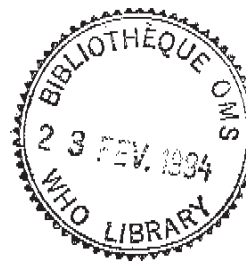


Fertility Regulating Vaccines

Report of a meeting between women's health advocates and scientists
to review the current status of the development of
fertility regulating vaccines

Geneva, Switzerland
17-18 August 1992



UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and
Research Training in Human Reproduction

World Health Organization
Geneva
1993

The Special Programme of Research, Development and Research Training in Human Reproduction was established by the World Health Organization in 1972 to coordinate, promote, conduct and evaluate international research in human reproduction. The Special Programme brings together administrators, policy-makers, scientists, clinicians and the community to identify priorities for research and for the strengthening, in developing countries, of research institutions.

The current priorities of the Special Programme include research into new methods of fertility regulation for both women and men, the introduction of methods to family planning programmes, the long-term safety of already existing methods and other aspects of epidemiological research in reproductive health, social and behavioural aspects of reproductive health, and into methods of controlling the spread of sexually transmitted disease which can cause infertility. The Special Programme also carries out activities to strengthen the research capabilities of developing countries to enable them to meet their own research needs and participate in the global effort in human reproduction research.

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Development and Research Training in
Human Reproduction**
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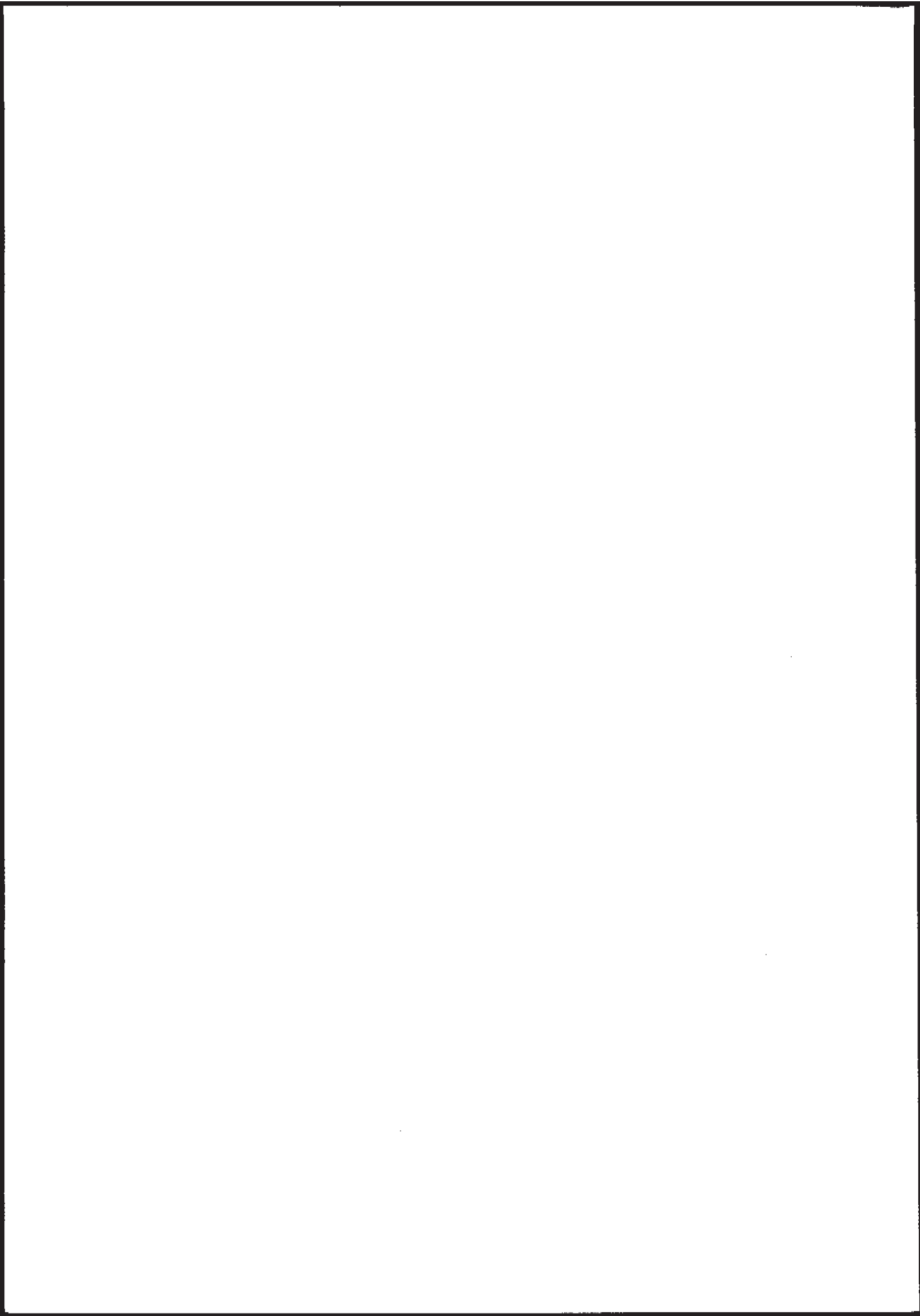
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Foreword

At present, people who want to regulate their fertility can be offered five types of family planning methods: steroidal preparations of one form or another; intrauterine devices; barrier methods; surgical sterilization; and the so-called "natural" methods. It is clear that this limited number of options does not meet the different and changing needs of men and women throughout the various stages of their reproductive lives or in the wide variety of cultural, religious, and service settings that exist in the world.

Part of the mandate of the Special Programme of Research, Development and Research Training in Human Reproduction, therefore, is to develop new and improved methods of fertility regulation in order to increase the choices available to the users of family planning services. The development and introduction of these new and improved technologies involves a careful evaluation of user needs and service delivery issues, and requires a close collaboration between method developers, consumer advocates and service providers.

Research on fertility regulating vaccines is an important area which the Programme is pursuing. The research is still at an early stage and it must be realized that questions regarding the safety, efficacy and acceptability of such vaccines can be answered only after the completion of a number of further carefully designed and properly conducted animal studies, clinical trials and user perspective studies.

To begin a productive dialogue with users' advocates, the Programme has sponsored a meeting (the first of its kind) between vaccine developers and women's health advocates, that would set a clear example of the Programme's commitment to increase collaboration between all parties concerned. We hope this will be a continuing and fruitful process.

The meeting provided a valuable forum for the exchange of information and the discussion of concerns about the development and testing of fertility regulating vaccines. This report records the consensus that was reached on some issues as well as the considerable differences of opinion that remained at the end of the meeting. In the interests of objectivity and completeness, the different viewpoints expressed at the meeting have been reflected in the report, including those with which the Programme does not agree.

We strongly believe that the studies being supported, independently, by the Programme and other agencies and institutions will help to bridge the gaps that still exist by providing answers to most, if not all, of the questions that are being raised and help determine if these vaccines will prove to be a valuable additional choice for future users of family planning methods.

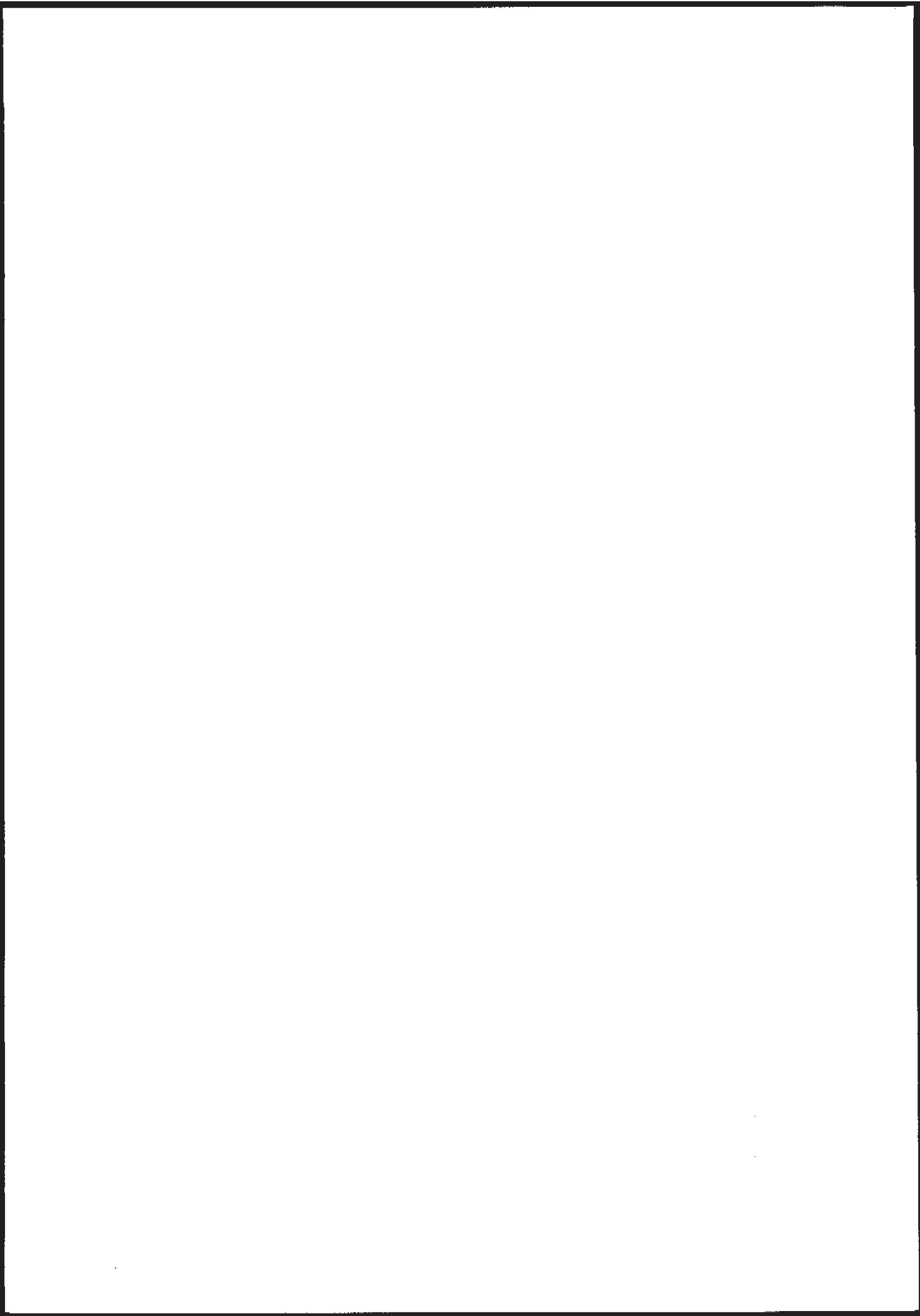
Obviously, having started this exercise, we remain committed to a continuing and constructive dialogue, even in the presence of major differences of opinion.

The goal of the Programme remains a strong commitment to serve the needs of consumers in the field of fertility regulation, by developing whatever methods are acceptable to them.



Dr Giuseppe Benagiano

Director
Special Programme of Research,
Development and Research Training
in Human Reproduction



Executive summary

The UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) is organizing a series of meetings, between women's health advocates and reproductive health researchers, aimed at fostering greater understanding between those groups and at helping to incorporate women's perspectives into HRP's research and institution-strengthening activities.

In August 1992 such a meeting was held in Geneva on the specific topic of research on fertility regulating vaccines (FRVs). There were 20 participants at the meeting: ten scientists and clinicians from Australia, Europe, India and the USA, involved in conducting or funding research on FRVs; and ten women's health advocates from Africa, North and South America, Asia and Europe, with backgrounds in immunology, service delivery and social and clinical research, as well as a wide experience of working with women.

The purpose of the meeting was to provide a forum for an open exchange of information, opinions and ideas between scientists and women's health advocates about this fundamentally new approach to fertility regulation.

The scientists presented a review of the research being carried out, independently, by the Indian National Institute of Immunology (NII) in New Delhi, by the Population Council in New York, and by HRP. FRVs use the body's own immune system to prevent pregnancy in essentially the same way that it provides protection against diseases. The scientists considered the advantages of FRVs to be that they would: (a) provide 12-18 months protection against unplanned pregnancy following a single administration, (b) not produce the

bleeding irregularities and other side-effects associated with hormonal methods of fertility regulation, (c) be easy to administer and not require constant attention as with a daily pill, and (d) be relatively inexpensive to produce, store and deliver. Two disadvantages are envisaged: the variability in different people's response to the vaccine; and the inability to "switch off" the effect of the vaccine.

Research is being carried out on a number of different FRVs for both men and women, but research on a vaccine against the hormone, human chorionic gonadotrophin (hCG) for use by women, is most advanced. Discussion focused on the safety, efficacy, and reversibility of FRVs. Some of the questions raised and discussed were: What effect would a FRV have on the immune system generally? Would these vaccines have effects on diseases, in particular HIV infection? What effects would the vaccine have on a fetus if pregnancy occurred as a result of vaccine failure? How would women know when the effects of the vaccine had worn off? If the vaccine's effect lasts for one or two years, how could a woman who wanted to become pregnant in the meantime, reverse the effect of the vaccine? Most of the concerns raised by the women's health advocates were shared by the scientists, and these concerns are being addressed in ongoing research. It was agreed that they would need to be resolved before any such vaccine could be marketed.

The women's health advocates presented the situation of health services in different countries and the problems that women face in trying to make decisions about their sexuality and fertility. It was reported that population programmes in many developing countries tend to be oriented towards achieving targets of

contraceptive "acceptors" and because of this, little attention is given either to quality of care or to women's overall health needs. The quality of the health services available tend to be inadequate for the proper screening, provision and follow-up needed to provide systemic methods of contraception. The women's health advocates felt that the potential for abuse of FRVs was very great, both deliberately by coercion and accidentally by possible confusion of a FRV with an anti-disease vaccine.

There was some discussion on the way in which biomedical research on new fertility regulation methods is carried out. Documented cases of lack of proper informed consent procedures or lack of monitoring for ethical practices in some clinical trials have given rise to severe criticisms by women's health advocates for many years. It was agreed that the current international standards for ethical guidelines in biomedical research need to be distributed more widely, and that women's health advocates should be more involved in monitoring and evaluation of research. A strong plea was made for honesty and openness in reporting research results, and for making information about current research efforts in this area available in a more accessible form.

Questions were raised about the priority being given to, and funds being allocated for, FRV research. Across the different agencies involved, it was estimated that approximately 10% of the current annual contraceptive research budget is devoted to FRV research.

This meeting was recognized as being a first opportunity for women's health advocates to review with scientists many of the technical aspects of the research being carried out into immunological methods of fertility regulation. It also provided scientists with an opportunity to hear the perspectives of women's health advocates about contraceptive research in the context of current population policies. Two recommendations were made by the participants: (1) that women's perspectives should be included at all stages of the research process involving products which are designed for use by women; and (2) that information pertaining to ethical guidelines for research, to past and current trials of FRVs, and to what is known about the safety and efficacy of FRVs, should be made more widely available.

Introduction

Since its inception in 1972, the goal of the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) has been to coordinate, promote, conduct, and evaluate research in human reproduction. Over this same period, an international women's health advocacy movement has developed with deep interests in, among other issues, women's control over their fertility. In 1990, HRP decided to initiate a dialogue with representatives of the women's health advocacy movement in order to foster greater understanding of women's reproductive health needs and to allow HRP to fulfil its mission more effectively.

One of HRP's first actions in this regard was to convene a meeting of scientists and women's health advocates on Women's Perspectives on the Selection and Introduction of Fertility Regulation Technologies. The meeting was co-sponsored by HRP and the International Women's Health Coalition and produced a number of suggestions for future action, including the establishment of mechanisms through which women's perspectives can be taken into consideration throughout the research and development process (see *Creating common ground: women's perspectives on the selection and introduction of fertility regulation technologies*. Report of a meeting between women's health advocates and scientists, Geneva, 20-22 February 1991. Unpublished WHO document No. WHO/HRP/ITT/1991). One specific recommendation to come out of that meeting was that HRP should convene a similar meeting to discuss the development of fertility regulating vaccines (FRVs).

A meeting to review the development of FRVs was convened, therefore, in August 1992. Prior to this meeting, most of the women's health advocates had little or no information on FRVs and few of the scientists were aware of the concerns of the women's health advocates. The primary objective of this meeting, therefore, was to initiate an open exchange of information, opinions and ideas between scientists and women's health advocates about this fundamentally new approach to fertility regulation by reviewing the current status of research in this area.

The meeting was held in conjunction with a Steering Committee meeting of HRP's Task Force on Vaccines for Fertility Regulation, and involved 20 participants (see Annex 6). The scientists (both male and female) came from Australia, Europe, India and the USA and were all involved in conducting or funding research on FRVs. The ten women's health advocates came from Africa, North and South America, Asia and Europe with backgrounds in immunology, health service delivery, and social and clinical research, as well as wide experience of working with women in health-related activities.

The meeting was structured so that scientists first provided information on the rationale for the development of FRVs as well as information on the current status of the research in terms of studies completed, currently being undertaken or planned.

Information was then presented by the women's health advocates on the situation of women and on the existing family planning services in developing-country settings. This led to a discussion

of how such a new technology as FRVs might realistically be provided in such situations. The meeting concluded with a discussion of the research and development process and of the development of FRVs in the context of priorities for new and improved methods of fertility regulation and women's reproductive health needs.

This report summarizes and synthesizes the issues, questions, and concerns discussed during the meeting.

One of the recommendations from participants (see page 32) calls for more public information about FRV research. In this spirit, the report contains a number of annexes, covering more,

detailed explanations about the immune system and the vaccines being developed, about the current status of research and about funding for the research. A selected reading list and a glossary are included, as well as the usual list of participants and agenda.

In order to orient readers, two background notes are provided as a supplement to this Introduction. The first background note addresses the scientific rationale for research on FRVs as viewed from a biomedical perspective. The second note briefly reviews the origins of the women's health movement and summarizes the women's health advocates' perspectives and overall concerns about contraceptive research.

Background note

Scientific rationale for research on fertility regulating vaccines

Applied research on FRVs started more than 20 years ago and is currently being supported by public sector agencies in Europe, India, and the USA, and by HRP. When HRP was set up in 1972, the development and assessment of new and improved methods of fertility regulation was established as a major objective, and immunization as a means of regulating fertility was considered a promising area for investigation.

HRP's rationale for the development of FRVs was that they would:

- be suitable for use at all stages in reproductive life (i.e., for delaying first pregnancies, for spacing births, and for preventing pregnancy when the desired family size has been achieved);
- provide long-term (but not permanent) protection against unplanned pregnancy following a single administration of the vaccine;
- not produce the menstrual cycle disturbances and metabolic side-effects associated with some other methods of fertility regulation;
- not require constant attention as with a daily pill;
- be easy to administer, in that they would not require insertion of an implant or device, surgical intervention, or specially trained professional staff;
- not present storage and disposal problems;
- be relatively inexpensive to produce and deliver;
- be inconspicuous and not interfere with sexual relations.

The scientists and clinicians involved in the development and assessment of FRVs considered that, if FRVs could be developed which met the above criteria, they should prove to be an attractive and valuable addition to the options currently available to both the users and providers of family planning services. It was recognized, however, that as a consequence of the nature and novelty of the approach, the development of FRVs would be a long-term and complex undertaking requiring research on a large number of issues relevant to the safety, efficacy and acceptability of FRVs, such as:

- ensuring the specificity of the immune response elicited by the vaccine;
- minimizing the lag time between vaccine administration and attainment of effective immunity;
- minimizing the expected variations in the magnitude and duration of individual immune responses.

Studies carried out over most of the past two decades have confirmed the complexity of the problems and of the work required, but have also demonstrated the feasibility of the FRV approach from a biomedical point of view. Recent advances in the fields of molecular biology, immunology and vaccine formulation, many of them pioneered by HRP, have permitted the design and production of vaccine components and vaccine formulations of defined properties, characteristics and performance profiles that were not

envisaged when HRP initiated studies in this area. However, much further basic and clinical research and product development need to be carried out before FRVs will be available for general use.

As in the development of any new contraceptive method, the usual first step is to demonstrate the general feasibility and overall safety of the approach. This involves preclinical safety and efficacy studies in animals followed, if justified, by small-scale clinical safety and efficacy studies in human volunteers.

Virtually every step in the reproductive process, from secretion of the gonadotrophin-releasing hormone (GnRH) from the hypothalamus to implantation of the blastocyst (fertilized egg) in the uterus, can be inhibited or interrupted immunologically (Figure 1).

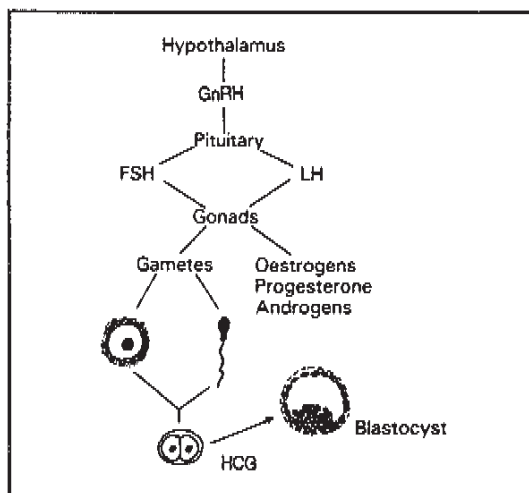


Figure 1 Schematic representation of components of the human reproductive process and possible points of intervention to prevent pregnancy.

The most advanced research on FRVs involves vaccines directed against hCG. HCG is produced by the cells surrounding the early embryo (and later by the placenta) and is required for the establishment and maintenance of pregnancy. Studies in primates have shown that immunization with anti-hCG vaccines will render the animals infertile without any detectable alteration to their menstrual cycles. Anti-hCG vaccines are being developed, independently, by the National Institute of Immunology (NII) in New Delhi, the Population Council in New York, and HRP. Research is also under way on a number of FRVs directed against other reproduction-specific molecules (for example, hypothalamic hormones, pituitary hormones, spermatozoa, ova, and non-hormonal products of fertilization). Most of this work is still in the experimental stage in animal models but two other vaccines have also reached the stage of clinical testing. Anti-GnRH vaccines are currently being tested by the NII and the Population Council in men with prostatic cancer and, if they prove safe in these studies, the same vaccines are envisaged to be used to regulate male fertility. The anti-GnRH vaccine under development by NII is being assessed also as a means of prolonging postpartum amenorrhoea which may extend the period of infertility following childbirth. An anti-follicle-stimulating hormone (FSH) vaccine is also undergoing clinical testing in India for the regulation of male fertility. Further information about these FRVs is provided in Annex 2.

Background note

The women's health movement and concerns about contraceptive research

Towards the end of the 1960s, women's groups in a number of countries began to examine what it meant to be a woman, how women were viewed by society, and what their opportunities were in relation to those of men. One of the most important questions was whether or not a woman's identity was primarily defined in terms of motherhood. At the same time, the first oral contraceptive pills were beginning to come on the market in a number of countries.

As these groups evolved into a fully-fledged women's movement, freely available contraception and abortion on demand became one of the cornerstones of the political agenda of the early 1970s, at least in Western countries. Controlling their fertility was seen by women to be central to controlling their lives. At the same time, women began seriously to question the nature of the methods of contraception available to them. As they began to question the long-term safety of the pill, women realized that, unlike the scientific and medical community, they generally had very little information about their own bodies and reproductive functions, about menstruation, sexuality, pregnancy, childbirth, infections, or the menopause. What information women did have, tended to be medically oriented and based on a scientific process of which they were not a part.

During the same decade, emerging women's health and rights groups in various countries had begun to document cases of abuse in family planning programmes which were geared primarily to achieving targets of contraceptive use, sometimes through the use of incentives.

There were cases of women being sterilized without their knowledge and of being enrolled in trials of oral contraceptives or injectables without being asked to give their informed consent. In some countries women were not informed of possible side-effects of methods such as the intrauterine device (IUD). The result was suspicion about programmes or policies which seemed to be 'pushing' family planning. Indeed, it is clear from an examination of the demographic and population policy literature of the 1960s and 1970s that the demographic goal of controlling population growth was the prime motivation for the research and introduction of the early "modern" contraceptives (e.g., the pill and the IUD), based on the hypothesis that reducing the rate of population growth would contribute to economic development. Women's movements, in both developing and developed countries, began to see contraceptive research and population policies as part of a global attempt to control population by targeting women's bodies, without consideration for their integrity, health or well-being. This was identified as just one of the ways in which, across national and cultural boundaries, women's rights were being violated, or not even recognized.

Today, women's groups in many countries of the world place the continued lack of women's fundamental rights at the top of their international agenda. The right to control their own fertility is considered to be only one amongst others, such as the right to freedom from violence, the right to equal opportunities for education and employment, and the

right to equal access to appropriate health care. In many situations social taboos and discriminatory norms about sexuality and bodily functions continue to seriously hamper the attainment of these rights by women.

It is important to note that there is a great diversity among women's groups and that their approach to working for women's health and rights varies considerably both across and within different cultures. Broadly speaking, however, the concerns of women's health groups about contraceptive research can be summarized by saying that, for the most part, research has:

- focused on controlling population growth, too often ignored women's health, and sometimes resulted in coercive approaches;
- produced methods more reflective of scientists' interests than women's preferences;
- ignored the risks posed by provision and use of systemic and clinic-based methods in inadequate, inaccessible or inappropriate health services.

In the years during and since the United Nations' Decade for Women (1976-1985), women's health advocates in countries all over the world have identified needs relating to reproductive health that require urgent action. These include, among others:

- the empowerment of women so that they may control their own fertility and sexuality with maximum choice and minimum health problems;
- the provision of complete, objective information about the potential health risks and benefits of fertility regulation methods and provision of the widest possible choice among them;
- accountability mechanisms at all stages, from initiation of research to service delivery, to reduce the possibility of misuse;

- services that take a "reproductive health" approach, i.e., one in which women's health and reproductive needs shape the services given, and which enhance women's confidence in their ability to make appropriate reproductive health decisions;
- the provision of safe and accessible abortion services;
- ways of encouraging men to take an equal responsibility in all reproductive health matters.

In addition, the current AIDS pandemic has brought to the fore the need for protection, not only against unwanted pregnancy, but also against sexually transmitted diseases of all forms. Thus women's health advocates maintain that any fertility regulation method being developed today needs to be carefully evaluated in terms of:

- its ability to protect against sexually transmitted infections including the human immunodeficiency virus (HIV);
- its potential for abuse;
- its likely appropriateness given the currently available health services;
- the extent to which it is user-controlled;
- the extent to which its provision and use increase women's knowledge and control of their bodies.

Understanding how a systemic contraceptive method works is important for many women because it is a pharmaceutical product given to healthy women on a continuous basis, unlike therapeutic drugs.

The science involved in the development of FRVs is particularly complex, and this makes the sharing of information and the promotion of dialogue between women's health advocates and scientists a difficult task. This HRP meeting is one attempt at this task and has been designed to promote dialogue between the developers of FRVs and women's health advocates.

Current status of research and development on anti-hCG vaccines

HCG is a hormone produced by the egg a few days after it has been fertilized. This hormone is needed to complete the process of implantation (embedding of the fertilized egg in the lining of the uterus). It is still not clear exactly how immunity to hCG prevents the establishment of pregnancy - this is the subject of ongoing research (Figure 2). However, its effect must be exerted after fertilization has taken place since no hCG is present until after this has occurred. Furthermore, from the animal studies and clinical trials conducted to date, it appears that immunity to hCG prevents the completion of implantation since the menstrual cycles of immunized animals are not lengthened as would be expected if the vaccine was interrupting an early pregnancy. An anti-hCG vaccine, therefore, will exert its effect only in fertile menstrual cycles, i.e., those in which successful fertilization occurs.

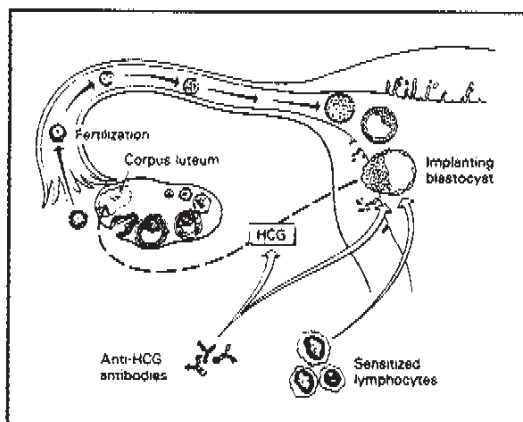


Figure 2 Possible modes of action of an anti-hCG vaccine. Antibodies capable of neutralizing hCG may inhibit its action on the corpus luteum or disrupt the fertilized egg.

The hCG molecule, like some other hormones (e.g., follicle stimulating hormone (FSH) and luteinizing hormone (LH)), consists of two separate subunits, an alpha(α)-subunit and a beta(β)-subunit. The α -subunits of these hormones are identical whereas the β -subunits are different from each other. The anti-hCG vaccines currently under development are based on the β -subunit of hCG in order to prevent producing immunity that cross-reacts with the other hormones. There are currently two main types of anti-hCG vaccines. The National Institute of Immunology (NII) in New Delhi and the Population Council in New York are developing vaccines based on the whole natural β -subunit of hCG (β -hCG), whereas HRP is developing a vaccine based on a synthetic peptide, the carboxy-terminal peptide (CTP), representing a portion of the β -subunit of the hCG molecule (β -hCG-CTP). Several versions of these β -hCG and β -hCG-CTP vaccines have been tested for safety and efficacy in animal studies and in completed or planned clinical trials in small numbers of women volunteers (see Annex 1 and table on the following page).

A summary of the current status of the basic and clinical research on each of these three vaccines was presented. It was noted that the research on all three anti-hCG vaccines is still at an early stage and that a further 5-10 years of testing, evaluation and further development will probably be needed before any of these vaccines would be suitable for marketing.

The ensuing discussion focused on a number of issues related to the safety and efficacy of anti-hCG vaccines. It became clear that many of the issues of concern to

Table: Anti-hCG vaccines developed and tested in clinical trials

Institution/Funding Agency	Immunogen ¹	Status	Comments
National Institute of Immunology (NII), New Delhi, India	Pr- β -hCG:TT	Phase I completed 1975 Phase II stopped 1976	Vaccine immunogenic Vaccine ineffective
	HSD α -oLH:: β -hCG:TT/DT	Phase I completed 1990 Phase II under way 1992	Vaccine immunogenic Vaccine effective
Population Council, New York, USA	β -hCG:TT	Phase I completed 1990	Vaccine immunogenic
World Health Organization (WHO), Geneva, Switzerland	β -hCG-CTP:DT	Phase I completed 1988 Phase II planned 1993	Vaccine immunogenic

¹ Key to immunogens: Pr- β -hCG:TT = natural beta hCG 'processed' by passage over an anti-LH affinity column and conjugated to tetanus toxoid; HSD α -oLH:: β -hCG:TT/DT = heterospecies dimer of natural alpha ovine LH associated non-covalently with natural beta hCG and conjugated to tetanus toxoid and diphtheria toxoid; β -hCG:TT = natural beta hCG conjugated to tetanus toxoid; β -hCG-CTP:DT = synthetic peptide of the carboxy-terminal 109-145 region of beta hCG conjugated to diphtheria toxoid.

the women's health advocates are also considered high priority research issues by the scientists and had been addressed in the past or are the focus of ongoing research activities.

The following sections of this report summarize the discussions resulting from the questions raised by the women's health advocates with respect to the intrinsic characteristics of FRVs.

Safety aspects

The main focus of this discussion was on the theoretical health risks posed by anti-hCG vaccines themselves, and on whether these vaccines might bring about unforeseen acute or long-term adverse effects in the user which may not become apparent until after the anti-fertility effect had passed. These might be due to:

- cross-reactions with other molecules in the body;
- reactions with hCG produced in other parts of the body;
- impact on the immune system; and,
- intrinsic properties of the components of the vaccine.

In addition, questions were raised about the possible adverse effects on the developing fetus if pregnancy occurs in the presence of a non-protective level of immunity.

Like any other non-barrier method, FRVs will not protect against infection with HIV or other sexually-transmitted microorganisms.

Cross-reactions with other molecules in the body

A range of opinions was expressed by the scientists about the extent to which immune cross-reactions should be regarded with caution.

For example, the hCG molecule contains a part (the β -subunit) that is structurally similar to the β -subunit of another hormone, human luteinizing hormone (hLH) which is secreted by the pituitary gland. Because of this similarity, β -hCG vaccines which contain the entire β -subunit of hCG induce the production of antibodies that cross-react with hLH in laboratory tests. This means that these anti-hCG vaccines may affect the

production and/or biological function of hLH. Since hLH is needed for maintaining normal menstrual cycles and is involved in the process of ovulation, it was feared that β -hCG vaccines could lead to inhibition of ovulation and menstrual cycle disturbances in women. It was also feared that the continuing presence of antibodies cross-reacting with hLH might induce long-term problems caused by autoimmunity in the organ in which hLH is produced, the pituitary gland.

The Population Council carried out long-term safety studies in rhesus monkeys immunized with sheep LH in order to assess the consequences of chronic exposure to anti-LH immunity. No adverse events were reported in these studies. The investigators conducting the clinical trials carried out to date with the NII and Population Council β -hCG vaccines, have indicated that no menstrual cycle disturbances or inhibition of ovulation have been reported or detected in these studies. Nevertheless, there is a possibility that the cross-reactivity with hLH that is elicited by the β -hCG vaccines might have long-term effects as yet undetected in the animal studies and clinical trials carried out so far. Furthermore, cross-reactivity with other unidentified substances in the body could not be ruled out and might go unrecognized.

The β -hCG-CTP vaccine being developed with support from HRP uses a smaller part of the β -hCG molecule, which is not represented in hLH, and antibodies raised to this vaccine do not cross-react with hLH. Some of the serum samples obtained in the Phase I clinical trial of the β -hCG-CTP vaccine cross-reacted, *in vitro*, with sections of pancreas. There was no consistent pattern to these reactions, in that they were observed with both pre-immunization and post-immunization samples, and there was no correlation between the results obtained by two

different laboratories sent the same serum samples. The nature and consequences of this reaction, should it occur *in vivo*, will be investigated.

Reactions with hCG produced in other parts of the body

Research has established that the pituitary gland and certain types of lung cancers may also secrete hCG. It is not known if there are other elements in the body which also secrete hCG. The effect (beneficial or deleterious) that the immune response produced by anti-hCG vaccines may have on such hCG-producing tissues is also as yet unknown.

Impact on the immune system

The use of FRVs by women whose immune system may already be challenged by microbial infections and parasitic infestations or weakened by HIV infection was discussed. While there are no reports that anti-disease vaccines have aggravated illness in these populations, the effect of the extra demand placed on the immune system by a challenge with a FRV is not yet known in terms of either existing or future infections. This was felt to be of particular importance in view of the rapidly increasing prevalence of HIV among women, and the difficulty of identifying infected individuals.

Components of FRVs

The prototype anti-hCG vaccines that have been used for the initial safety and efficacy testing consist of β -hCG or β -hCG-CTP joined to a "foreign" molecule which functions as an immunological carrier necessary to elicit an immune response. The main carriers currently being used in these prototype vaccines are diphtheria toxoid (DT) and tetanus toxoid (TT) as they function well for this purpose and are clinically accepted molecules.

The women's health advocates felt, and most of the scientists agreed, that there were potential medical and service delivery problems associated with the use of DT or TT in a FRV. The medical complication of most concern is the possible development of hypersensitivity reactions to the DT or TT component of the vaccine after repeated booster injections. From the service delivery aspect, there is a risk of confusion, by accident or design, between FRVs and anti-diphtheria and anti-tetanus vaccines. Most participants felt that if FRVs can be confused in any way with other vaccines, such as those used in mass immunization programmes, then entire immunization programmes could be jeopardized. The scientists pointed out that the anti-hCG vaccines under discussion were prototype preparations and that HRP and NII are actively researching alternative carrier components for use in an optimized FRV that will obviate the need for DT, TT or other similar macro-molecules.

Effects on the developing fetus

Pregnancies can occur in the presence of sub-effective levels of anti-hCG immunity, either during the rising or falling phases of the immune response or if the level of immunity achieved in a vaccine recipient is inadequate. No evidence of fetal abnormalities has been observed in studies, specifically designed to detect such effects, that have been carried out with the β -hCG-CTP vaccine in rats and rabbits. In addition, no miscarriages or fetal anomalies were observed in immunized baboons and rhesus monkeys which became pregnant after anti-hCG antibody levels had declined below the efficacy threshold. One of the women who took part in the Phase I clinical trial of the β -hCG-CTP vaccine subsequently underwent sterilization reversal, became pregnant and delivered a normal infant at term. Furthermore, in an earlier Phase II clinical trial of a NII β -hCG vaccine in

India, three of the immunized women who became pregnant elected to continue with their pregnancies and were reported to have produced normal term babies. These results are reassuring but not conclusive.

The difficulty of carrying out meaningful studies in relevant animal models to evaluate the risk to a fetus of immunization with the anti-hCG vaccines was discussed at length. HRP is planning to carry out teratology studies in baboons prior to Phase III clinical trials although it was appreciated that these studies will provide only an approximation to the corresponding situation in women. It was recognized that large numbers of women and their offspring will have to be followed to confirm the absence of deleterious effects of sub-effective immunity on the fetus.

Efficacy and factors affecting efficacy

For FRVs to be attractive as an additional option for fertility regulation, the scientists have proposed that they should be as effective as the better of the currently available methods of fertility regulation. The efficacy of FRVs depends on their ability to elicit a sufficiently large immune response to neutralize the function of their respective target molecules (e.g., hCG). In common with other vaccines, the immune response elicited by FRVs will vary from one individual to another and will depend on the constitution and the genetic, nutritional and health status of the user. In addition, there will be a lag period between the time of vaccine administration and the attainment of an effective level of immunity. Furthermore, the magnitude of the immune response will also determine, to a large extent, the duration of the period of effective immunity.

Efficacy of the anti-hCG vaccines

The efficacy of the β -hCG and β -hCG-CTP vaccines has been demonstrated in a number of non-human primates and was a necessary prerequisite, together with toxicity studies in these and other animals, for seeking approval to conduct clinical trials.

In common with most other new methods of fertility regulation, clinical trials to evaluate safety and immunogenicity (Phase I) of the anti-hCG vaccines have been carried out in previously electively sterilized women volunteers. These Phase I trials were intended solely to evaluate the safety of the vaccine and could not, directly, assess the efficacy of the method. However, an indirect index of potential efficacy was obtained, subsequently, by measuring the level of antibodies produced and extrapolating this to the level estimated by HRP (50 ng/ml of hCG binding capacity) to be required for preventing pregnancy in fertile women.

In HRP's Phase I trial, all of the women who responded to the β -hCG-CTP vaccine produced anti-hCG antibodies which persisted above the estimated efficacy threshold for an average of six months; the magnitude and duration of the response being dependent on the dose of vaccine received. Similar results were reported by the investigators responsible for the Phase I clinical trials carried out with the NII and Population Council β -hCG vaccines.

NII is carrying out Phase II clinical trials among fertile women to test the efficacy of its β -hCG vaccine. The trial is designed so that only those women who maintain anti-hCG antibody levels above

the estimated efficacy threshold of 50 ng/ml for three or more months are included in the efficacy calculation. At the time of the meeting, it was reported that 80 out of a total of 105 immunized women had responded sufficiently well to be entered into the efficacy phase of the trial. Only one pregnancy was reported in this group after an accumulated total of 900 woman-months of otherwise unprotected intercourse, whereas an undisclosed number of pregnancies occurred in the 25 women whose antibody levels did not reach the estimated threshold for efficacy at all, or for the full three months required for entry into the efficacy phase.¹

HRP is planning to conduct a Phase II clinical trial with the β -hCG-CTP vaccine starting in 1993 in Sweden; the Population Council has no immediate plans for a Phase II trial with its β -hCG vaccine.

In the discussion of the various clinical trials, some concern was expressed by the women's health advocates that it is not yet known what antibody level is required to protect against pregnancy. The scientists explained that this level has been calculated, theoretically, on the basis of the amount of hCG circulating in the blood at the time of implantation. Antibodies in excess of this theoretical level were achieved in the Phase I clinical trials of all of the anti-hCG vaccines. It will not be possible to determine the effective antibody level for any of the vaccines with any great accuracy until Phase II and further safety and efficacy trials (Phase III) have been conducted in larger numbers of women volunteers and a sufficient volume of data has been accumulated.

¹ In additional information provided after the meeting, NII indicated that 148 women entered the study and received the complete immunization schedule. Of these 148 women, 119 (80%) responded with anti-hCG antibody levels which exceeded the threshold level estimated to provide protection. Of these 119 women, 88 (60% of those entering the study) had antibody levels that remained above the threshold for three consecutive months or more.

Variability in responsiveness

It is known that, for a variety of genetic, dietary, disease and other reasons, the immune response to a given dose of a vaccine can exhibit marked individual variations in human populations. This has been confirmed in the Phase I and Phase II clinical trials of the anti-hCG vaccines and led to a discussion of a number of approaches to resolving this problem.

One way in which this variation in responses can be dealt with is to give the vaccine at the dose, determined in Phase II and Phase III clinical trials, that is required to ensure and maintain effective levels of immunity in, say, at least 98% of recipients. This would mean that some vaccine recipients would be given a higher dose of vaccine than they needed to achieve and maintain protection. Scientists believe that, provided this approach does not pose any hazards, it may be the most practical solution.

Since recent research has shown that people infected with HIV are generally unable to mount a protective immune response to other disease-causing microorganisms, it was generally agreed that FRVs would not be recommended for individuals at high risk of infection with HIV, or with other conditions which adversely affect the immune system (see also page 23).

Lag time between vaccine administration and protection

The immune response to a vaccine is an active process of the body which requires a certain interval of time before it reaches an effective level. In all of the anti-hCG vaccine clinical trials undertaken to date, an average of eight weeks was required for the antibody levels in the immunized women to reach the theoretical efficacy threshold.

While it may be possible to reduce this interval by making improvements in the vaccine's formulation and presentation, it is certain that recipients of the vaccine will not be protected immediately after receiving the vaccine. They will need to use an additional birth control method for a few weeks until the effective level of immunity is achieved. The additional method used would need to be reliable and safe and should not interfere with the immune response elicited by the vaccine. In addition, these other methods would need to be available at locations where the vaccine is provided.

The women's health advocates were particularly concerned about this aspect of the vaccine, because little is known about the interactions between the vaccine and some of the additional contraceptive methods that would need to be used during the lag period or about the duration and variability of the lag period. Furthermore, the need to use an additional method during this lag period was seen to be a disadvantage. The scientists indicated that information relevant to the question of possible method interactions would be obtained from animal studies and information on the length of the lag period would be obtained in ongoing and planned clinical trials.

Duration of effective immunity

Unlike anti-disease vaccines, FRVs are being designed to provide protection for a comparatively short period of time, up to a maximum of 12-18 months. The women's health advocates stressed that since FRVs may not be reversible during their period of effectiveness, it would be better to develop vaccines of a shorter duration of action, so that women who change their minds and want to become pregnant do not have to wait such a long time for their fertility to return or for potential side-effects to disappear. Some

scientists proposed the possibility of developing a range of FRVs with different durations of effect but this approach was considered by the women's health advocates to be unattractive because of the risk of confusion at the service provider level.

Variability in effective immunity

Because the immune response to vaccines exhibits individual variations, the effects of the vaccine may last for very different periods of time from one woman to another. For instance, in the HRP Phase I clinical trial, in which 5 dose levels of the β -hCG-CTP vaccine were evaluated, it was found that the effect of the vaccine persisted for almost six months in some women, and for nearly 10 months in two of the women who received the highest dosage of the vaccine. In the NII Phase II trials, 13 women were protected for 18-27 cycles, while 30 women were protected for only 6-11 cycles.

In view of the expected variability in the duration of effectiveness it will be necessary either to give booster injections at an interval determined in clinical trials, to confer protection in, say, at least 98% of recipients or to develop simple, reliable and inexpensive kits (for use at home or in clinics) to monitor the level of immunity on an individual basis.

Women's health advocates raised questions about the effects of being given a booster injection when antibody levels are still adequate to prevent pregnancy. They felt that use of a home-based test kit was impractical, particularly in many developing countries, not only because of the difficulty of such a test kit being made regularly available, but also because of the potential hazards of taking a finger-prick blood sample in unhygienic conditions.

Scientists indicated that the consequences of too frequent booster injections had already been investigated in hyperimmunization studies in baboons and no adverse side-effects had been detected. Further relevant information would be obtained in future clinical trials. The possibility of using a skin patch or saliva-based test (both of which would be non-invasive) to monitor the level of antibodies is also being considered and this area is already the focus of intensive research efforts for other applications.

In addition, women's health advocates were concerned about how long the FRVs might be used on a repeated basis: for two years, five years or as long as ten years. The scientists agreed that there is no reason why a FRV could not be taken on a repeated basis to provide protection for up to 10 years or even longer, if the user so desired. However, the safety of this extended usage would need to be investigated in long-term toxicology studies in relevant animal models and, subsequently, in Phase III clinical trials and introductory studies before a FRV was adopted by family planning programmes.

Reversibility

All long-acting provider-dependent methods raise concerns about reversibility that may be required for medical or personal reasons. Like injectable steroid contraceptives, FRVs will need to be regarded by the user as irreversible for the period of intended protection. While there is a theoretical possibility that the effect of the anti-hCG vaccine might be reversed by administering progesterone or by other interventions, such treatments would need to be carefully assessed in terms of their safety before being advocated for clinical use. The women's health advocates viewed this fairly complicated treatment as somewhat impractical because of the service delivery implications.

Injection versus oral administration

The question of whether an orally-active FRV would be preferable to a vaccine which needs to be injected was discussed in terms of whether such a modality should be developed. Women from Asia and Latin America, where demographic concerns have shaped family planning programmes, were concerned about the greater likelihood of abuse with an oral vaccine (because women might not be told what it is), whereas the African participant felt less threat from this potential kind of abuse and more worry about the use of syringes and needles in the context of HIV transmission.

Comments about other FRVs

A vaccine intended to neutralize gonadotrophin-releasing hormone (GnRH) is also under development at the NII in New Delhi and the Population Council in New York. GnRH is produced in the hypothalamus and controls the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary gland. An anti-GnRH vaccine, therefore, will interfere with the release of both of these hormones (see Annex 1 for more details). A disadvantage of this method cited by the scientists was that it would require estrogen replacement when used by women or testosterone replacement when used by men. Again, the notion of an endocrine intervention in addition to immune intervention seemed inappropriate to the women's health advocates who felt that the consumers' goal is to manage their fertility with minimal interference with normal physiological processes. Some scientists agreed with this view, pointing out that this, together with the potential for inducing immunopathology in the hypothalamus and pituitary, was the reason why HRP is not pursuing this area of research.

Overall comments on intrinsic characteristics of FRVs

Overall, women's health advocates were surprised that after twenty years of research and development many of the questions to be addressed during the FRV development process - efficacy, safety, mechanism of action, reversibility, cost and ability to meet women's needs - have not yet been fully answered. Some expressed concern that the answers might be learned only after a large number of clinical trials and considerable financial resources.

The scientists indicated that the pharmaceutical industry generally estimates that up to 30 years and 250 million US dollars can be required to develop a new drug from original concept to marketing. In the case of the anti-hCG vaccine being developed with support from HRP, approximately 10 million US dollars have been spent so far over the 18-year period, 1974-1992. Furthermore, in view of the nature and novelty of the approach and the lack of relevant previous experience, it is considered essential that the development and testing process is undertaken as carefully as possible. This inevitably means that the time frame becomes extended. The current anti-hCG vaccines are still at a relatively early stage of development. They are prototypes - developed to test the principle of effectiveness and safety - and the eventual product will need to be a much improved version of the vaccine which will overcome the drawbacks described earlier. The safety and efficacy of these prototype preparations have been investigated in animal studies and are being investigated in clinical trials. Studies on the mechanism of action and reversibility are planned. Questions of cost and acceptability can be addressed meaningfully only when the products are at a more advanced stage in the development process.

Service delivery issues

In addition to the intrinsic characteristics of FRVs, there was considerable discussion about the requirements for adequate service delivery of this novel technology. Numerous examples of what happens to clients and to services in weak health infrastructures and target-oriented programmes were discussed and it was questioned whether these problems could be overcome in the foreseeable future.

Will development of new products provide expanded choice for individual women?

The justification for developing FRVs is to increase the number of methods that are available to users of family planning services. However, women's health advocates pointed out that increasing the number of methods available does not automatically lead to expanded choice. For instance, in some programmes, largely for reasons of logistics, demographic targets, and clinical interest, policy makers and providers have been biased toward long-acting, provider-dependent methods. The persistent lack of availability of condoms in Africa and of condoms and diaphragms in Latin America were cited as examples.

Screening and counselling of users

Family planning programmes often fail to screen and counsel users adequately. These functions are essential for the appropriate provision of existing methods of fertility regulation and especially so for new technologies about which the public may have little information. Screening and counselling are particularly essential for provider-dependent methods, such as FRVs, whose antifertility effects (and side-effects) may not be immediately reversible. A number of examples were

given by the women's health advocates of the difficulties women encounter in obtaining accurate and complete information from providers and in discontinuing methods that are provider-dependent.

It was also pointed out that the addition of another method can pose problems for the already overworked staff of the family planning service. Research has shown that the availability of two different kinds of injectable steroid contraceptives can cause confusion and can lead to bad medical practice. For instance, if a woman on a three-monthly injectable comes to a clinic where supplies of that contraceptive have run out, but where a two-monthly injectable is available, she could be given the two-monthly method without necessarily receiving information concerning this change. In such a context, the problems involved in adding another injectable method, but one which works in a totally different way, may contribute to the confusion and existing burden in clinics already providing the currently available injectables. For these reasons, the women's health advocates felt that it would be difficult and impracticable to introduce an injectable FRV into many of the existing service settings. In addition, the development of FRVs with different durations of effect (e.g., 6, 12 or 18 months) as proposed by some scientists would compound these problems.

Problems related to HIV or autoimmune disease

The women's health advocates felt that scientists should give priority to assessing whether seropositivity or risk of HIV infection are contraindications to FRV use (either because of reduced contraceptive effect or because of enhanced disease progression). They suggested that any

negative relationship between FRV use and HIV would effectively rule out use of this technology in some settings until the AIDS pandemic is resolved, given that it is neither ethical nor practical to test all potential users for HIV. Even if the only risk for HIV-positive women is one of lowered efficacy, "low-responders" to a FRV might be suspected, without their knowledge, of being HIV cases. This might produce a situation where a patient is discriminated against without medical confirmation of being HIV positive, or where she might be led to thinking she is HIV positive with all the trauma that this implies for her and her family.

Women's health advocates were particularly concerned about this aspect since it is difficult to assess who is at high risk. There may be many women who appear to be at low risk but who are not. Service providers would be unable to screen for such risks in many service settings.

Scientists felt that the discussion of HIV applied to other contraceptive methods as well, in that individuals at risk of transmitting or becoming infected with HIV should be counselled to use effective barrier methods. They also felt that, since there are many couples who are not at risk of infection with HIV, there is room for additional, effective fertility regulating methods which may not provide any protection against the transmission of sexually transmitted diseases including HIV.

Follow-up procedures

A question was raised about the feasibility of monitoring anti-hCG antibody levels, to ensure an effective level of immunity had been reached, because follow-up systems are notoriously weak in most family planning programmes in developing countries.

Providers often have to focus on reaching new "acceptors" and thus little encouragement is given to users to make return visits, which may often be inconvenient for them as well. The scientists emphasized that antibody testing would not be needed after the clinical trial stage since the injection-to-efficacy interval would have been determined and fixed before the product is made available.

Another problem relevant to follow-up is the high drop out rate if more than one clinic visit is needed for the provision of a method. The prototype anti-hCG vaccines need to be given more than once, at intervals of several weeks, in order to elicit a protective level of immunity. The scientists indicated that the development of a single injection anti-hCG vaccine which will provide 12 months protection against pregnancy has been a high priority of FRV research over the past few years, and progress has been made in this area. In this version of the anti-hCG vaccine, the vaccine components are incorporated in microscopic "spheres" which slowly dissolve to release the vaccine over a period of several months. HRP is planning to carry out preclinical studies with such a vaccine in the 1994/1995 biennium, subject to the availability of funds.

Provision of appropriate information

It was generally agreed that it is very important to define the mechanisms of action of FRVs so that they can be explained to potential users. Because the concept of producing immunity to prevent pregnancy is quite complex, and because it is not yet known exactly how FRVs work, developing appropriate educational materials will be particularly challenging.

Cost

One of the proposed advantages of FRVs is their comparatively low cost. Estimates are based on the low intrinsic cost of the components, the fact that the marketed product will only need to be given once every twelve or so months, the long shelf-life of the vaccine, and its ease of storage at room temperature. As with most other methods of fertility regulation, the cost of FRVs would also include the development and provision of information material, provider training and other product-specific service delivery factors.

During the discussion, however, the question was raised as to whether the cost would in fact be so low, given the possible need for women to return to the health service at annual intervals for their immune status to be checked, and the need for hormone or other treatment if the effect of the vaccine is to be reversed early on demand. These costs cannot be calculated at present, and the scientists felt that as the product develops the question of monitoring the immune status may be resolved through the development of a simple blood or self-use saliva test kit or by adoption of the 'minimum interval' principle (see Annex 2, page 42). The feasibility of reversing the effect of the vaccine on demand, before the period of intended protection was completed, poses more difficulties. Further animal studies are planned by HRP in order to devise appropriate reversal strategies and to determine the safety and likely cost of these procedures.

Potential for abuse

The women's health advocates elaborated on reasons why a method should not be assessed in isolation from its potential societal and service delivery environments, and described how a vaccine could be seriously abused in a number of ways. They gave illustrations of how fertility control operates in societies in which human rights, and most particularly the rights of women, are held in low regard: financial incentives give service providers a strong reason to promote certain methods over others, and coercion has occurred in countries where demographic concerns take precedence over the concern for individual rights. Participants cited many examples from their direct experience.

The scientists recognized that target-oriented programmes and use of incentives were undesirable, and that the question of potential abuse was important but that this was an issue that was not confined to FRVs.

For many of the women's health advocates, the concerns about FRVs go beyond questions about the quality of services for vaccine provision. They see the ability of women to take charge of their fertility and sexuality as a fundamental element of their well-being and of the full attainment of their rights in society. In situations where these rights have not yet been attained, the women's health advocates felt that the introduction of a fertility regulation method which is open to abuse could hinder or even reverse this process.

The research process

The scientists' presentations on the current status of research on FRVs gave rise to some more specific questions about the research process itself.

Animal models

In the development of any drug, studies in animals always precede trials with human subjects. In the case of the anti-hCG vaccines, studies have been carried out mainly in non-human primates (rhesus monkeys, marmosets and baboons) since the chorionic gonadotrophins (CGs) are produced only in primates. However, the vaccines used in these animal models are based on human, rather than the animal's own (homologous) CG. Concern was expressed by some participants about proceeding with human trials without conducting corresponding studies, for example, with an anti-baboon CG vaccine in baboons. The HRP-supported researchers had worked for 10 years to produce an anti-baboon CG vaccine, without success. There was some difference of opinion regarding this issue. One scientist argued that it was inappropriate to proceed to clinical trials on the basis of animal studies carried out under less than ideal conditions. Others felt that differences would still exist between the baboon and human situations and that the increasing volume of data being generated in clinical trials is more relevant than animal data in this regard.

While few of the women's health advocates were in a position to make an assessment of the utility of the baboon CG vaccine as a predictor of safety of the hCG vaccine in the human, they were not reassured by the fact that research has continued despite the lack of scientific consensus about the validity of the animal models.

Usage of the terms "safe", "effective" and "acceptable"

It was agreed that the words "safe", "effective" and "acceptable" are often used too liberally in connection with drugs and vaccines which have been tested in a limited number of animal studies and on a very small number of people.

In the case of the anti-hCG vaccines, some researchers have claimed that they are "safe" and "effective" on the basis of results obtained in Phase I or II clinical trials and it was felt that this was misleading. A special effort should be made to be more accurate in reporting data. There was also a need to educate the media in this regard. One scientist stated that it is impossible to demonstrate that a drug or device is absolutely safe (even after it has been used by thousands of people for many years). The most that can be said is that "in the studies carried out so far the drug or vaccine has demonstrated no adverse side-effects".

Criticism was levelled also at informed consent forms used in clinical trials which often imply that there are no problems or side-effects associated with use of the method. It was agreed that complete and objective information on risks and side-effects should be provided in consent forms and that any other approach is unethical.

Definitions of "side-effects" and "acceptable"

The question of how "adverse side-effects" are defined was raised by the women's health advocates. They believe that what scientists and drug regulatory authorities consider to be "adverse" may differ considerably from users' definitions. Researchers check that organs such as the liver, ovaries, pituitary gland and the

heart are functioning normally. They also have the women in the trials keep detailed menstrual diaries, but menstrual disturbances are not generally counted as "adverse side-effects". It was suggested that menstrual problems are considered to be an adverse side-effect by many users of current fertility regulation methods. One scientist pointed out that there are fairly strict rules for efficacy, but not for side-effects, and that much depends on what information is sought and recorded during the trials.

A related question is what constitutes "acceptable". Again, women's health advocates believe that researchers often conclude that a method is "acceptable" on medical grounds rather than those defined by the user. They urged that biomedical research and clinical trials: (a) be accompanied by independent social science research into "safety", "efficacy" and "acceptability" viewed from the users' perspective; and (b) involve women's health advocates in the process of research design, monitoring and evaluation.

Which product should be tested in clinical trials?

The scientists emphasized that the anti-hCG vaccines currently being used for Phase I and Phase II clinical trials are prototype preparations and that the final, marketed product is likely to be substantially different in composition.

Some women's health advocates raised the question of how ethical it is to begin Phase II trials with a prototype product which will not be tested any further. The scientists explained that it is rare in the

process of drug development for the product tested in early clinical trials to be identical to the final product.

Adjustments such as changes in dose, composition and formulation are made as a result of the experience gained in assessment of the preparation's performance in clinical trials. It is necessary, after satisfactorily completing appropriate safety and efficacy studies in animals, to carry out Phase I and Phase II trials with a prototype preparation in order to determine the feasibility of the approach and to generate data to justify further development towards the final product. The aim is to test the principle, and investment in a more sophisticated product can only be made once the principle (i.e., basic efficacy and safety) had been proven. In addition, it was argued that it could be considered unethical **not** to do a clinical study with a short-acting version of a method before exposing women to a longer-acting formulation.

International standards for ethics in biomedical research

On the assumption that a single vaccine will not respond to the needs of all potential users, the NII researchers are working on six different FRVs. One of these is an anti-GnRH vaccine whose effect would be to extend lactational amenorrhoea, the temporary infertility due to breast-feeding postpartum as manifested by lack of menstruation. This vaccine has been tested in a Phase I trial in 12 postpartum women to find out: (a) if GnRH action can be prevented or suppressed; and (b) if anti-GnRH antibodies are secreted in the milk. The final results of this study are not yet available.¹ Most of the participants

¹ At the meeting, it was disclosed that this Phase I study, involving 12 lactating women in two centres in Delhi, had been completed and that the vaccine had been found to be acceptable and free of any side-effects. In additional information provided after the meeting, NII indicated that hardly any anti-GnRH antibodies were found in the milk samples taken during the study. On investigation, it was discovered that the batch of vaccine used in this Phase I trial had been stored inappropriately and was inactive. Trials have not been conducted with the active anti-GnRH vaccine. NII indicated that these studies will be carried out at a later date, after the vaccine has been tested in non-lactating women.

were extremely concerned about postpartum, breast-feeding women and their infants being exposed to a product whose safety and efficacy have not been established in a non-breast-feeding population. The NII researchers emphasized that the necessary clearances had been obtained from the national drug control authorities and institutional ethics committees.

In the ensuing discussion, the major question which emerged was whether there are international standards for conducting research of this kind, and whether such research is monitored appropriately. Some international guidelines exist, such as the Helsinki Declaration on Biomedical Research Involving Human Subjects, and the WHO guidelines on preparing a research project proposal (specifically on human reproduction research). The Council for International Organizations of Medical Sciences (CIOMS), in collaboration with HRP and others, has just updated its *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. The United States Food and Drug Administration (USFDA) also has ethical guidelines which are often used in other countries.

The women's health advocates expressed a need for international and national guidelines for conducting human reproduction research and for research protocols and informed consent forms to be made more widely available. They indicated that research results would only have credibility among potential users and women's organizations, if researchers are more communicative about the studies they are conducting and fully disclose the results obtained in clinical trials.

Legitimization of the research process

The women's health advocates expressed concern about their role in the meeting. They were afraid that their names and presence would be used to legitimize both the content and the process of research in an area about which many were doubtful. The organizers reiterated that the women's health advocates had been invited to participate in order to air concerns, share information and to encourage an ongoing dialogue.

FRVs and priorities in contraceptive research

In his welcoming address, the Director of HRP defined reproductive health as not just the absence of disease but as a condition in which the reproductive process is accomplished in a state of complete physical, mental, and social well-being. He indicated that a woman who cannot control her fertility cannot be considered as having the full components of health.

Although this meeting was not intended to address the wider issue of research priorities and funding policy in contraceptive development, some of the discussion did focus on these questions in relation to FRVs. It was noted that applied research on FRVs has been going on for more than twenty years and is expected to take another five to ten years before a product can be made available. It was estimated that this research absorbs roughly 10% of the new contraceptive research and development budget worldwide each year (see Annex 3).

Some of the women's health advocates suggested that research on FRVs may not be justified when the most basic information is still not available on, for example, the effectiveness and acceptability of withdrawal or the diaphragm in developing country settings, and on whether the diaphragm needs to be used with a spermicide to be effective.

The scientists agreed that such research was important but that it should not preclude work in other areas. It was argued that if money were withdrawn

from research on FRVs, it would not automatically be invested in the improvement either of existing methods or of the services through which they are provided.

The women's health advocates responded that the allocation of resources is a political process and suggested that there be an ongoing debate about research priorities, among scientists, policy makers and consumer representatives. Many argued that greater investments in research aimed at improving the availability, effectiveness, and acceptability of user-controlled methods which protect against sexually-transmitted diseases, do not have systemic side-effects, and foster empowerment which comes from knowledge about one's body, would provide a more cost-effective strategy for achieving the state of well-being described by the Director of HRP in his opening address at this meeting.

The scientists agreed that there is need for ongoing debate, but suggested that this debate be undertaken by another, broader based group. They felt that discussions on research policy and priorities should address all aspects of family planning needs in the developing countries and not be restricted to any one method. They suggested that there is a need to determine the current needs of the users of family planning services in developing countries, and, from this, to review what is feasible to develop and provide in terms of biological principles, technological capability and health service delivery infrastructures.

Other issues

Several issues were touched upon during the meeting but were not discussed in detail. These included whether major investments of time and money ever lead to research taking on a momentum that is difficult to stop and the extent to which the acceptability of a method depends on its mechanism of action.

As far as research momentum was concerned, the scientists indicated that several promising lines of FRV research in HRP had been terminated in the past as a consequence of unforeseen problems which would have made those particular vaccines ineffective or unsafe. The same criteria are being applied to the anti-hCG vaccine whose development is being supported by HRP, irrespective of the substantial financial inputs that have been made so far. Nevertheless, the women's

health advocates expressed concern that there may be a momentum for research on methods that are shown to be safe and effective scientifically, even though their use might be inappropriate given the existing service delivery limitations, in some settings.

On the question of mechanism of action of the hCG vaccine, the scientists recognized that a post-fertilization method will not be acceptable to all potential users and it is important, therefore, that the mechanism of action of anti-hCG vaccines (and other FRVs) is determined so that full information on the method can be made available to future users to assist them in deciding if the method meets their requirements from a personal, religious and sociocultural perspective.

Conclusions

This meeting brought together scientists involved in the development of immunological methods of fertility regulation and women's health advocates from a variety of backgrounds, disciplines and experiences. It provided an opportunity for women's health advocates to review with scientists the technical information on these methods, and for scientists to hear the women's health advocates' perspectives on contraceptive research and family planning programmes and how they may affect women's lives. The participants were not asked to elaborate on policy implications but to identify and discuss issues and concerns related to this research. Nevertheless, many of the issues raised were related, inevitably, to questions of policy and this was reflected in the discussion. The opinions expressed by the participants differed widely and many of the questions could not be resolved at the current stage of development of FRVs.

As far as the intrinsic characteristics of FRVs are concerned, it was recognized that many of the concerns expressed by the women's health advocates are also of concern to the scientists, had influenced their work over the past 20 years, and continue to be the subject of ongoing research. It was recognized also that the FRVs under development and in clinical trials were still at an early stage of development and that many of the concerns raised were applicable to these prototype vaccines which are unlikely to be the ones to proceed to final product development. The scientists emphasized

that, as with any new method of fertility regulation, if the remaining questions regarding the safety, efficacy and acceptability of FRVs were not resolved satisfactorily, the method would not be marketed.

The discussion about service delivery requirements of FRVs led to the identification of broader problems which the women's health advocates saw as critical to the discussion of any potential fertility regulation method. Two issues in particular were emphasized: the potential for abuse of FRVs; and the problem of the global spread of HIV infection. While the scientists felt that these issues could not be addressed at this stage in the development of FRVs, the discussion raised the question of research priorities and whether, from the consumers' point of view, research on FRVs should be a priority.

After two days of in-depth discussion, the women's health advocates still had many questions and concerns. Some said they needed more information from the ongoing and planned clinical trials to make an informed judgement about this research. Others felt they needed more time to reflect about whether trials should continue. Others felt that further investments should not be made in FRVs at this time. All agreed that greater information sharing and careful consideration of the issues is needed to assess whether and under what conditions FRVs may be an appropriate fertility regulation option for women.

Recommendations

Two main recommendations were agreed upon by the meeting participants:

1. Women's health perspectives should be taken into account, by appropriate representation, at all stages of the research process involving products which are designed for use by women, including setting of research priorities.
2. Information on the following should be made more widely available:
 - (a) ethical guidelines and standards for conducting clinical trials in the area of human reproduction;
 - (b) an inventory of past and current trials of FRVs, including how many women are involved and how many children were born of unintended pregnancies;
 - (c) the informed consent forms from all clinical trials of FRVs;
 - (d) complete information on what is known about the safety and efficacy of the FRVs evaluated in clinical trials to date.

Annex 1

Antifertility vaccines: some basic concepts

Adapted from: Schrater AF. Contraceptive vaccines: promises and problems. In: Holmes HB, ed. *Issues in reproductive technology I: an anthology*. New York, Garland, 1992:31-52.

Introduction

Antifertility vaccines are unique from all other contraceptives in that vaccines utilize innate physiological processes, immune responses, to regulate fertility. Researchers began developing vaccines nearly two decades ago after realizing that some cases of infertility in women and in men were due to an immune response to sperm, a response that prevented fertilization (Menge 1980; Mathur et al. 1987). If an "accident of nature" could cause infertility, then it might be possible to develop vaccines to induce infertility by immunological pathways. Thus was born the concept of immunocontraception.

The immune system

The immune system is a functionally integrated collection of vessels, organs, cells, and molecules that help protect an individual from disease and illness caused by a "foreign" substance or microorganism. For example, it recognizes microorganisms such as viruses and bacteria to be foreign antigens, then generates specific, protective responses. To the immune system, foreign is "non-self", that is anything chemically unique from one's own cells and molecules. An antigen is any substance that induces an immune response; it is the ultimate, specific target as well.

Immunity can be classified into two broad categories, antibody-mediated and cell-mediated. In the first, specialized cells, B cells, (in concert with other cells and molecules), recognize antigen, then synthesize and secrete protein molecules called antibodies (immunoglobulins).

Antibodies induced by a particular antigen recognize and bind to that antigen. If the affinity (tightness of binding) of antibody is sufficiently high, binding initiates a chain of events culminating in removal of antigen from the system.

The second type of immunity is mediated by various subpopulations of other specialized cells known collectively as T cells. For example, cytotoxic T cells can recognize antigen on a cell and cause death of that cell, again resulting in antigen removal.

Natural protective levels of immunity are not reached until two to three weeks after initial contact with antigen. In the case of severe illness and/or infection with extremely pathogenic organisms, death can occur before immunity is effective. Generally, however, immune responses help one recover from the consequences of exposure to foreign antigens, then prevent reinfection. The three cardinal features of an immune response are specificity, self/non-self discrimination, and memory. These features determine vaccine design and govern assumptions about efficacy and safety.

Specificity

Immune responses and the subsequent molecular reactions are exquisitely specific. Antibody and immune-reactive cells induced by one antigen can react with a different antigen only if the latter displays recognition sites identical or similar to those on the eliciting antigen. Immune recognition of the same or similar sites on two different molecules is called cross-reactivity.

Self/non-self discrimination

Cells capable of reacting to self are either continuously deleted during one's lifetime or are functionally suppressed by immunoregulatory cells (Burnet 1959; Goodnow et al. 1990; Ramsdell and Fowlkes 1990). Without self-tolerance, autoimmune disease ensues, i.e., the destruction by the immune system of one's own cells and molecules.

Occasionally self-tolerance does break down; some forms of anemia, diabetes, and rheumatoid arthritis are autoimmune-induced. Autoimmune diseases seldom are fatal but often are debilitating. In general, women suffer a higher incidence of autoimmune disease than do men (Sinha et al. 1990).

Intentional bypass of the immunological injunction against self reactivity can be achieved by presenting self antigen physically linked to non-self antigens; the immune system acts upon the entire complex as if it were non-self. This ability to induce an autoimmune response provides the immunological basis for contraceptive vaccines.

Memory

Immunological memory prevents re-infection or illness upon subsequent exposure to the original inducer of a response. Initial contact causes proliferation of specific immune-reactive cells, thereby increasing the numbers of cells recognizing that antigen. Qualitative changes also occur. Under complex conditions of stimulation and antigen deposition, some cells (of both B and T lineage) become long-lived, with functional life spans ranging from years to decades (Beverley 1990; Klinman and Linton 1990). Memory B cells synthesize antibodies with a higher average affinity for antigen than that of antibodies synthesized by primary cells. The

expanded, qualitatively different, yet highly specific cell populations provide immunological memory. When the individual reencounters the original antigen (or a cross-reactive one), the immune system responds with more speed and vigor than it could upon initial exposure. The most important point to remember is this: because of memory, immunity is seldom reversible though it may wane to low activity.

Traditional vaccines

The development and use of vaccines to prevent many common infectious diseases stands as a prime accomplishment of twentieth century biomedical research. Traditional vaccines are directed against non-self, against the immunologically relevant but non-infectious/non-toxic antigens of disease-causing microorganisms. They prime the immune system for future encounters with infectious agents and prevent life-threatening or debilitating disease. Traditional vaccines owe their effectiveness to immunological memory.

Antifertility vaccines

Vaccines to regulate fertility differ from traditional ones in several important aspects. Contraceptive vaccines prevent pregnancy rather than disease. They induce immune responses against internal self antigens, one's normal molecular constituents, rather than against external non-self antigens. (The exceptions to self in this context would be anti-sperm vaccines designed for women.) Because their immunological targets are self, they carry the potential for inducing disease, i.e., auto-immunity, rather than preventing it. Lastly, vaccines to regulate fertility are intended to induce a functionally reversible response rather than the irreversible memory generally induced by traditional vaccines.

Several different vaccines designed to control or regulate fertility are being developed (reviewed in Ada et al. 1985; Griffin 1986; Naz and Menge 1990; Stevens 1986, 1990; Talwar and Raghupathy 1989). Some induce immune responses that affect gametes, i.e., sperm and ova (or eggs). Depending on the target antigen they could immobilize sperm, destroy sperm, or prevent union of sperm and egg at the egg's surface. Anti-gamete vaccines would control fertility by preventing fertilization.

Other vaccines candidates are the hormones that participate in reproductive processes. Two pituitary gonadotrophins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) control development of eggs in women; FSH controls sperm development in men. Secretion of both hormones is regulated by gonadotrophin-releasing hormone (GnRH), a small peptide synthesized in the brain by the hypothalamus. All three hormones transit via the bloodstream and so are vulnerable to interception by antibody molecules. Immunity to these hormones could prevent development of sperm and eggs.

The most promising candidate, the hormone human chorionic gonadotrophin (hCG), is first synthesized by the fertilized egg, and ultimately by the placenta. HCG stimulates production of progesterone, a hormone necessary for implantation, and for establishment and maintenance of the early stages of pregnancy. The hCG vaccines could control fertility by antibody-mediated and/or by cell-mediated mechanisms (Stevens et al. 1981). In the former, antibodies would bind to hCG and neutralize its pregnancy-sustaining effects, resulting in resumption of an apparently normal menstrual cycle. If cell-mediated immunity were operative, cytotoxic T cells could destroy the cells that produce hCG. A combination of mechanisms is likely.

Human chorionic gonadotrophin vaccines

Chorionic gonadotrophin is the one antigen that fulfils criteria for an ideal contraceptive vaccine. (1) It is present only transiently during reproductive processes. (2) Its biological function is understood, so questions of efficacy and safety are more easily answered. (3) Its antigenic determinants are defined, thereby enabling design of a vaccine whose response is restricted to the target antigen. (4) Its chemical characteristics are known, thus manufacture would be easy.

The native hormone hCG consists of two subunits, alpha and beta. Alpha is structurally similar to alpha subunits of the pituitary hormones such as FSH and LH. Beta likewise is similar to pituitary hormone beta subunits, especially to that of human LH (hLH). Were the intact hormone used as immunogen, it could induce cross-reactivity with all three pituitary hormones. When the entire beta subunit is used, it induces antibodies cross-reactive with hLH. Since a consequence of antibodies binding to antigen is removal of that antigen from the system, cross-reactivity could alter pituitary hormone levels and disturb menstrual cycles and/or gamete formation. One end of beta hCG, however, has a 35 amino acid sequence (peptide region) that is not shared by hLH. The peptide provides beta hCG with antigenic determinants distinct from those of hLH, thereby eliminating cross-reactivity to pituitary hormones.

Two hCG vaccines exist, differing mostly in the molecules used as primary immunogen. One, the hCG beta subunit vaccine, utilizes the entire beta subunit. The second, the synthetic hCG peptide vaccine, uses a synthetic peptide of the 35 amino acid sequence unique to beta hCG. Both vaccines have been tested in several animal species for safety and efficacy. Both have undergone Phase I (safety) clinical trials in women in India and Australia (see Annex 3).

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Annex 2

Fertility regulating vaccines: a background paper

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Introduction

This short paper is an attempt to present the rationale for fertility regulating vaccines (FRVs) in the context of their potential impact in the family planning arena and in terms of the feasibility of their development and production. This novel approach to birth control is being considered in terms of the value that such vaccines might have for future users; the information is presented, therefore, from the perspective of new technology development and not in terms of family planning policy. It is well recognized that FRVs, like any other method of birth control, will be an attractive option to some users and an unattractive option to others, for a variety of reasons. The objective in developing FRVs is not to produce replacements for existing birth control technologies but to widen the choice of safe, effective, acceptable and affordable family planning methods.

The need for greater choice

Although the number and type of family planning methods now available have never been greater, an increasing proportion of users, in both developed and developing countries, are dissatisfied with the currently available options. The reasons for this dissatisfaction include annoying and uncomfortable side-effects, concerns about the long-term safety of the method, and practical issues such as difficulties of storage and inconvenience of use. In addition, the currently available methods do not satisfy the widely differing cultural, religious and socioeconomic requirements of users, particularly those in the developing world. This situation has led to a demand for a greater variety of family planning methods that would meet the

needs of individual users in different settings and at different times throughout their lives.

In many developing countries, health budgets are often extremely low and health systems greatly overstretched. In these situations, the provision of family planning services is often rudimentary and ensuring access to and use of family planning methods that may be widely available and well accepted in industrialized nations often presents major logistical problems to both the providers and users in developing countries.

Why fertility regulating vaccines?

The challenge, then, is of meeting two sets of requirements: the development of a greater range of methods that satisfy the varied and personal needs of the user, and the development of methods that can be provided within the constraints of limited family planning services.

When the WHO Special Programme of Research, Development and Research Training in Human Reproduction was set up in 1972, the development and assessment of new and improved fertility regulating methods was established as a major objective. Following a detailed review of the options for the development of new methods, immunological intervention was considered a promising area for investigation, the objective being to use the body's own immune system to provide protection against an unwanted pregnancy in essentially the same way that it provides protection against unwanted diseases. In other words, to develop a fertility regulating vaccine.

Sufficient information was already available at that time to indicate that it should be feasible to develop FRVs that:

- are free of overt pharmacological activity and the metabolic, endocrine and physical disturbances that often accompany other methods of birth control;
- can confer mid- to long-term (3 months to 1-2 years) but not permanent protection following a single administration;
- are easy to administer without manipulation of the genitalia;
- remain effective without continuous conscious action by the user;
- are inexpensive.

Studies carried out over the past decade or more have confirmed the feasibility of this approach and recent advances in the fields of molecular biology and immunology have permitted the rational design and production of vaccine components and vaccine formulations of defined properties and characteristics. Furthermore, by subtle alterations in the chemical composition of, for example, the vaccine delivery system it is possible to develop a range of preparations with different predetermined durations of action. It is not unrealistic to imagine, therefore, that if/when FRVs reach the market place, the user will be able to select from preparations offering, for example, three months, six months, 12 months or 24 months of protection.

Specific requirements for fertility regulating vaccines

It is important to stress, at the outset of any discussions on this topic, that while anti-disease and FRVs both make use of the immune system in order to achieve their intended effects, there are fundamental and profound differences in the philosophies behind the development of these two types of vaccine, in the strategies used in their design and

evaluation, and in their mode of action and duration of effect. These differences can be summarized in the following comparison of the intended characteristics of the two types of vaccine.

Anti-disease vaccines

- provide protection against debilitating and often life-threatening infectious diseases;
- are often the only means available for protecting against, or controlling the effects of, these diseases;
- are designed to generate long-term (ideally life-time) protective immunity, often aided by natural boosting throughout the lifetime of the individual as a result of intermittent, sub-clinical exposure to the natural antigen;
- are based on and directed against foreign antigens which usually elicit an immune response.

Fertility regulating vaccines

- will be used by healthy, fertile individuals to protect against an unwanted pregnancy;
- will be just one of a number of alternative methods of family planning available;
- will have a generally predictable and comparatively short duration of effect and, to avoid permanent infertility, will not be boosted by exposure to the natural target antigens;
- will be directed against antigens to which the recipient is immunologically tolerant in the natural state and which do not normally elicit an immune response.

Criteria governing fertility regulating vaccine development

As for any other method of birth control, it is imperative that the most stringent safety, efficacy and acceptability criteria are employed in the development of FRVs.

Safety

There are two aspects of safety in connection with the use of FRVs. One is the need to ensure that the components of the vaccine, either singly or in combination, do not present a risk to the user in terms of toxic effects. The second is to ensure that the immune response elicited by the vaccine does not cause any unacceptable, adverse or potentially hazardous endocrine, metabolic or immunological disturbances. If an appropriate target is selected there should be no disturbance of the menstrual cycle or other normal body functions and the risk of producing autoimmunity should be minimized. However, there is a risk of producing unexpected cross-reactions with body constituents other than the intended target. Preclinical and clinical studies are carried out to determine if this occurs and if it does, what its consequences are, both short- and long-term. Although recent evidence suggests that many healthy people have varying amounts and types of autoimmune antibodies in their circulation, it is still not known whether these antibodies are always harmless or whether they may sometimes denote the presence of an underlying autoimmune disease that may become apparent clinically after many years.

Efficacy

To be an attractive addition to the range of contraceptive options, it is envisaged that FRVs would need to be as effective in preventing an unwanted pregnancy as the best of the currently available alternative methods.

Acceptability

Unlike safety and efficacy, which are universal criteria, acceptability is a variable criterion which depends on the individual perceptions, beliefs and needs of the user. The anticipated attributes of FRVs listed earlier, namely - lack of

chemical activity and metabolic, endocrine and physical disturbances; prolonged but not permanent protection following a single administration; ease of administration without manipulation of the genitalia; continuous protection independent of user action; and low cost - may be attractive and would make these methods highly acceptable to some users. Others, however, might find some of these attributes unattractive in a family planning method.

It is important from an ethical standpoint for potential users of birth control methods to know how they work so that they can choose a method which is in harmony with their individual beliefs and needs. This is particularly important for FRVs which can work at a number of different points and stages in the reproductive process.

Options for fertility regulating vaccine development

The early stages of mammalian reproduction comprise a complex sequence of events which, for convenience, can be divided into three stages.

- The production and transport of the male and female gametes (sperm and ova).
- The interaction of the gametes leading to fertilization.
- The process of implantation of the developing embryo into the uterine endometrium.

A large number of studies have been carried out over the past two decades or more which have demonstrated clearly that immunization against many of the functionally and structurally important molecules present during these three stages of the reproductive process can produce varying types and degrees of anti-fertility effects. These effects appear to be mediated through neutralization of the biological actions of hormones,

through inhibition of enzyme activities, and through inhibition of cell to cell contact and interactions. However, the endocrine and other metabolic disturbances and/or the potential for eliciting immunopathology associated with many of these effects make them unacceptable as an approach to human fertility regulation. It is necessary, therefore, to establish a number of criteria by which those leads can be selected which represent suitable candidates for development into FRVs for human use.

The criteria used by the WHO Task Force on Vaccines for Fertility Regulation to identify candidate molecules for anti-fertility vaccine development, or to eliminate from further consideration molecules which are likely to elicit hazardous and/or ineffective immune responses, require that these molecules:

- when eliminated or neutralized by immunological means will result in a safe, effective and acceptable means of fertility regulation;
- are restricted to the intended target so that cross-reactions can be avoided;
- are present in a site where a controlled immune response will not lead to immunopathology;
- are present transiently and/or at low levels compared to the anticipated immune response;
- will not elicit other undesirable immune responses;
- are, or can be, chemically characterized and easily produced in large quantities and at low cost.

The molecules most closely satisfying these criteria are found on the mature gametes (sperm and/or ovum) and the trophoctoderm of the preimplantation embryo. WHO, other public sector agencies and national research councils have supported, and are still supporting, research on FRVs directed against all of these targets.

Current status of development

Most advanced

The most advanced work in this area involves the development of FRVs based on human chorionic gonadotrophin (hCG). Two different types of anti-hCG vaccine have been developed and have reached the stage of clinical trials.

One type of anti-hCG vaccine developed by the Population Council in New York and by the National Institute of Immunology (NII) in Delhi is based on the whole beta subunit of the hormone. The Population Council anti-hCG vaccine has been tested in a Phase I clinical trial and has been reported to be immunogenic and free of short-term side-effects that would make the vaccine unacceptable for clinical use (Thau et al., 1989). The NII anti-hCG vaccine has been tested in both Phase I (Talwar et al., 1990) and Phase II clinical trials and has also been reported to be free of short-term side-effects that would make the vaccine unacceptable for clinical use, as well as being effective in preventing pregnancies.

The other type of anti-hCG vaccine, developed with support from the WHO Task Force on Vaccines for Fertility Regulation, is a vaccine based on a portion (the carboxy-terminal peptide or CTP) of the beta subunit of the hormone (Stevens et al., 1981abc). A Phase I clinical trial has been conducted with this anti-hCG vaccine (Jones et al., 1988) and a Phase II clinical trial is planned (Griffin and Jones, 1991).

All of these anti-hCG vaccines require multiple injections to achieve and maintain levels of immunity that are considered effective. Studies are under way to develop a range of long-acting formulations of these vaccines that will provide durations of protection of from several months up to 1-2 years following a single injection.

The reason for these two different approaches to the development of anti-hCG vaccines is that in 1974 WHO opted for the theoretically safer approach of the CTP vaccine following demonstration of the cross-reactivity of antibodies raised to the whole beta subunit with another hormone, hLH, and the concerns that this raised about possible ovulation inhibition, menstrual cycle disturbances and clinical immunopathology. Such antibodies are not raised by the CTP vaccine. Although recent data from the Population Council and NII clinical trials with their respective whole beta hCG vaccines indicate no menstrual cycle disturbances and no effect on ovulation, the question of long-term immunopathological or other sequelae, if any, of cross-reactive immunity to hLH, is still unresolved. Resolving this issue through appropriately designed studies in relevant animal models should be a high priority for current and future research with this vaccine.

Less advanced

The Population Council and NII are currently investigating anti-GnRh vaccines for the treatment of prostatic cancer. These same vaccines could possibly be used by men for family planning purposes although testosterone replacement would be needed. NII is also proposing the use of an anti-GnRH vaccine by women for prolonging post-partum amenorrhoea although concerns have been raised about the inhibition of gonadal steroid secretion and the adverse secondary effects, such as on bone metabolism, that might follow. An anti-FSH vaccine for men is currently undergoing a clinical trial in India (Moudgal et al., 1988). This vaccine would have the advantage of not needing testosterone replacement. With both of these approaches, questions still remain about the long-term sequelae of immunity to these target hormones that are

continuously present in, and produced by, the hypothalamus and pituitary gland.

Least advanced

Although an attractive prospect because of their truly contraceptive mechanism of action, anti-sperm and anti-ovum (ZP) vaccines have so far proved disappointing. Anti-sperm vaccines have shown poor efficacy probably because the immune response is needed in the lumen of the female reproductive tract and because of the enormous antigen load that is presented there at each act of coitus. The risk of inducing auto-immune orchitis and/or auto-immune epididymitis remains a major problem if such vaccines are used by men. ZP vaccines have similar problems in that all of the anti-ZP vaccines tested so far in animals have produced reactions in the ovary, indicative of potential clinical immunopathology and menstrual cycle disturbance, that would make these current vaccines unacceptable for human use. In order to increase the efficiency and safety of these vaccines, sperm and ovum antigens are being sought that are involved in and necessary for fertilization and, in the case of ovum antigens, that are expressed only at the periovulatory stage of ovum development.

Potential features of fertility regulating vaccines

Perceived advantages

As indicated earlier, the perceived attractions of FRVs are that they would provide an addition to the current range of methods since they would:

- be free of overt chemical activity and the metabolic, endocrine and physical disturbances that often accompany other methods of birth control;
- confer mid- to long-term (3 months to 1-2 years) but not permanent protection following a single administration;

- be easy to administer without manipulation of the genitalia;
- remain effective without continuous conscious action by the user;
- be inexpensive.

A method to be used by men and women

A further attraction of FRVs is that, depending on the immunogen on which the vaccines are based and the target antigen against which they are directed, they could, at least in principle, be used by men (anti-GnRh, anti-FSH, anti-post-testicular antigens) and/or women (anti-GnRh, anti-ovum [ZP], anti-sperm, anti-hCG).

However, with the exception of anti-hCG and anti-sperm vaccines for use by women, these approaches would involve immunization against a normal and constantly present body constituent. The long-term sequelae of the use of such vaccines would need to be carefully assessed over a long period of time before the safety of this approach could be determined.

Issues that need to be addressed before FRVs are introduced

Reversibility

The feasibility of 'turning off' the effect of FRVs on demand if unforeseen problems occur or if the user changes her mind and wants to try to conceive prior to the end of the elected period of immunity needs to be investigated. There are some preliminary animal data to suggest that, for example, the antifertility effect of anti-hCG vaccines might be reversed by administering progesterone or by in vivo absorption of the antibodies with free hCG peptide. At present it is not known if these procedures could be advocated for clinical use. The Task Force is planning to carry out studies which may

provide insights into how the anti-hCG vaccine's effect can be reversed on demand but for the time being the vaccine would need to be regarded as irreversible during the designated period of its effect. For users who desire a long-acting method, for example those who have attained their desired family size or who require a method that can be used infrequently until the end of their reproductive life, the inability to reverse the effect of the vaccine on demand may not present a problem.

Unpredictability

Because of the genetic diversity of human populations, immune responses to vaccines often show marked differences from one individual to another in terms of magnitude and duration. These differences may be partly or even completely overcome with appropriately engineered FRVs and by improvements in our understanding of what is required to develop and control the immune response elicited by different vaccines. However, if differences in individual responses remain, two options are being considered. The first option is to offer a booster injection of vaccine at the minimum interval determined in clinical trials to confer protection in all users. This will mean that users will receive a booster injection before it was needed but provided this was not associated with any increased health risks it may be an acceptable approach. The second option is to develop simple, rapid, robust, reliable, and inexpensive test kits for home or clinic use to permit users to check their immune status in order that they can determine if they are still protected and decide whether or not to have another injection of the vaccine. Kits requiring only a finger prick blood sample and simple reagents are already available for measuring antibodies to, for example, Rubella, and the same type of system is being considered for monitoring the level of immunity to hCG.

Lack of user control

Many users require a family planning method over which they have total control. However, it is not clear if methods that are under the direct control of the user and which depend on user intervention in order to work are necessarily going to be the first choice of all of the existing and potential users of family planning methods in the developing countries. There are a number of logistical, practical and social reasons why FRVs may appear a more attractive alternative in some settings.

Non-barrier method

FRVs, like other non-barrier methods, may not be the method of choice where there is a high risk of sexually transmitted disease (STD) transmission.

Potential for abuse

To avoid the risk of confusion and deliberate abuse, it is important that if and when FRVs become available, they are provided either through family planning services or through carefully monitored primary health care outlets but certainly not through immunization programmes for disease control. There is, of course, nothing to prevent deliberate abuse of any non-user controlled prophylaxis or therapy, but the non-permanent nature of the vaccine's effect and the possibility of reversing the effect on demand would tend to alleviate the consequences of such abuse should it occur.

Future needs

Long-term safety

While FRVs are designed to have a comparatively short duration of effect, some people may use them repetitively to provide protection for a period of several years. It is imperative, therefore, that long-term safety studies are carried out to determine the nature, extent and consequences of such long-term use, particularly if cross reactive immunity is detected. Tests of both structural and functional effects need to be conducted. In addition, careful examination in a relevant animal model is needed of the effect, if any, on the mother and fetus/offspring if a pregnancy occurs when immunity has waned to a point at which the user is no longer protected but at which antibodies are still detectable.

Mechanism of action

FRVs could act by preventing sperm production, by interfering with ovulation, by inhibiting fertilization, or by preventing implantation of the blastocyst. It is important that studies are carried out to clearly determine how each FRV works. By understanding their mechanisms of action, more efficient and predictable FRVs can be prepared and rational intervention strategies can be developed to reverse the effects of the FRVs on demand. In addition, the user should be fully informed of the known or suspected mechanisms of action of FRVs so that he or she can choose a FRV that is compatible with their personal beliefs and needs.

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Annex 3 Current research on fertility regulating vaccines

All FRVs are being researched with a view to developing long-acting but not permanent methods which would be easy to administer, with minimal side-effects

Method	Mechanism of action	Product description	Current status	Agencies/institutions supporting/ conducting research
ANTI-hCG VACCINE (hCG=human chorionic gonadotrophin)	Antibodies prevent or disrupt implantation by binding with hCG (hormone necessary for establishment of pregnancy)	Heterosppecies Dimer (HSD) consisting of β subunit of hCG associated with alpha subunit of ovine LH linked to tetanus toxoid or diptheria toxoid or cholera toxin Chain B β -hCG vaccine - β subunit of the hCG linked to tetanus toxoid; could also be conjugated to diptheria or cholera toxoid Prototype consisting of synthetic peptide of hCG-specific portion of β -hCG (CTP) linked to diptheria toxoid	Phase I studies completed in 1990 Phase II efficacy studies of the vaccine completed in 1993 in India Phase I studies completed in 1991	NII (DBT Government of India), IDRC, RF Population Council
			Phase I trials completed 1988 Phase II trial planned to start in 1993	WHO/HRP Ohio State University, USA Flinders Medical Centre, Adelaide, Australia WHO/HRP Ohio State University, USA Karolinska Institute, Stockholm, Sweden University Hospital, Uppsala, Sweden
ANTI-TROPHOBLAST VACCINE	Antibodies prevent or disrupt implantation	Advanced prototype (C-terminal peptide β -hCG) - same as Prototype but formulated in polymer-delivery system to give a single-injection preparation. Vaccines based on molecules found on surface of preimplantation embryo	Pre-Phase I toxicity studies planned to start in 1994 Phase I clinical trial planned 1994/5 Laboratory and animal studies	WHO/HRP Ohio State University, USA WHO/HRP

FOR
WOMEN

Method	Mechanism of Action	Product Description	Current Status	Agencies/Institutions Supporting/Conducting Research
ANTI-SPERM VACCINE	Antibodies prevent or disrupt fertilization	Vaccines based on sperm specific proteins (e.g. LDH-C4, SP-10, PH20)	Laboratory and animal studies	CONRAD, NICHD, NII, Population Council and many others
ANTI-OVUM VACCINE	Antibodies prevent or disrupt fertilization	Vaccines based on components of zona pellucida	Laboratory and animal studies	CONRAD NII
ANTI-GnRH VACCINE (GnRH=gonadotropin releasing hormone)	Antibodies bind with GnRH and inhibit ovulation	GnRH - 6-D lysine linked through a spacer to diphtheria toxoid	Animal studies Clinical trials in lactating women	NII (RF, South to South) NII
ANTI-GnRH VACCINE	Antibodies bind with GnRH and inhibit sperm production through preventing gonadotrophin production	GnRH - 1 - conjugated to tetanus toxoid	Clinical trials in men with prostatic cancer (Austria, India, Mexico)	NII (Austria, India, Mexico) Population Council NICHD
ANTI-FSH VACCINE (FSH=follicle stimulating hormone)	Antibodies bind with FSH and prevent spermatogenesis	Ovine FSH absorbed on anhydrogel	Laboratory and animal studies Phase I clinical trial started in India	CRBME, CONRAD, ICMER, Population Council IISc

FOR
MEN

CONRAD = Contraceptive Research and Development Program, Arlington, Virginia, USA
 CRBME = Centre for Reproductive Biology and Molecular Endocrinology, New Delhi, India
 DBT = Department of Bio-Technology, Government of India
 ICMER = Instituto Chileno de Medicina Reproductiva, Santiago, Chile
 IDRC = International Development Research Centre, Canada
 IISc = Indian Institute of Science, Bangalore, India
 NICHD = National Institute for Child Health and Human Development (Centre for Population Research), National Institutes of Health, Bethesda, Maryland, USA
 NII = National Institute of Immunology, New Delhi, India
 Population Council = Population Council, New York, New York, USA
 RF = Rockefeller Foundation, New York, New York, USA
 South to South = South to South Cooperation in Reproductive Health, Bahia, Brazil
 WHO/HRP = Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland

Annex 4

Estimated expenditure on contraceptive research and development

ROCKEFELLER FOUNDATION
1134 AVENUE OF THE AMERICAS
NEW YORK, NY 11036, USA

1987-1992		US\$ 000s (% of total)
Vaccines	National Institute of Immunology, Delhi	800 (6.2)
	South-to-South	242 (1.9)
	Other vaccine work	381 (3.0)
All other contraceptive research	South-to-South	2,155 (16.7)
	Other	9,319 (72.3)
TOTAL		12,897

BREAKDOWN OF FUNDING SOUTH-TO-SOUTH COOPERATION IN REPRODUCTIVE HEALTH

	US\$ 000s (% of total year's expenditure)			Total (% of total)
	1987-91	1991-92	1992-93 (estimate)	
Vaccines	237 (12.6)	5 (1.0)	30 (3.8)	272 (8.6)
Uniplant-normgestrel acetate	276 (14.7)	341 (66.1)	250 (32.1)	867 (27.3)
Vaginal contraceptive pill	738 (39.3)	116 (22.5)	100 (12.8)	954 (30.0)
Gossypol studies	343 (18.2) *	9 (1.7)	150 (19.2)	502 (15.8)
Polyherbal vaginal cream	--	45 (8.7)	50 (6.4)	95 (3.0)
Abortion prevention study	286 (15.2)	--	100 (12.8)	386 (12.2)
Uniplant for sickle cell	--	--	100 (12.8)	100 (3.1)
TOTAL	1,880	516	780	3,176

* US\$110,520 for contraceptive studies and US\$232,600 for STD/HIV prevention studies

Estimated expenditure on contraceptive research and development

HRP, WHO
20, AVENUE APPIA
CH-1211 GENEVA 27, SWITZERLAND

	US\$ 000s (% of total year's expenditure)							Total (% of total)
	1987	1988	1989	1990	1991	1992		
Vaccines	1,085 (16.6)	854 (17.4)	1,134 (12.8)	638 (13.2)	968 (10.7)	946 (16.3)	5,625 (14.1)	
Social sciences	712 (10.9)	372 (7.6)	659 (7.4)	899 (18.6)	722 (8.0)	732 (12.6)	4,096 (10.2)	
Infertility	298 (4.6)	254 (5.2)	398 (4.5)	41 (0.8)	233 (2.6)	132 (2.3)	1,356 (3.4)	
Epidemiology (including Norplant PMS)	1,251 (19.2)	1,059 (21.6)	1,527 (17.2)	469 (9.7)	1,727 (19.1)	1,440 (24.8)	7,473 (18.7)	
Intrauterine devices	-	-	-	-	-	147 (2.5)	147 (0.4)	
Long acting systemic agents	1,643 (25.2)	873 (17.8)	2,973 (33.6)	525 (10.8)	892 (9.9)	424 (7.3)	7,330 (18.3)	
Natural methods	296 (4.5)	668 (13.6)	570 (6.4)	311 (6.4)	1,148 (12.7)	423 (7.3)	3,416 (8.5)	
Introduction and transfer of technology	-	-	-	1,048 (21.6)	1,579 (17.5)	844 (14.5)	3,471 (8.7)	
Indigenous plants	309 (4.7)	-	-	-	-	-	309 (0.8)	
Post ovulatory methods	492 (7.5)	479 (9.7)	833 (9.4)	407 (8.4)	1,083 (12.0)	275 (4.7)	3,569 (8.9)	
Male methods	443 (6.8)	355 (7.2)	759 (8.6)	505 (10.4)	686 (7.6)	445 (7.7)	3,193 (8.0)	
TOTAL	6,529	4,914	8,853	4,843	9,038	5,808	39,985	

Estimated expenditure on contraceptive research and development

POPULATION COUNCIL
ONE DAG HAMMARSKJOLD PLAZA
NEW YORK, NY 10017, USA

	US\$ 000s (% of total year's expenditure)							Total (% of total)
	1987	1988	1989	1990	1991	1992		
Vaccines	556 (11.7)	559 (10.3)	802 (14.9)	716 (11.1)	574 (8.1)	693 (8.7)	3,900 (10.5)	
GnRH	(209)	(220)	(255)	(287)	(322)	(449)	(1,742)	
hCG	(347)	(399)	(547)	(429)	(252)	(175)	(2,089)	
Sperm	--	--	--	--	--	(69)	(69)	
Male subdermal implants	391 (8.2)	911 (16.8)	671 (12.5)	992 (15.3)	987 (14.0)	1,106 (13.9)	5,058 (13.7)	
Female subdermal implants	1,376 (28.9)	1,654 (30.5)	1,415 (26.3)	2,974 (45.9)	3,321 (47.1)	3,746 (47.1)	14,486 (39.1)	
Contraceptive rings	749 (15.8)	841 (15.5)	1,266 (23.5)	934 (14.4)	1,220 (17.3)	1,368 (17.2)	6,378 (17.2)	
Levonorgestrel IUD	376 (7.9)	425 (7.8)	310 (5.8)	208 (3.2)	162 (2.3)	182 (2.3)	1,663 (4.5)	
Copper IUDs	52 (1.1)	46 (0.8)	18 (0.3)	4 (0.1)	7 (0.1)	7 (0.1)	134 (0.4)	
Female probing studies	626 (13.2)	704 (13.0)	593 (11.0)	344 (5.3)	525 (7.5)	576 (7.2)	3,368 (9.1)	
Transdermal systems	--	--	--	--	--	(143)	(143)	
Injectables	--	--	--	--	--	(44)	(44)	
Intracervical device	--	--	--	--	--	(104)	(104)	
Abortifacients	--	--	(54)	(118)	(178)	(285)	(635)	
GnSIF	(155)	(77)	(84)	--	--	--	(316)	
Other	(471)	(627)	(455)	(226)	(347)	--	(2,126)	
Male probing studies	628 (13.2)	281 (5.2)	313 (5.8)	304 (4.7)	248 (3.5)	279 (3.5)	2,053 (5.5)	
Inhibin	(545)	(180)	(39)	--	--	(62)	(826)	
No-scalpel	--	(42)	(237)	(225)	(70)	(217)	(791)	
Other	(83)	(59)	(37)	(79)	(178)	--	(436)	
TOTAL	4,754	5,421	5,388	6,476	7,044	7,957	37,040	

58 Estimated expenditure on contraceptive research and development

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, CONTRACEPTIVE DEVELOPMENT BRANCH
6100 EXECUTIVE BLVD.
BETHESDA, MARYLAND 20892, USA

	US\$ 000s (% of total year's expenditure)						Total % of total
	1987	1988	1989	1990	1991	1992	
Vaccines	400 (4.6)	370 (4.6)	390 (4.9)	300 (3.5)	1,981 (18.2)	2,670 (18.1)	6,111 (10.4)
Barrier methods	400 (4.6)	--	153 (1.9)	--	2,580 (23.7)	2,880 (19.6)	6,013 (10.2)
GnRH analogues	745 (8.6)	346 (4.3)	1,888 (23.9)	--	1,518 (14.0)	973 (6.6)	5,470 (9.3)
Transdermal	404 (4.7)	360 (4.4)	933 (11.8)	262 (3.1)	560 (5.1)	479 (3.3)	2,998 (5.1)
Male methods synthesis	750 (8.7)	649 (8.0)	997 (12.6)	1,201 (14.0)	331 (3.0)	508 (3.4)	4,436 (7.5)
Implants	444 (5.1)	485 (6.0)	280 (3.5)	--	--	800 (5.4)	2,009 (3.4)
Gonadal peptides isolation	1,161 (13.4)	1,203 (14.8)	--	3,044 (35.5)	202 (1.9)	999 (6.8)	6,609 (11.2)
Nonhuman primate gonadotroph	1,153 (13.3)	969 (11.9)	--	1,097 (12.8)	--	252 (1.7)	3,471 (5.9)
HIV/SIV	--	1,100 (13.5)	430 (5.5)	600 (7.0)	600 (5.5)	700 (4.8)	3,430 (5.8)
Clinical general	400 (4.6)	--	--	500 (5.8)	400 (3.7)	149 (1.0)	1,449 (2.5)
Biological testing facilities	2,146 (24.8)	1,845 (22.7)	1,553 (19.7)	1,429 (16.6)	2,147 (19.7)	2,707 (18.4)	11,827 (20.1)
Toxicology	--	--	--	--	--	578 (3.9)	578 (1.0)
Synthesis service	661 (7.6)	688 (8.5)	1,147 (14.5)	50 (0.6)	430 (4.0)	942 (6.4)	3,918 (6.7)
Support services	--	104 (1.3)	118 (1.5)	100 (1.2)	127 (1.2)	90 (0.6)	539 (0.9)
TOTAL	8,664	8,119	7,889	8,583	10,876	14,727	58,858

Estimated expenditure on contraceptive research and development

OFFICE OF POPULATION
US AGENCY FOR INTERNATIONAL DEVELOPMENT
WASHINGTON, DC 20523-1819, USA

CONTRACEPTIVE RESEARCH AND DEVELOPMENT PROGRAM (CONRAD)

	US\$ 000s (% of total year's expenditure)							Total (% of total)
	1987	1988	1989	1990	1991	1992		
Immunology *	218 (23.6)	178 (14.0)	285 (15.2)	306 (14.6)	725 (24.8)	454 (13.9)	2,166 (17.6)	
Drug delivery systems	--	268 (21.1)	82 (4.4)	385 (18.4)	285 (9.8)	178 (5.4)	1,198 (9.7)	
Male methods	99 (10.7)	163 (12.8)	273 (14.6)	258 (12.3)	444 (15.2)	581 (17.7)	1,818 (14.7)	
Extramural support	5 (0.5)	2 (0.2)	11 (0.6)	60 (2.9)	65 (2.2)	50 (1.5)	193 (1.6)	
Fellowships	--	--	26 (1.4)	45 (2.2)	45 (1.5)	71 (2.2)	187 (1.5)	
AIDS (Centres for Disease Control)	--	--	--	--	7 (0.2)	985 (30.1)	992 (8.0)	
AIDS (NICHD)	--	396 (31.2)	738 (39.4)	873 (41.7)	751 (25.7)	382 (11.7)	3,140 (25.5)	
Barrier methods	60 (6.5)	224 (17.6)	355 (19.0)	128 (6.1)	591 (20.2)	477 (14.6)	1,835 (14.9)	
Basic research	--	--	59 (3.2)	--	--	--	59 (0.5)	
Gonadotropins	444 (48.0)	15 (1.2)	--	--	--	--	459 (3.7)	
Sterilization technology	99 (10.7)	25 (2.0)	12 (0.6)	38 (1.8)	10 (0.3)	--	184 (1.5)	
STDs (NIAID)	--	--	--	--	--	96 (2.9)	96 (0.8)	
TOTAL	925	1,271	1,841	2,093	2,923	3,274	12,327	

* Contraceptive vaccine research including funds spent under an Indo-US bilateral project which CONRAD executes

Annex 5

Selected reading list

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Annex 6

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Mrs Lynda Pasini, Secretary, HRP
Mrs Lynn Sellaro, Secretary, HRP
Ms Glenda Allen, Secretary, HRP

Annex 7 Agenda

Monday, 17 August 1992

Preliminaries

Welcome (Mahmoud Fathalla)

Introduction to the purpose of the meeting (David Griffin and Jane Cottingham)

Introduction of the Chairperson (Kerstin Hagenfeldt)

Introductions

Each person presents himself/herself: work, background, and specifically what brings him/her to this meeting

Presentation of vaccine research

What anti-fertility vaccines are, what reproductive processes can be targets for vaccines, mode of action, advantages and disadvantages from a scientific perspective, WHO research (David Griffin)

Lessons learned from the WHO clinical trial (Warren Jones)

Research in other agencies

- Population Council, New York (Rosemarie Thau)
- National Institute of Immunology, New Delhi (Pran Talwar)

Discussion (technical aspects)

Women's perspectives

Overview/general issues on contraceptive research (Maria Bettania Avila)

Discussion

Balance between efficacy and safety (Eke Williams)

Other intrinsic characteristics (Rani Bang)

Discussion

Service delivery issues (Ninuk Widyantoro)

Discussion

Tuesday, 18 August 1992

Women's philosophical and ethical concerns (Sandra Kabir)

An overview of funding for vaccine research (Jeff Spieler)

Discussion

Taking an inventory of concerns and issues (a) for further discussion here, and
(b) for action elsewhere

Annex 8 Glossary

Antibody	Protein molecules produced by certain cells of the immune system in the body in response to challenge by a foreign antigen (immunogen). Antibodies bind to the antigen, a process which, if successful, results in the removal of antigen from the body.
Antigen	A molecule which reacts with an antibody.
Auto-immune	A pathological immune response which is directed against the body's own tissues or products instead of against a foreign substance. It can result in the destruction of tissue or interference with normal body functions.
Blastocyst	The ball of cells formed by the dividing fertilized egg prior to implantation in the uterus.
CTP	Carboxy-terminal peptide. A synthetic peptide representing a portion of the β -subunit of the hCG molecule.
Carrier	A molecule that is linked to an antigen to make it into an immunogen. If the antigen is part of a molecule normally present in the body, then the carrier is needed to make it appear foreign to the immune system.
Corpus luteum	The gland formed by the cells left behind in the follicle in the ovary after ovulation.
Cross-reaction	Antibodies raised against a specific immunogen sometimes also cross-react with other molecules that have a similar antigenic structure.
Endocrine	The hormonal system of the body in which substances are secreted into the blood or lymph and have a specific effect on another organ or part of the body.
Follicle	Fluid filled structure in the ovary containing the ovum and its supporting cells. The follicle ruptures at ovulation and releases the egg.
FSH	Follicle stimulating hormone. A hormone, released by the pituitary gland at the base of the brain, which stimulates egg development in women and the production and maturation of sperm in men.
GnRH	Gonadotrophin releasing hormone. A hormone, produced in the hypothalamus of the brain, which regulates the release of FSH and LH.

HCG	Human chorionic gonadotrophin. A hormone which is produced by the fertilized egg cell soon after fertilization, and by the placenta throughout pregnancy. It maintains the production of progesterone by the ovary.
Immunogen	Any molecule which elicits an immune response.
Immunopathology	Abnormal structural and functional changes in the body caused by immune reactions.
Lag time	The period of time following immunization during which the immune response is building up to an effective level.
LH	Luteinizing hormone. A hormone, released by the pituitary gland at the base of the brain, which stimulates egg development, ovulation and the production of estrogen in women and the production of testosterone in men.
Seropositivity	The presence of an infectious agent or of antibodies to it in the blood. This term is most commonly used to refer to the existence of antibodies to HIV indicative of infection with this virus.
Teratology	The branch of science which deals with the abnormal development of the fetus and congenital malformations.
Zona pellucida	The jelly-like coat surrounding the egg.