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THE DEVELOPMENT OF ANTI-FERTILITY VACCINES CHALLENGING THE IMMUNE SYSTEM

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Over recent decades, researchers have been exploiting new contraceptive methods to use in family planning programmes in the South. Within the scope of medical application of modern biotechnologies, the development of anti-fertility vaccines is a new approach. However, these new vaccines do not really benefit the user, says Ute Sprenger.
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Modern biotechnologies in the health care sector not only serve as a basis for prevention, new diagnostic methods and cures for diseases. They also make intervention into the domain of human reproduction possible through the development of a variety of new methods and products to control fertility. While the significance of artificial insemination is negligible for the majority of people in the South, the possibility to prevent pregnancy is of major importance. Many advocates of population control policy envisage anti-fertility vaccines, once on the market, as a promising contraceptive. Unlike conventional methods, such as the intra-uterine device, the pill, hormone injections and implants, contraceptive vaccines use the immune system to induce antibodies against hormones or other molecules involved in human reproduction. Although these vaccines can be used by both men and women, most of the research is directed towards women, as scientists perceive the female cycle to be the easiest target.

Proponents of anti-fertility vaccines claim that they offer a wider choice of family planning methods. However, from a user's perspective two questions need to be answered: (1) does this new technology empower women to gain more autonomy over their fertility?; and (2) does it improve their health?

STRATEGY

Over the last two decades world wide research on fertility regulating vaccines has been conducted under the auspices of the *World Health Organization* (WHO). Some prototype vaccines have undergone or are currently undergoing clinical trials in several countries. The entirely new immunological approach is based on the idea that a long-term contraceptive method, intended for use in family planning programmes in countries with

low levels of medical care, should require little motivation of the user, should be cheap, and should be simple to apply by the provider.

The approach is an integral part of the strategy of demographic control, which has provided a series of long-lasting, provider- dependent birth control methods since the 1960s. At a 1989 WHO symposium on the safety and efficacy of anti- fertility vaccines the chairman summarized the debate: "Foremost in my mind during these discussions was our difficulty in assessing the urgency of the demographic crisis. To the extent that the impact of that crisis increases, the need for more effective family planning technologies must increase. At the very least, failure to develop something that may provide a more effective technology would be to take a grave and unnecessary risk."

APPROACHING THE HORMONAL CASCADE

The anti-fertility vaccines that are being researched refer to the mode of action of conventional vaccines against diseases. They are based on the stimulation of the immune system, but unlike anti-disease vaccines which target foreign substances, anti-fertility vaccines evoke antibodies against the body's own substances like molecules. As a result, the body's self-protection is reprogrammed to attack targets the body normally tolerates. To that end, the targeted, normally tolerated molecule, has to be linked to a foreign protein, rendering the entire product foreign and inducing an antibody reaction. Currently six variations of these vaccines are at different stages of development. Commonly identified as the most suitable candidates for vaccine development are certain molecules on the surface of the sperm and the egg, molecules on the surface of the fertilized egg and the early embryo, and *human chorionic gonadotrophin* (hCG). The hormone hCG is secreted by the surface of the early embryo to remain implanted in the womb. If hCG is blocked, the level of progesterone declines and the blastocyst (fertilized egg 5 days after fertilization) is expelled, thereby terminating the pregnancy. Anti- hCG vaccine consists of a part of the hormone linked to a bacterial or viral carrier inducing the antibody reaction. However, researchers admit that it is not known exactly how immunization against hCG impairs fertility.

The prototype version of an anti-hCG vaccine consist of an immunogen, formed from a (synthetic) peptide of hCG conjugated to a toxoid carrier molecule, mixed with an immunostimulant, and suspended in a fluid vehicle.

Other more advanced approaches that have reached clinical trials are vaccines inhibiting the *gonadotrophin-releasing hormone* (GnRH), produced within the diencephalon. The diencephalon (hypothalamus) is a part of the brain that lies beneath the thalamus where the flow of steroid hormones is regulated. The hormone is involved in the fine-tuning of these steroid hormones. Because this vaccine, developed by the *Population Council*, brings the hormonal cascade to a total standstill both male and female recipients need synthetic steroid hormone replacement in order to counteract unwanted side-effects such as the loss of bone density. In women a reaction similar to an artificial menopause is induced.

The first clinical trials with anti-fertility vaccines began in the 1970s. Until early 1994, about 400 experimental subjects, mainly women, were involved. By far the most researched and clinical tested are anti- hCG vaccines. Two prototypes, developed by *National Institute of Immunology* (NII) and the *Special Programme of Research, Development and Research Training in Human Reproduction* (HRP), are being tested on women in India, Australia, Brazil, Chile, Dominican Republic, Finland and Sweden. The NII has started experiments with live vectors. In order to prolong antibody response, beta- hCG genes were transferred into a vaccinia virus, which reproduces itself. The stability of the vaccinia, pathogen of cowpox, is controversial.

ACTORS INVOLVED

In the early 1970s a group of scientists came together at the WHO to discuss the impact of the advances in biosciences on birth control. In 1973 the WHO established the *Task Force on Vaccines for Fertility Regulation*, as part of the HRP. The HRP, today under the auspices of the *United Nations Development Programme*, the *United Nations Population Fund* (UNFPA), the WHO and the *World Bank*, concentrates on research and development of contraceptive methods and services in developing countries and its social, ethical, legal and regulatory issues.

The Task Force acts as a global coordinating body for anti-fertility vaccine R&D in the various working groups and supports research on different approaches, such as anti-sperm and anti-ovum vaccines and vaccines designed to neutralize the biological functions of hCG. The Task Force has succeeded in developing a prototype of an anti-hCG-vaccine. Currently five large and a number of small institutions are conducting research on anti-fertility vaccines. The five large institutions involved are:

- * *WHO/HRP*, Switzerland. Major supporters of the programme are the governments of Sweden, United Kingdom, Norway, Denmark, Germany and Canada, as well as the UNFPA and the World Bank.
- * *The Population Council*, United States. Among the Council's financiers are the Rockefeller Foundation, the National Institutes of Health and the US Agency for International Development.
- * *National Institute of Immunology*, India. Major financiers are the Indian government, the Canadian International Development Research Centre and the Rockefeller Foundation.
- * *The Contraceptive Development Program* (CONRAD), United States. Publicly funded.
- * *The Center for Population Research* at the National Institute of Child Health and Development/the National Institutes of Health (NICHD/NIH), United States. Publicly funded.

Various smaller research teams conducting basic, pre-clinical research and clinical trials with anti-fertility vaccines are based at universities in Kenya, Germany and France, or at institutes like the *Medical Research Council* (MRC) in England. They receive public funds or are supported by pharmaceutical companies such as *Schering* (Germany) or *Organon* (the Netherlands). According to WHO/HRP, of the approximately US\$ 57 million spent annually on overall contraceptive research, an estimated 10 per cent is devoted to anti-fertility vaccines. WHO/HRP figures indicate an expenditure of US\$ 946,000 or 16.3 per cent of the programme budget in 1992. According to David Griffin, manager of HRP Vaccines Task Force, the Programme has spent approximately US\$ 10 to 11 million on anti-fertility vaccines between 1973 and 1993.

HAZARDS

The following hazards concerning contraceptive vaccines have been suggested: *Auto-immune disorders* and *cross-reactivity*. In order to achieve immuno-contraception, the body's mechanism of self-protection must be induced to attack the molecules on the sperm, eggs or hormones. Though researchers involved emphasize that until now no side-effects or unintended reactions of the immune system have occurred, it can not be excluded that allergic reactions, cross reactions on others than the target-cell or molecules, or auto-immune diseases might appear in the medium or long-term. After all, the immune system is an open system that weakens with stress, injuries, illness, and age. Normally the immune system distinguishes between what immunologists call "self" and "non-self": it tolerates the body's own substances like tissue, cells, proteins and attacks foreign substances. However, since the 1960s the number of diseases of "unknown etiology" classified as immune-system-related diseases has been increasing. An estimated two-thirds of the adults in Europe and North America suffering from an auto-immune disorders are women. Particularly in view of an increase in immune-related diseases it may be risky to manipulate the highly complex mechanism of "self" tolerance of the human organism.

Moreover, there is a possibility of a cross-reactivity of vaccine candidate antibodies with other hormones. For instance, the hormone hCG is a member of the family of glycoprotein hormones, which also includes lutropin (LH), follitropin (FSH) and thyrotropin (TSH). Parts of the structure of these four hormones are similar, so that antibodies elicited against hCG may interfere with other pituitary hormones. Some experts have also warned of a risk of an auto-immune attack against the ovaries.

Unexpected cross-reactivity has already been observed against pancreatic cells.

Other unexpected side-effects. Trials under the auspices of WHO/HRP at the Karolinska Hospital in Stockholm, Sweden were suspended in June 1994. According to a programme document, the first seven volunteers to receive the vaccine all experienced totally unexpected side-effects which included pain at the injection site, fever and sterile abscess formation. The Task Force researchers suspect batch related causes and are investigating

the material to eliminate side-effects.

Medical needs. Even if the technology itself gets more sophisticated and some of the medical problems can be solved, the danger remains that anti-fertility vaccines will be used in regions lacking the necessary medical care. Angeline F. Schrater, women's health advocate, describes the imperative structural medical needs of anti-fertility vaccines as follows: "*Women must be screened for pregnancy before immunization and monitored for protective immunity after. They also must be tested for allergic reaction to the vaccine prior to each injection. Further, reversibility cannot be guaranteed and women must be so informed.*"

Abuse. Due to the lack of user control, the approach also bears a high potential for abuse. The method might encourage efforts to control female fertility for demographic purposes as it is easy for medical or paramedical staff to administer without a woman's full knowledge or consent. The design of anti-hCG vaccines allows the antagonist to be coupled with vaccines against diseases, i.e. diphtheria, tetanus or measles. As admitted at the 1989 WHO-Symposium, due to this potential for abuse, the method might even discredit health care and general vaccination programmes conducted in countries of the South.

Duration. It is generally assumed that the final product will be a anti-fertility vaccine, administered by injection or orally and lasting for one to two years. Once the treatment is administered it cannot be discontinued and women or men affected must wait until the immunological effect decreases. Though the WHO/HRP is considering counter-vaccines to "switch on" fertility if required, nothing concrete has been researched so far. In fact, when and whether fertility is regained depends not only on the individual immune response, but also on the ethnic response. Within the scientific community there is debate about irreversibility and thus "non-surgical sterilization" as appreciated effect.

Working. Clinical trials with women have shown that the differences in immune response is not only relevant concerning reversibility but for the effectiveness of the contraceptive as well. Thus it is reported that women in clinical trials with the Indian made prototype conceived and some even gave birth to children. Yet nothing is known about the possible ill-effects on the children of these vaccinated women, and no research on this is being carried out.

PROTESTS

More than twenty years after researchers began to investigate the use of antibodies for contraceptive purposes, many related questions concerning efficacy, safety and the ability to meet women's needs, remain unanswered. Additionally, by supporting a practice based on population policy they are likely to undermine women's rights for reproductive self-determination.

During the last decade, in many Southern countries demographic targets were introduced, and field workers and para-medical staff are stimulated to distribute effective contraceptives to reduce the birth rates. Long-term, provider-dependent methods are seen

as most suitable to meet these requirements. Considering that there seems to be a growing tendency to oblige poor women from the South to control their fertility, it is doubtful whether such a climate has stimulated the right of women to determine their family planning methods, or even whether they want to use contraceptives at all. Certainly, women and men need access to safe and convenient methods of birth control as well as safe methods of abortion. But will women, being at the receiving end of modern contraceptive R&D yet again, be content with this new kind of provider-dependent and invasive vaccine? Many may not, as shown by the appeal of more than 400 groups advocating women's health, from about 40 countries (including Australia, Chile, Germany, India, USA and Zimbabwe). They recently called for the termination of research on anti-fertility vaccines, and for a re-orientation of contraceptive research, away from the technology fix. Instead of demographic considerations directing contraceptive research, the research should enable people to gain control over their own fertility.

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Additional Source

UNDP/UNFPA/WHO/World Bank Special Programme for Research, Development and Research Training in Human Reproduction (1995), Annual Technical Report 1994. Geneva: World Health Organization.

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