A new look at male contraception

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As a first step towards a new form of male contraception — sperm cryopreservation, vasectomy and eventual artificial insemination — the military services should begin a large-scale sperm cryopreservation programme.

THE prognosis for a new male contraceptive by the year 2000 is nil, because the development, testing and regulatory approval of a truly novel, systemic male contraceptive requires 15–20 years[1]. Given the absence of serious research and development in male contraception by major pharmaceutical companies — and only they can bring such a product to the general public — the expectation for a 'male Pill' even after 2010 is dismal. Does this mean that condoms and *coitus interruptus* remain the only feasible options for 'reversible' male contraception?

Alternatives

One alternative is surgical sterilization, now among the most widely practised methods of birth control in the world, with more than 40 per cent of Chinese, 30 per cent of US and 23 per cent of UK couples having one sterilized partner[2]. Consider the male sterilized partner: most men who have chosen this form of contraception (more than 500,000 annually in the United States) do so only after the birth of a child. Yet, because of divorce, many vasectomized men remarry while still young enough to desire a second family, creating demand for surgical reversal of sterilization[3]. Nevertheless, given its cost, the dearth of surgeons qualified to perform such microsurgery and the inevitable decline of fertility with time after vasectomy, surgical sterilization must for practical purposes be considered irreversible.

Why do two to three times more women than men choose sterilization, despite the fact that vasectomy, performed under local rather than general anaesthesia, is easier and less expensive than tubal ligation? Not only do males desire to keep their reproductive options open for much longer than is operatively and culturally feasible for women, but many also fear the real or imagined sequelae of vasectomy[4], although, in general, vasectomy has been considered "the simplest and safest" form of sterilization by an advisory panel of the World Health Organization[5]. Although two large cohort studies concluded that vasectomy may increase the risk of prostate cancer[6], a special review panel convened by the US National Institutes of Health reiterated that it must still be considered "safe and highly effective"[7].

If successful reversal could be 'guaranteed', young men who have never fathered children might become candidates for vasectomy, transforming it into a new method of reversible male contraception. Attempts to make vasectomy reversible by inserting valves or easily removable plugs into the vas deferens have proved to be unsuccessful[1]. But there is another option, previously considered[1] but rejected for practical difficulties: collection and cryopreservation of semen before vasectomy. Recent techniques and data make this combination the only new form of reliable, male contraception potentially introducible within the next decade. As vasectomy and sperm cryopreservation are established clinical procedures, no new medicine, science or law would be required for young men to begin practising this form of contraception. Steps for persuasive demonstration of the method's efficacy are outlined below.

The key lies in the use of artificial insemination (AI) to produce pregnancy. Human fecundability (percentage of women becoming pregnant per menstrual cycle during which intercourse occurs) varies from 18 to 28 per cent[8]. A similar percentage is infertile (no pregnancy after one year of unprotected intercourse)[9], prompting a burgeoning clinical practice and research in human reproductive biology, in contrast to the precipitous drop in research into contraception. For more than 25 years, male infertility has been primarily treated by the use of AI with fresh sperm, resulting in cumulative pregnancy rates of around 75 per cent[10].

Because the optimum time for insemination can now be identified fairly accurately by home urine tests for detecting the rise in luteinizing hormone, the use of AI to treat infertility is increasing. A US survey[11] found that some 172,000 American women annually underwent AI, spending $164 million to obtain the services of 11,000 physicians. Most women who undergo AI are undoubtedly seeking treatment for infertility, but the actual procedure (intrauterine, intracervical or intravaginal) is simple and takes minutes to perform[10], often by nurse-practitioners or paraphysicians. The most common method, especially for cryopreserved sperm, is to inject washed specimens directly into the cervical canal. In the United States, the cost ranges from $250 for a single treatment to $1,500 for a 'package deal' of five cycles of inseminations, including hormone measurements and sperm washing.

On a practical level, inseminations can be timed and used most efficiently with sperm cryopreserved in liquid nitrogen at −196 °C. Although pregnancy rates with frozen semen are lower than with fresh, the overwhelming logistic advantage of cryopreserved sperm is its at-call availability. Semen can be 'banked' for extended periods in $1,000 liquid-nitrogen refrigerators (1,500-sample capacity) that can maintain their temperature of −196 °C for almost a year without any electricity.

What has now changed on the male side of the reproductive equation to make the outlook for practical long-term storage of human semen so favourable?

In recent years, tens of thousands of pregnancies have been produced around the world with frozen–thawed sperm, 17,000 in France alone[12]. (About 46 million head of cattle, as well as thousands of females of other domestic species, are annually inseminated with frozen semen[13], attesting to the efficacy of the techniques of sperm cryopreservation.)

A 'normal' man's ejaculate of 2–5 ml may contain $20-60 \times 10^6$ sperm per ml, which is usually 'extended' or diluted with a cryoprotectant to yield several samples. If 20 million sperm were frozen, and only 1 per cent survived, the 200,000 survivors of a single sample might result in pregnancy, because even this low sperm concentration is sufficient for fertilization[14]. Intrauterine insemination, or induced ovulation by hormonal treatment, can significantly increase the likelihood of conception[15]. And with the newest methods of assisted reproduction, the injection of a single spermatozoon directly into the cytoplasm of a human oocyte (intracytoplasmic sperm injection, or ICSI) has resulted in high rates of fertilization and pregnancy[16].

Viability

If young men are to agree to vasectomy, the 'shelf life' of cryopreserved sperm at very low temperatures becomes relevant. There is considerable evidence that sperm viability does not decline at −196 °C (absence of thermally driven reactions) and that its fertilizing capability should persist for centuries. Women inseminated with sperm stored for more than 10 years have given birth to normal children[17]. Animal studies provide more extensive data. For instance, the lambing rate after AI of ewes with sperm cryopreserved for 5 years was the same as that with sperm frozen for 2 weeks[18]. Recently, bovine sperm frozen 37 years ago has been used to fertilize

oocytes, which developed normally[19]. More rigorous evidence of functional survival after extended storage in liquid nitrogen comes from experiments with cryopreserved mouse embryos. The functional survival of embryos stored for more than 1 year was almost identical to that of embryos stored for 13 years, and live mice have been produced from embryos stored in liquid nitrogen for this long[20].

Will cryopreserved sperm undergo genetic alteration in the frozen state? Use of frozen sperm by the entire international industry of cattle breeding rests on the assumption that cryopreservation does not cause genetic alterations, let alone damage to sperm. Hundreds of thousands of cattle bred by AI with frozen semen for specific phenotypic traits exhibit those traits. Cell death and chromosomal damage of tissue-culture cells subjected to various doses of X-irradiation in the frozen state at −196 °C was about four times lower than at room temperature, leading to the estimate that cells stored in liquid nitrogen would require 32,000 years to accumulate damage equivalent to that caused by an acute dose of X-rays at 22 °C (ref. 21). Direct cytogenetic analyses of human sperm found that cryopreservation did not cause any increase in chromosomal anomalies[22]. Collectively, these data indicate that cryopreservation is highly unlikely to cause any genetic alterations.

The advent of single-cell polymerase-chain-reaction methods[23] will make it possible to type and encode semen samples at the time of freezing and thawing, thus eliminating problems of mistaken identity[1]. In addition, storage devices are being developed in the form of magnetic tape, carrying either bar or magnetic codes, made from plastic laminates (such as those used to package dry cereal) that are flexible in liquid nitrogen. Attaching cryopreserved semen samples to these films will enable many samples to be stored in the frozen state, yet to be retrieved as quickly as magnetic tapes are scanned by computer[24].

Vasectomy coupled with semen storage will turn into 'reversible birth control' only if fertility of the stored sperm can be assured. Men who have already fathered a child present little difficulty, but what about those whose fertility is unknown? If their concerns can be addressed, then the pool of candidates may well include many post-pubescent males. So far, there is no way to guarantee fertility to all couples, but many procedures have been devised for predicting the fertility of semen specimens with an overall accuracy of more than 80 per cent[25,26]. Such tests and the normal pregnancies resulting from single sperm injection[16] show that sperm cryopreservation, coupled with the latest techniques of assisted human reproduction, should substantially increase the likelihood of even a male with very few sperm becoming a father — an impossible prospect by conventional sexual intercourse.

Clearly, this extension of vasectomy to a wide constituency will work only in relatively affluent countries where AI can be practised efficiently, and it is there that feasibility must first be established. It is in this context that we make the following proposal to start serious debate and possible implementation.

Until now, human birth control has been achieved by interfering at some point of the reproductive cycle of a *fertile* person. In the future — through vaccines and, probably much sooner, through vasectomy coupled with sperm cryopreservation — the 'normal' reproductive state of an adult may be *infertility*, a subsequent deliberate step being needed for fertilization. As mentioned, the scientific basis for accomplishing this in males is now with us. What is missing is confidence by a much wider circle of the medical community than reproductive specialists: by policymakers (including ethicists and legal experts), entrepreneurs, health insurers and, most importantly, potential male users. Note the absence on this list of the pharmaceutical industry and government regulatory agencies, as neither is likely to be involved in implementation.

Because most men are fertile, most of the potential users will also be fertile. Before vasectomy, they will have been examined to verify that they produce sperm suitable for cryopreservation. As outlined above, the success rate of AI (to be covered by health insurance) in normal couples is now high. Nevertheless, the question remains: "But how do you *really* know what will happen on a large scale with preserved sperm over 5, 10, 15 . . . years?" The only convincing answer is to take the first step, *requiring no vasectomies*, through the establishment of comprehensive facilities for storage over many years of a vast number of human semen samples whose donors can be followed up in terms of their subsequent reproductive experience. We propose a swords-into-ploughshares initiative for financial, operational and motivational reasons:

- The military services are the source of the largest number of young men with detailed medical records and the potential for follow-up. With little difficulty and relatively minor expenditure, tens of thousands of volunteers could collect their own semen to be cryopreserved by the military for years. This step alone would generate an invaluable resource for studies on male fertility and for eventual spin-offs of the Human Genome Project.
- At triennial intervals, the military or public health services, or both, would subject these sperm samples to laboratory analyses[25,26], providing statistically meaningful and invaluable data on the fecundity of the stored specimens.
- Quinquennially, questionnaires would be distributed to the sperm donors, enquiring whether they had successfully fathered any children, or, if not, whether they had attempted to do so. Responses would be matched with accumulated records to establish the predictive value of the sperm tests.
- Men whose occupations place them at risk from genetic damage to their sperm might view sperm cryopreservation as a form of genetic insurance. This is certainly relevant to the armed services, where procreation after death in military conflicts might be an option, subject to legal definition of sperm ownership.

Only time will tell whether men — and women — will buy the idea of this new form of contraception. The indispensable first step is to start the clock running on a large-scale, long-term sperm cryopreservation programme combined with follow-up protocols. Once the requisite confidence in the technical, operational and legal–ethical questions has been established, one can envisage decentralized, entrepreneurially funded and operated programmes (covered by health insurance) taking on some or all of the components of a new approach to male birth control: sperm cryopreservation, vasectomy and artificial insemination. □

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