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Male fertility regulation: The challenges for the year 2000

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The search for new, safe, effective and reversible contraceptive methods for men is being pursued by several agencies. The most likely developments before the year 2000 would appear to be: the introduction of more easily reversed procedures of vas occlusion; hormonal means of sperm suppression based on infrequent injections of androgens either alone or combined with other gonadotrophin-suppressing agents. Methods based on new drugs or vaccines are unlikely to be developed by the end of the decade.

Research is needed to understand the basis of the differences in efficacy of contraceptive steroids in men of different ethnic origin. Equally there is a need to monitor the safety and acceptability of hormonal methods for men. New targets for drug intervention should be pursued through support of basic science, taking advantage of modern cellular and molecular biological techniques. Finally, the subject of Andrology needs to be strengthened throughout the world so that scientists in developing countries can participate fully in this work.

Research to develop safe, effective, reversible and acceptable methods of fertility regulation for men has been supported by several international agencies, many national research councils and some pharmaceutical companies. Over the last 2 decades clinical and biomedical investigations have grown out of the basic physiological studies performed during the 2 preceding decades. Recently, through increased public awareness, statements supporting research on male methods and

the greater involvement of men in reproductive health have been forthcoming from several quarters, including international women's organisations. Together with strong support from the governments of some developing countries with major population growth, eg the People's Republic of China and Indonesia, these trends are encouraging. The clinical and scientific bases for the research have been well reviewed in recent years.[1–5] The present review will attempt to show the global implications and to suggest the likely future developments until the year 2000.

VAS OCCLUSION

Prevalence of vasectomy can be taken as a measure of male participation in family planning programmes. The rates vary widely, with the developed countries of North America and Europe having higher prevalence rates compared with those of most developing countries.[6] There are extreme examples and some striking exceptions. For example, about 1:3 of all couples of reproductive age in New Zealand use vasectomy. In China, the ratio is about 1:12 overall although in one province, Sichuan, with a population of about 100 million people, nearly 5 times as many men accept vasectomy as women accept tubal ligation.[7] There are also notable regional increases in the acceptance of vasectomy, largely through the efforts of local surgeons, often with support from the Association for Voluntary Surgical Contraception.[6] Active programmes exist in countries in Latin America, eg Brazil and Columbia; in Asia, eg India, Indonesia and Thailand; and in Africa, although at a lower level, eg Kenya and Morocco.

Safety of vasectomy

The safety of surgical vasectomy has been carefully monitored in the interests of the reproductive health of men. For example, a major collaborative study in Sichuan in the period 1983–1986 allayed concerns that vasectomy might be associated with increased risk of cardiovascular ill-health,[8] the same conclusion being reached in other study populations.[9] More recently, some case-control studies suggested that vasectomy may predispose to prostate cancer whereas other studies found no increase in risk.[10] In addition, an association between vasectomy and possibly pre-existing testicular tumours was suggested in some hospital-based studies.[11, 12] A WHO Consultation reviewed the available evidence and reported the following as its main conclusions:[13]

- any causal relationship between vasectomy and the risk of cancer of the prostate or testis is unlikely;
- no changes in family planning policies are warranted.

While these conclusions are encouraging, it will be important to continue to monitor the safety of vasectomy.

Reversibility of vas occlusion

It has been recognised for some time that two main factors limit the acceptability of vas occlusion: one is the necessity for a skin incision, which is unacceptable in some cultures, and the other is the lack of certain reversibility should the circumstances require this. Amongst many attempts to develop simplified methods to overcome these limitations, research in China, which started in 1970, has led to two major technical improvements: the isolation and ligation of the vas through a puncture (non-scalpel) opening in the skin; and the development of a technique for the percutaneous injection into the vas lumen of sclerosing or occluding agents through a hypodermic needle.

Encouraged by Chinese success with the percutaneous injection of materials to form plugs for intravasal occlusion,[14] collaborative studies with Chinese investigators have been initiated to explore the efficacy of the method when silicone is used as the occluding material. Preliminary observations suggest that the method is effective but that the disappearance rate of sperm from the ejaculate may be slower than in conventional vasectomy.[15] Data on the ease of removal and recovery of fertility are being accumulated.[16]

HORMONAL METHODS

The suppression of sperm production by hormonal means has been a general research strategy for all agencies interested in male contraception.[1–3] There are 3 main aspects to this strategy: the suppression of the secretion of gonadotrophins, either of both LH and FSH or of FSH alone; the recovery of circulating androgen to physiological levels without re-stimulation of spermatogenesis; and the assessment of the functional capacity of residual sperm, should the treatment fail to achieve azoospermia in all cases. Various agencies approach this goal with emphases on the different aspects.

For the World Health Organization, a major consideration is the affordability of the drugs for use in developing countries. At present, for example, this factor would tend to exclude the use of peptide hormones such as GnRH antagonists or inhibin, even though the former have been shown to be highly effective[17] whereas the latter has yet to be shown to

have contraceptive potential. To date, suppression of spermatogenesis by hormonal means has been shown to be fully reversible in all clinical and non-human primate studies.[1–3]

Contraceptive efficacy of testosterone enanthate-induced azoospermia and oligozoospermia

The first-ever multicentre contraceptive efficacy study of normal men receiving a prototype hormonal regimen, which was conducted during 1986–1990, provided convincing evidence that, once the laboratory diagnosis of azoospermia had been achieved, normal men were rendered infertile and able to sustain safe, effective and reversible contraception for at least 12 months.[18] There were variations in the rate of achievement of azoospermia among men of the same genetic background. Also, men in the Chinese centres achieved azoospermia more frequently than men in the Caucasian centres (91% vs 60%; see Fig. 1). The second stage, to find out if hormonally-induced severe oligozoospermia (less than 5 million spermatozoa per ml) is associated with an acceptable level of contraceptive efficacy, started in 1990. If this study demonstrates that the contraceptive efficacy is high even when spermatogenesis is not fully suppressed, the goal of developing a male hormonal antifertility agent will be greatly simplified.

Long-acting androgen preparations

The studies on androgen suppression of spermatogenesis to date have been conducted with relatively short-acting preparations.[1–3] More physiological means of androgen replacement with prolonged duration would be needed, not only for the treatment of male hypogonadism but also in the development of all types of hormonal methods for men. These are now becoming available, for example biodegradable testosterone microcapsules[19] and testosterone pellets.[20]

WHO, in collaboration with the National Institute of Child Health and Human Development, has concentrated its efforts on establishing the pharmacokinetic and pharmacodynamic features of testosterone buciclate, a testosterone ester. The first clinical study on hypogonadal men has revealed that circulating levels of serum testosterone were restored into the low normal range for 12 weeks by a single intramuscular injection of 600 mg (*see* Fig. 2).[21] Preliminary findings suggest that higher doses prolong the period of androgen supplementation. The first clinical study to explore the suppression of spermatogenesis by testosterone buciclate in normal men has started. In view of the ethnic variations in response to contraceptive steroids, all such studies are planned to be conducted in several centres including some in China and Indonesia.

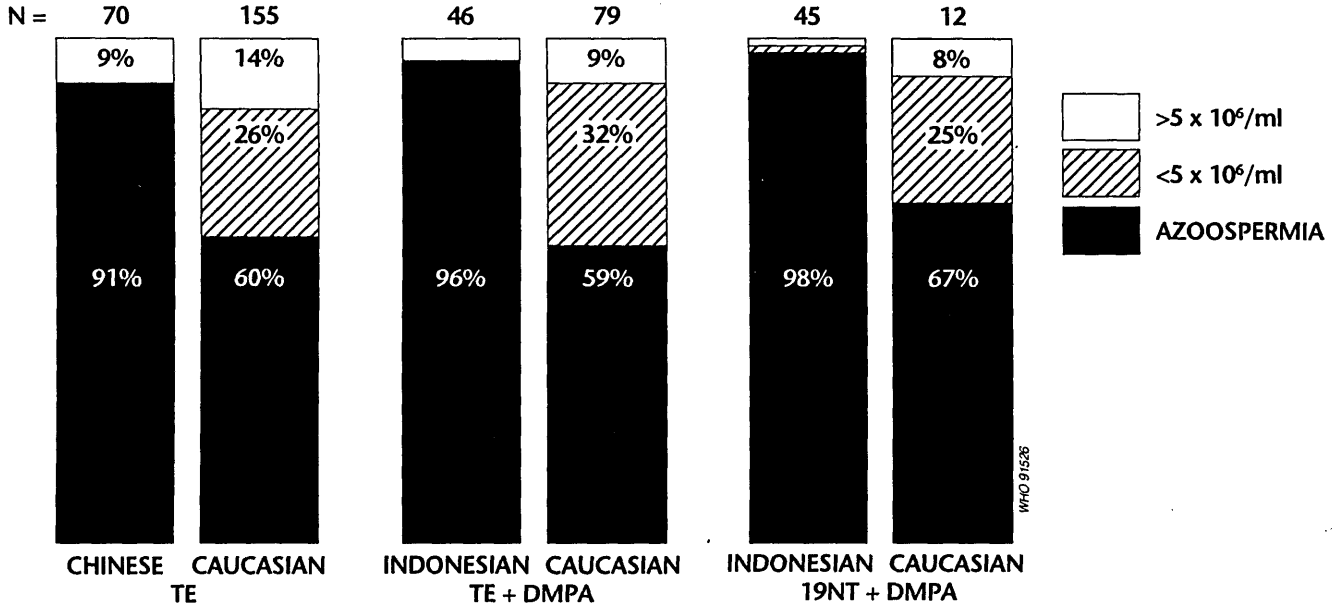

Fig. 1 The different rates of achievement of azoospermia in men of different ethnic groups during treatment with contraceptive steriods. **Left columns**: Higher azoospermia rate in Chinese compared to non-Chinese men in the WHO contraceptive efficacy study;[18] TE, testosterone enanthate 200 mg IM per week. **Centre and right columns**: Higher azoospermia rate in Indonesian men treated with depot medroxyprogesterone acetate (DMPA) and either TE or 19-Nortestosterone ester (Anadur) compared to Causcasian men in equivalent studies.[3, 22]

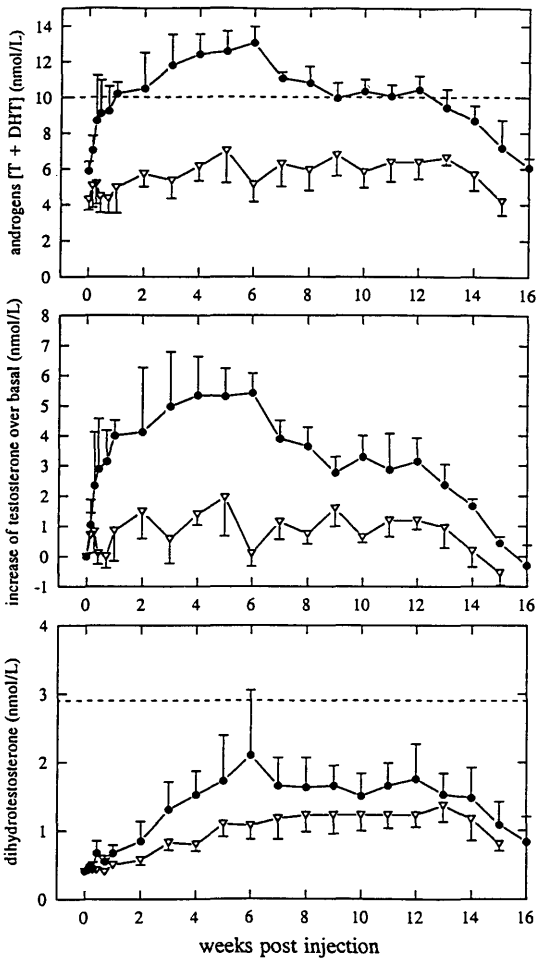

Fig. 2 The pharmacokinetics of a new long-acting testosterone ester, testosterone buciclate, offer good substitution therapy for male hypogonadism and the promise of a 3 or 4 times a year injectible method of contraception for normal men.[21]
Single dose IM injections of 200 mg (open triangles) or 600 mg (filled circles) testosterone buciclate to hypogonadal men.
Upper panel: Serum concentrations (mean ±SEM) of androgen (sum of testosterone and dihydrotestosterone), broken line indicates the lower normal limit.
Middle panel: Testosterone increase over basal values.
Lower panel: Dihydrotestosterone concentrations, broken line indicates upper normal limit.
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Progestogen-androgen combinations

Studies in the 1970s with such hormonal regimens established their safety and relative effectiveness in sperm suppression in Caucasian men but rarely achieved more than 50% incidence of azoospermia.[2] Recently, it was demonstrated that 3 injections at monthly intervals of depot-medroxyprogesterone acetate (DMPA, 200 mg or 100 mg) and testosterone enanthate (250 mg or 100 mg) caused suppression of spermatogenesis to azoospermia in 19 out of 20 Indonesian men.[22] A 5-centre study in Indonesia assessed the comparative efficacy of 2 androgens, testosterone enanthate and the longer-acting 19-nortestosterone-hexyl-oxy-phenylpropionate, when each was combined with DMPA. It established that, in both androgen replacement groups, the azoospermia rate reached more than 97% during 6 months of treatment (*see* Fig. 1). These 2 Indonesian studies, together with the results of the multicentre contraceptive efficacy studies, have underlined the importance of comparing the pharmacokinetics and pharmacodynamics of contraceptive steroids in men of different ethnic origins. They have also rekindled interest in the potential of a combination contraceptive drug regimen based on long-acting progestogens and androgens. One advantage of such a regimen would be that the dose of exogenous androgen required would be much less than in an androgen-alone approach. Several agencies are evaluating long-acting formulations of progestogens developed for female applications, for their potential for fertility suppression in men. All would require long-acting androgen supplementation.

GnRH analogue-androgen combinations

Clinical studies[17, 23] and studies in non-human primates[24] have shown that GnRH antagonists are more potent in the suppression of gonadotrophin secretion and of sperm production than are GnRH agonists. When combined with androgens, a depot-release form of GnRH agonist even had a blunting effect on the suppression of pituitary and testicular function.[25] Research on these compounds is well justified for their application for the treatment of cancers but the cost of synthesis of peptide hormones such as the GnRH antagonists is likely to remain too high for contraceptive use in developing countries.

Safety of hormonal methods for men

Just as it has been important to monitor the safety of the contraceptive steroids used by women, it is equally important to establish the safety of such methods for men. The testosterone enanthate selected as the prototype hormone to be used in the contraceptive efficacy studies is acknowledged as a safe drug from more than 30 years of clinical experience. Nevertheless, this application requires even more careful

assessment and monitoring because the volunteers in such studies are young and healthy. For this reason, all assessment protocols routinely include a wide range of conventional clinical chemistry assessments to monitor general health status. Discontinuation criteria are correspondingly strict and clinical investigators are alerted to all requirements through surveillance of the study forms. Medical discontinuations in the contraceptive efficacy studies[18] were infrequent and mostly due to acne. Current clinical studies should include more sophisticated monitoring procedures when available, including prostate size by ultrasound or by measurement of prostate-specific antigen.

The proceedings of an Androgen Workshop[26] emphasized that androgens could have benefits as well as risks and recommended the safeguards needed for all therapeutic uses of androgens. WHO plans to issue a booklet entitled 'Guidelines for the Use of Androgens in Men', based on the findings of this meeting, which will contain recommendations for the safe use of androgens for medical and contraceptive applications.

Acceptability of hormonal methods for men

Preliminary studies to explore the acceptability of hypothetical hormonal methods to men of different cultures have been published[27] but the results must be interpreted with caution. Now that feasible options are becoming available, eg a 3–4 month injectable hormonal method and a potentially reversible vas occlusion method, acceptability in different cultures can now be explored with the hope of more realistic answers emerging. Indeed, some of the Demographic Health Service (DHS) surveys, currently being conducted, include a male questionnaire and provide an opportunity to add questions concerning acceptability.

NON-HORMONAL AGENTS ACTING DIRECTLY ON SPERMATOGENESIS

A large number of chemical agents have been described[4] 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 8000 men were conducted.[2] Because of the high incidence of irreversibility[29] and potentially serious side effects such as hypokalaemia,[29, 30] gossypol use for contraception has been discontinued.

Physical agents such as irradiation, ultrasound and high temperature also lead to spermatogenic arrest when applied at certain dose levels. Their limitations for contraceptive application lie in the equipment needed and the careful monitoring of the dosage that is required to

avoid irreversible damage. One exception is the local application of heat.[31, 32] Recent clinical studies have shown that long-term mild elevation (1–2°C) 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.[33, 34] Evidence is being accumulated on the safe reversibility, contraceptive efficacy and potential acceptability of this simple and inexpensive procedure.

DRUGS AND PLANT PRODUCTS FOR INHIBITION OF SPERM MATURATION

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. Clearly this approach would have some major advantages over hormonal methods. 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/or the 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 because of their toxicity.[4] Alpha-chlorohydrin and the 6-chloro-6-deoxy sugars were amongst the more interesting and best explored.[35] They at least established that the principle was attainable and, at antifertility doses, demonstrated the ideal characteristics of a post-testicular drug. A variety of other compounds and their analogues are currently under investigation by various agencies, eg 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.[36] A collaborative programme has been established between Chinese, Thai and UK centres to isolate, identify and screen pure compounds extracted from the plant for their antifertility action.[5] This is a high-risk venture offering some hope for the isolation of safe compounds with an action mainly on sperm stored in the epididymis. It is also a good example of technical co-operation between developing and developed countries.

CONTRACEPTIVE VACCINES

Passive or active immunisation against FSH has resulted in significant decreases in sperm counts in macaque monkeys but inconsistent effects on fertility.[37, 38] Classical immunologists would prefer to avoid immunisation against a molecule so central in endocrine control, for fear of creating autoimmune reactions. This dogma may be changing and the Population Council has developed a vaccine strategy based on GnRH. Several agencies are supporting studies to establish if sperm surface proteins, crucial for sperm-egg interactions, offer hope as immunogens for the development of a vaccine.[1, 39] However, such a vaccine would be more likely to lead to a contraceptive method for the female, given the difficulty of access of antibodies to the male reproductive tract.

CONCLUSIONS

The research to develop male antifertility methods is lively and progressive. There is reasonable hope that, by the year 2000, there may be methods for men based on infrequent steroid injections, reversible vas occlusive systems and possibly other affordable options. However, unless serendipity turns up a post-testicular drug already in clinical use for another application, it seems unlikely that any newly discovered drug could be developed through the long and expensive route of toxicological and regulatory requirements by the end of the century.

On the other hand, several events could dramatically accelerate the process. Since the major demographic increases are occurring in the developing world, an understanding of the basis of ethnic differences in response to contraceptive steroids, and possibly other methods, could lead to appropriate options not, as in the past, required to be based on the physiology of Caucasian men. A recovery of interest by the pharmaceutical industry would also be a major factor. Despite the poor politico-legal environment for such a recovery of interest elsewhere, there are encouraging signs that some drug companies have not entirely lost faith. Several other events could accelerate the quest. For example, the identification of simple biochemical tests of sperm function, together with their transformation into home-use, 'dipstick', methods by which a man could check his own fertility status, would be one significant achievement.

Perhaps the most important factor of all is the acknowledgement that men everywhere have the right and obligation to share in family planning options. The ease with which clinical studies attract volunteers suggests that the new generation of men is more ready to respond than has been generally believed.

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Contraception for the year 2020

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Novel methods for the regulation of human fertility in the post-HIV era are discussed, based on the control of regulatory peptides and their respective genes. Three mechanisms are examined, each representing a step-wise increase in target or functional specificity. These centre on the selective control of the genes encoding the gonadotrophins and/or the interception of circulating gonadotrophins by receptor antagonists or binding proteins, the selective neutralisation of hCG and other signals involved in the maternal recognition of pregnancy by receptor antagonists and antibodies, and the interception of the putative disintegrin-integrin recognition events involved in sperm-oocyte recognition and fusion. A brief consideration is given to the use of vaccination procedures and somatic gene therapy for the long term regulation of fertility. By 2020, it is predicted that contraception, abortion and unplanned pregnancy could be replaced by reversible sterilisation based on the molecular interception of events involved in sperm-oocyte recognition and fusion. Contraceptive-like steroids will still be available but their use will be targeted to the provision of positive health care, with particular regard to breast cancer, osteoporosis and well-being.

The regulation of human fertility will continue to be based on the use of steroids, barriers, sterilisation and abortion well into the 21st Century. The oral contraceptive pill has been subject to perhaps more research and more post-marketing surveillance than any other pharmaceutical product. Current low dose formulations provide positive health care for those under 30 years of age by reducing the risks of ovarian and endometrial cancer. Positive benefits probably continue until the age of 40 years, when balanced against the risks of an unwanted pregnancy.[1] Contraceptive pills of the future (including steroidal formulations delivered

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