidence that progestins can exert their negative effects directly at the level of the testis. The goal of combining these two classes of steroids is to accelerate and increase the extent of spermatogenic suppression. In addition, the use of a progestin allows lower doses of androgens to be administered, reducing the possible negative effects of exogenous testosterone administration on the cardiovascular system and on the prostate; androgen administration must be adequate to provide complementary suppression and to maintain appropriate circulating testosterone concentrations.

Most trials conducted on androgen and progestin combinations have evaluated the responses of only small numbers of men. These limited trials have provided evidence that the level of spermatogenic suppression achieved varies according to the steroidal compound(s) and route(s) of administration chosen. Several regimens have produced excellent results, indicating that a combined hormonal approach can be used to induce azoospermia and severe oligozoospermia in a high percentage of men.

In one clinical trial of a promising combined regimen, TU was administered in combination with depot medroxyprogesterone acetate (DMPA) to male volunteers in Indonesia. Results demonstrated that injections of TU alone did not adequately suppress sperm counts in Indonesian men, but that adding DMPA to the regimen caused all the volunteers to achieve levels of sperm suppression that would indicate infertility (fewer than 1 million sperm/ml semen) within 12 weeks of initiating the study. The effect was long-acting, but reversible.

Other progestins that are being or have been considered as potential components in a combined male hormonal contraceptive include levonorgestrel, especially in the form of an implant such as Norplant; cyproterone acetate; Net-Enanthate; desogestrel; and a novel compound being developed by WHO and NIH, levonorgestrel butanoate.

Androgens and gonadotrophin-releasing hormone (GnRH) receptor ligands

Gonadotrophins can be suppressed by either continuous occupation of the pituitary GnRH receptors or by a blockade of the normal stimulation of this receptor. These results can be accomplished by the use of either a GnRH agonist or antagonist, respectively. Either of these approaches can lead to rapid and reversible gonadotrophin suppression. Agonists require several weeks to down-regulate the receptors, while the administration of antagonists results in fully suppressed LH and FSH levels almost immediately. The use of either of these classes of receptor ligands requires the administration of replacement androgens.

While these synthetic peptides are still considered experimental, administration of such combinations has demonstrated promising results in monkeys and in small scale clinical trials, as measured by the frequency and rate of sperm suppression. The use of antagonists appears to offer better promise as a potential male method. The cost of these compounds is quite high and they are currently formulated to be administered as daily injections. Such a product may not be appropriate for or feasible in developing countries or in the public sector, unless the cost could be decreased and the frequency and route of administration made more flexible. Current research is geared toward the investigation of new protocols for drug administration and the development of a less expensive, long-acting or oral preparation.

Immunocontraception

Studies to identify appropriate antigens for a male immunocontraceptive have focused on at least four classes of targets. Antibodies have been raised against GnRH, gonadotrophins and their testicular receptors, sperm-specific proteins, and epididymal proteins. *In vitro* results have provided some promising data on sperm, sperm behavior, and ability to penetrate oocytes when certain sperm or epididymal proteins are “immunoneutralized” by an antibody. However, animals and humans immunized against GnRH or FSH demonstrate inconsistent immune responses and sperm suppression, and no reliable decrease in fertility. It is unlikely that one single molecule would be necessary and sufficient for male fertility; redundancy seems a more likely possibility, and it may be that the only way to develop an immunocontraceptive would be to evaluate the combined effects of multiple antibodies against a range of proteins.

BASIC SCIENCE RESEARCH LEADS TOWARDS MALE FERTILITY REGULATION

All basic science research related to male reproductive physiology may – eventually – be related to contraceptive development or to the treatment of infertility. However, in a portfolio geared toward the development of male methods of contraception, it is important to focus on goal-oriented or applied research that is closely related to product development. Research on the molecular and cellular aspects of spermatogenesis/spermiogenesis, the acquisition of sperm-fertilising capacity, or identification of potential new targets for fertility regulation during the development of sperm or during acrosome and flagellar formation, for example, can help identify important events in the process of spermatogenesis and ways in which they can be targeted for male contraception. Specific examples and relevant results of targeted research activities will be discussed in the lecture.

ACCEPTABILITY AND BEHAVIOURAL STUDIES

Contraceptive acceptability and use are related to method and user factors¹³. Surveys have indicated that many men do believe that they should share responsibility of family planning and contraception with their partners, and men whose wives have experienced side effects from female methods of contraception may be even more concerned about shared responsibility. Indeed, many men who participate in male contraceptive clinical trials report that their main reason for participating was that the female partner had experienced problems with her method of contraception.

In the evaluation of the safety and efficacy of any new technology, it is important to carry out acceptability studies and assessments of emotional, mental and behavioural changes during the course of clinical testing. Both qualitative and quantitative methodologies are being used to collect information on contraceptive use acceptability, family size preferences, decision-making regarding contraceptive use, and perceptions on male contraceptives, including side effects and mood, and behavioral and cognitive end points. Focus group discussions and some in-depth interviews have been carried out with the partners of men taking part in the contraceptive trials. Instruments are being developed to assess changes in sexual behaviour, if any, among the participating men.

WHO has supported several studies in various settings to collect, develop, adapt and validate a novel range of psychometric tools that can assist researchers to quantify changes in mood and behaviour (especially aggression) in healthy adult men who are participating in contraceptive clinical trials. In addition to more traditional instruments to collect data on method acceptability, a male aggression questionnaire and a partner questionnaire, to assess the female partner’s perceptions of any behavioural changes, have been developed. Some results of acceptability research have been described above (e.g. TU injections in Chinese men as a potential method of hormonal contraception). Acceptability and social science research related to novel technologies, users, service delivery systems and public policy will continue.

CONCLUSIONS

Available scientific data suggest that the prospects of reversible male contraception appear promising. There is strong evidence that an androgen, with or without a progestin, can provide effective contraception and is well tolerated. Agencies continue to promote research towards acceptable contraceptive methods for use by men. Such research can focus on:

- Inhibition of sperm production;
- Interference with sperm function and structure;
- Interruption of sperm transport;
- Interruption of sperm deposition;
- Prevention of sperm-egg interaction.

Meanwhile, discussions are under way with some pharmaceutical companies to ensure the continued development and testing of hormonal male contraceptives and to ensure their availability at low cost to the public sector in developing countries.

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