Contesting Claims on the Safety and Acceptability of Anti-Fertility Vaccines

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This paper describes the controversy surrounding anti-fertility vaccines, focusing on the anti-hCG vaccine. It deals first with the rationale that researchers give for the development of anti-fertility vaccines, and the specific requirements that they set for the new contraceptive method. Two distinct prototypes of anti-hCG vaccines are clearly emerging, one of which might be characterised as maximising safety and the other as maximising efficacy. A vocal group of women's health advocates have opposed the development of both prototype vaccines, pointing to theoretical health risks and the potential for abuse, and call for a stop to further research. This paper shows how the scientists' discourse on safety and acceptability of the technology to future users has changed in response to the critique of women's health advocates. Finally, it reflects on the role of women's health advocates in contraceptive technology development, and the responses of researchers to their actions.

IN the past two decades, women's health advocates have raised concerns and controversy about the safety and health effects of diverse contraceptives, including the pill, the Dalkon Shield, Depo Provera, Norplant, and RU486. The potential for abuse of provider-dependent and longer-acting methods in family planning programmes has been a related and equally important issue in these concerns.[1]

One of the most interesting developments in the 1990s has been the increasing commitment shown by international research institutions, such as the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (WHO HRP) and the Population Council, to support greater dialogue and involvement of women's health advocates and potential users in priority setting and decision-making in contraceptive research and development. Two initiatives that illustrate this commitment include a meeting organised by WHO HRP and the International Women's Health Coalition on 'The selection and introduction of fertility regulation technologies' in 1991,[2] and a symposium on 'Contraceptive research and development for the year 2000 and beyond' in 1993, attended by research programme managers and women's health advocates. The latter recommended that:

'Women's health advocates and potential users should be represented in all decision-making mechanisms and advisory bodies that are established to guide the research process, including definition of criteria for safety, determination of research priorities, design and implementation of research protocols, setting and monitoring of ethical standards, and decisions on whether to pursue a fertility regulation method from one stage to the next, especially decisions to move from clinical trials to introductory trials, and from introductory trials to introduction of a method into family planning programmes.'[3]

In calling for more involvement of women's health advocates in contraceptive research and development, researchers and policymakers hoped to prevent or at least reduce the kind of controversy that threatens the future of research and at the same time, be better able to identify the needs and views of potential users to influence contraceptive technology in a positive way. Some women's health advocates have become involved in this process for similar reasons.

This paper is about a controversy that has

not disappeared, surrounding a new category of contraceptive currently under research – anti-fertility vaccines. It focuses on the so-called anti-hCG vaccine, the one that is most likely to come onto the market within the coming decade. Different versions of this vaccine have been through animal testing and some clinical trials. A group of women's health advocates have launched a campaign to stop further research on all anti-fertility vaccines, on the grounds of theoretical health risks and the potential for abuse. This paper raises questions about whether and how women's health advocates can represent the views and concerns of contraceptive users, and whether they have more authority to speak for users than scientists or family planning providers.

Dialogical approach

As a participant in the women's health advocacy movement, I have witnessed how the campaign to stop the research on anti-fertility vaccines has taken place and been involved in discussions about it. To describe this controversy, I have studied the campaign's materials and other texts from women's health advocacy groups, including correspondence with research institutions. To ascertain why scientists have been trying to develop an anti-hCG vaccine and what requirements they set for this new technology, I have reviewed more than 30 articles in scientific journals from the past two decades, which present the results of all the clinical studies on the anti-hCG vaccine, and of the 'state of the art'.[4] Further, I have interviewed the leading scientists during visits to the Population Council in New York, WHO HRP in Geneva and the National Institute of Immunology (NII) in Delhi.

Methodologically, I have been inspired by the 'dialogical approach',[5] which distances itself from the generally accepted academic belief that researchers should not engage in action. Instead, it fosters exchange between researcher and researched and analysis of this exchange. The dialogical approach is especially suitable for research that takes as its subject an ongoing controversy. Being a neutral observer is hardly possible; the researcher inevitably gets involved in the debate and is forced to reflect on her/his own role.

Developing an anti-hCG vaccine

The idea of regulating fertility by immunological means has its origins in turn of the century findings that infertility can be caused by the presence of anti-sperm antibodies in females.[6] The relatively new science of reproductive immunology has shown that conception and embryo implantation can be interrupted by immunological manipulation.[7] Though anti-fertility vaccines for use by men are also being studied, the anti-hCG vaccine, for use by women, is the most developed. The anti-hCG vaccine is intended to inhibit the function of human chorionic gonadotropin (hCG), a hormone produced by the pre-implantation embryo and necessary for the establishment of pregnancy.[8]

As early as 1976, Hearn[9] raised a number of issues regarding the safety of any anti-hCG vaccine, which remain valid areas for study. These were: the need to ensure reversibility; the need to prevent cross-reaction with other hormones; the risk of immune complex diseases; the risk that subsequent pregnancies would increase the immune response and cause miscarriage; and if pregnancy continued the effects of immunoreactivity on the fetus (teratological effects).

Because of the complexities involved, the WHO Task Force on Immunological Methods for Fertility Regulation developed guidelines for the testing and safety of anti-fertility vaccines, including the anti-hCG vaccine. Immunologists, toxicologists, reproductive biologists and drug regulatory agencies were consulted.[10] The guidelines called for the selection of target substances against which the body produces antibodies (antigens) with a relatively limited risk of so-called cross-reactivity, that are present in the reproductive process only for short periods of time.[7]

The concern about cross-reactivity is based on the fact that hCG is similar to a whole family of hormones produced in the pituitary gland, including luteinising hormone (LH) and follicle-stimulating hormone (FSH). Immunisation against hCG could theoretically also affect these other hormones, leading to potential disturbances in hormonal balance. To avoid cross-reaction, the Task Force decided that they would develop a vaccine based on a peptide that is a small part of the beta sub-unit of hCG, and has no similarity to any of the pituitary hormones.

In contrast, the Population Council and the NII, both of whom had doubts about the efficacy

of a vaccine based on such a small part of the beta sub-unit, opted for using the whole beta sub-unit of hCG as their candidate antigen.

Early clinical trials

In the late 1970s, the Population Council initiated pharmacological studies in 15 sterilised women, using a prototype vaccine based on the whole beta sub-unit of hCG, at clinics in Sweden, Finland, Chile and Brazil.[11] Shortly afterwards, the All India Institute of Medical Sciences tested an injectable prototype vaccine, also based on the whole beta sub-unit, in 23 healthy, parous women who did not want any more children and were reportedly reluctant to undergo sterilisation.[12] In this group, eight pregnancies occurred. This caused controversy among scientists on the ethics of including fertile women in such studies.

Two phase I clinical trials on safety aspects were conducted in the 1980s: under the auspices of the Population Council in India and Scandinavia, 88 sterilised women used a prototype based on the whole beta sub-unit of hCG,[13] and an HRP-sponsored trial of a prototype based on the beta-hCG peptide was conducted in Australia in 30 sterilised women.[14]

These phase I trials paved the way for phase II trials to assess contraceptive efficacy. They demonstrated the ability of the anti-hCG prototypes to induce antibodies against hCG with, in the words of Talwar and Raghupathy 'no notable adverse effects'.[15] Despite cross-reactions of the vaccine based on the whole beta sub-unit of hCG with LH, no menstrual disturbances were reported. Reflecting on the phase I trials, Griffin and Jones stressed that, despite the finding that the anti-hCG vaccines did not interfere with ovulation nor cause endocrine disturbances, there was a need to consider the long-term effects, and specifically that 'the long-term immunopathological sequelae of these reactions in the pituitary and hLH target tissues remain to be determined'.[16]

Why develop anti-fertility vaccines

The early development of the anti-hCG vaccines took place in a period of global concern about rapid population growth. The World Population Conferences in Bucharest (1974) and Mexico City (1984) called for urgent action, including the development of new contraceptives to be used in family planning programmes (the hardware approach) and improvements in the delivery of existing methods (the software approach). Those doing anti-fertility vaccine research refer to their work in scientific articles as contributing to the solution of the global population crisis. Two researchers at NII, for example, wrote:

'Most conservative estimates predict human global population to cross six billion by the end of the 20th century... It poses a major challenge for developing countries and demands mobilisation of additional resources... to maintain the complex relationship between growing population and environment. To overcome this problem it is pertinent to evolve new safe and effective contraceptive agents. Vaccines for immunocontraception are an interesting proposition as it will be cost-effective, and most developing countries have infrastructure for the appropriate delivery.'[17]

For the anti-fertility vaccines to be attractive the 1988/89 Biennial Report on Human Reproduction of WHO states that they should:

'...have long-lasting protective effect after a single course of immunisation; they would not cause menstrual-cycle disturbances and other hormone-dependent side effects; they would be easy to administer by a well-accepted procedure; and they could be manufactured at low unit cost.'[8]

'Long-lasting' was at that time defined as one to two years of protection. Three additional possible advantages put forward in 1989 by Indian scientists Talwar and Raghupathy were:

'The ideal vaccine would not interfere in the process of ovulation and sex-hormone production, in contrast to oral contraceptives which inhibit the hypothalamic-pituitary-gonadal axis. Moreover, immunisation would involve the injection of small amounts of the immunogen, in a few doses, sparing the system from constant drugging with synthetic compounds. Vaccines have the advantage of being free from risk of user-failure.'[15]

They suggest that a longer-acting injectable contraceptive which does not cause menstrual

disturbances would be attractive to users. Marshall argued as early as 1977 that:

'...if limited resources for developing new fertility regulating methods are to be wisely allocated, and if the acceptability of existing methods is to be improved, more feedback from consumers is necessary.'[18]

Yet none of the scientists refer to any such social science research being conducted at the time. This is surprising, as WHO HRP did have a Task Force on the Acceptability of Fertility Regulating Methods, which had been involved in cross-cultural research since 1973. This Task Force was elucidating which attributes of existing contraceptives were liked and disliked by consumers, and planned to study the acceptability of new contraceptives in clinical trial settings.

Different assessments of acceptable risks to users

While the researchers all agreed on the attractiveness of a longer-acting injectable immunocontraceptive for users, they differed in their assessments of acceptable risks. Of the two distinct prototypes of anti-hCG vaccine, I would characterise the one developed by the Population Council and NII as starting from a position of maximising efficacy, and the one being tested by WHO HRP as starting from a position of maximising safety. Griffin at WHO HRP and his colleagues had chosen to maximise safety by selecting one peptide of the beta sub-unit as an antigen, which had possible drawbacks for efficacy.

Talwar and his colleagues at NII in India used the whole beta-hCG sub-unit, in spite of the 1978 guidelines of the WHO Task Force on Immunological Methods. Ten years after these guidelines were published, they argued that some cross-reaction was acceptable as long as menstruation remained 'normal':

'A moderate degree of reactivity with LH is not considered undesirable. It contributes to the infertility action by rendering the corpus luteum deficient in progesterone production in response to gonadotropin, but does not prevent ovulation. Women...having antibodies partially cross-reactive with LH continued to ovulate normally and menstrual regularity was maintained.'[19]

Scientists Jones from Australia, Griffin at WHO HRP and Stevens from the USA felt in 1988 that even a moderate degree of cross-reaction 'raised concerns'. Reporting on their clinical trial with the beta-hCG peptide vaccine they pointed out that no such cross-reactivity was revealed, which 'gave evidence of serological and clinical safety to justify further trials of efficacy and acceptability'.[14]

Mitchison, who chaired the WHO Steering Committee of the Task Force on Vaccines for Fertility Regulation, of which Talwar was also a member, cautiously supported further development of both anti-hCG vaccine prototypes, as suggested here:

'With regard to the relative merits of the two types of vaccine described above, it is still too early to reach a conclusion. Quite possibly, both vaccines will find their place in the armamentarium of contraceptive agents. The cross-reactions elicited by the intact beta chain vaccine are worrying, but that concern diminishes as the number of women who have been vaccinated without adverse consequences increases.'[20]

In an interview, Talwar commented that the relative merits and demerits of both vaccine prototypes should have been tested in an 'impartial' collaborative phase II trial, in order to decide which one should be developed further. Mitchison supported this idea, he said, and he felt badly treated that this had not taken place. It is my impression that such a trial was not planned because the WHO researchers continued to be concerned about the theoretical risks of the whole beta sub-unit anti-hCG vaccine.[21]

Initial questions from a women's health advocate perspective

By the time of the 1989 WHO symposium on the safety and efficacy of vaccines for fertility regulation, there was acknowledgement of the need to consider the views of users in contraceptive development and introduction. The aim of the symposium was to review aspects of present and past work on the development of anti-fertility vaccines, particularly relevant to the

testing of their safety and efficacy.[22]

Two so-called consumer representatives were invited to this meeting from Health Action International, an international network of consumers and health and development organisations – Judith Richter from Germany and myself from the Netherlands. Of course, neither of us could represent the consumers of the world. But we did try to put forward concerns from our perspective as women's health advocates. It was at this meeting that she and I were first confronted with the controversy among the researchers on the relative safety of the two existing anti-hCG vaccine prototypes. Because no one else was willing to confront the NII researchers in plenary, we were urged to raise questions ourselves on the issue.

Afterwards, in a report on the symposium in the Women's Global Network for Reproductive Rights (WGNRR) *Newsletter*, I summarised the concerns raised by Richter and myself about both anti-hCG prototype vaccines,[23] regarding safety and service delivery, especially in settings where health care services were not adequate. In addition to all of those raised by Hearn, described above, these included:

- the need for a test to determine whether a woman still has a protective level of contraception;
- the need for additional protection until the immune response has developed to an effective level;
- the abuse potential if used in coercive population programmes (women could be injected with an anti-fertility vaccine without their full consent, or even without their knowledge).

I stressed the importance of being able to switch off the immune response in the case of women who experienced side effects, and suggested that the vaccine based on the whole beta sub-unit of hCG was inappropriate for development because of the potential health risks related to cross-reactivity.

Griffin responded in a letter to the editor, with assurances that the development of the vaccine would be stopped if serious adverse effects occurred that could not be eliminated, or if the vaccine was found to have teratological effects. With respect to the trials using the whole beta sub-unit vaccine, he said that the trials up to that time had not indicated menstrual disturbances due to cross-reactivity.[24]

Action and reactions

In spite of such assurances, concerns about safety and the potential for abuse caused many women's health advocates to oppose the development of this technology vehemently and to question the rationale for its development. During workshops and meetings held in the early 1990s, they rejected parameters for contraceptive development based on what scientists and policymakers felt was needed and called for a reorientation based on users' needs.[25] Faye Schrater, a feminist immunologist, wrote a review article in which she supported the concern of women's health advocates about possible 'allergy, auto-immunity, irreversibility and teratology' as well as possible abuse and direct or indirect coercion by the state. At the same time, however, she also acknowledged that the hCG vaccines held 'great promises – those of safety, ease of use, non-invasiveness and reversibility.' She ended by expressing cautious support for the research on the vaccine by WHO HRP and an openness as to what it would show. [26]

In August 1992 WHO HRP organised a meeting of researchers and women's health advocates to discuss the issues at stake with anti-fertility vaccines.[27] In a background paper on the 'state of the art' Griffin expressed a firm belief that technical solutions could be found for the potential problems related to anti-hCG vaccines. More animal studies and clinical trials were needed to clarify the exact mechanism of action, develop ways to reverse the contraceptive effect when required, and assess long-term safety. He believed that already available information was sufficient to indicate that anti-fertility vaccines could be developed that were free of overt pharmacological activity and the metabolic, endocrine and physical disturbances often accompanying other systemic methods of birth control. These, he said, could confer contraceptive protection for three months or up to one to two years, following a single administration, but not permanent protection. The user, he suggested, would be able to select from preparations with different durations of action.[27]

Although prior to the interventions of women's health advocates, scientists had been ex-

pressing concerns primarily over issues of safety, efficacy and low user-failure, some scientists such as Griffin have responded to calls for greater control by women, ie. by suggesting that users should be able to choose from among several durations of action. Further, the possibility of reversing the effect of the vaccine on demand, in Griffin's view, would help to alleviate the consequences of abuse should it occur – though only on an individual basis.

Women's health activists call for a stop

From the perspective of women's health advocates, these assurances were not to the point or were insufficient. In June 1993, 19 women's health advocates from 12 countries met in Bielefeld, Germany, hosted by the BUKO Pharmakampagne, to discuss anti-fertility vaccines.[28] Organisations represented were the Association for Health and Environmental Development (Egypt), SAHELI Women's Resource Centre (India), SAHSSO (South Africa), Health Action International, Colectivo Mujer y Salud (Dominican Republic), Red Nacional por la Salud de la Mujer (Argentina), Berne Declaration (Switzerland), Feminist International Network of Resistance to Reproductive and Genetic Engineering (FINRRAGE), Women's Global Network for Reproductive Rights (WGNRR), Colectivo El Telar and Foro Abierto de Salud y Derechos Reproductivos (Chile), and Women's Health Action Foundation (Netherlands).

The meeting had an open and closed section. Griffin was invited to present the scientific data on anti-fertility vaccines to the open session and was questioned at length about safety and efficacy. In the closed session, it was decided to call for a stop to research on anti-fertility vaccines and a campaigning document was drafted.[29]

In November 1993 this 'Call for a Stop of Research on Anti-Fertility "Vaccines"' was sent to research institutes and funders, signed by 232 organisations from 18 countries. It put forward the following reasons for this campaign:

'We, the undersigned, call for an immediate halt to the development of immunological contraceptives because of concerns about health risks, potential for abuse, unethical research, and the assumptions underlying this direction of contraceptive research... Immunological contraceptives will not give women greater control over their fertility, but rather less. Immunological contraceptives have a higher abuse potential than any existing method... Immunological contraceptives present no advantage for women over existing contraceptives... They interfere with complex immunological and reproductive processes. There are many potential risks: induction of auto-immune diseases and allergies, exacerbation of infectious disease and immune disturbances, and a high risk of fetal exposure to ongoing immune reactions...[T]he concept of anti-fertility "vaccines" was conceived in a "demographic driven, science led" framework.'

The word 'vaccines' was put in quotation marks to emphasise the difference between vaccines against harmful diseases and vaccines against non-harmful bodily substances like hCG. Those who signed this document opposed further development of any and all contraceptive vaccines. By May 1996, the 'Call' had been endorsed by 472 groups from 41 countries. Signatories in Brazil (around 120), India (95) and Germany (around 60) account for over half of these.[30]

Representatives of research institutions react

In the first half of 1994, WHO HRP, the Population Council, and the Contraceptive Research and Development Programme (CONRAD, USA) sent reactions to the 'Call for a Stop' to WGNRR, who were acting as the campaign's global secretariat. These refer to the routine procedures of contraceptive development. They state that safety and efficacy are being assessed in clinical trials and that the outcomes of these trials will resolve the issues. They stress their institutions' support for reproductive rights and that this potential new method can have benefits to users.[31] The then director of WHO HRP wrote, for example:

'I agree completely with the aim of WGNRR... the right of women to decide whether, when and how to have children.... It is, however, my contention that this aim also includes the right of women to choose what method of family planning to use, including, if they wish so, an anti-fertility vaccine... We feel that a fully developed and tested family planning method... will be an attractive option for those women who wish to

postpone their first pregnancy, to space births at an interval that has positive health benefits for the mother and her children....'

Debate on the issues

In an attempt to contribute to the dissemination of non-specialist information on anti-fertility vaccines and in response to the 'Call for a Stop' the May 1994 issue of *Reproductive Health Matters* contained an article[32] in which the researchers involved in the development of the beta-hCG peptide vaccine review the current status of anti-fertility vaccines.[33] In this review, they repeat their concerns about the safety of the anti-hCG vaccine developed by the NII and Population Council, stating that 'the theoretical consequences of this LH cross-reactivity are interference with ovulation and disruptions to the menstrual cycle and the risk of pathology in the pituitary gland in which LH is produced'. At the same time, they point out that in the NII data, there is no evidence of such adverse effects. They argue that antibodies to sperm and other reproductive tissues occur naturally, leading to infertility in healthy individuals, which shows that vaccine-induced antibodies are not intrinsically hazardous. Concerning the problem of abuse, they point to the need for improved quality of care and education.

The next issue of *Reproductive Health Matters* contained a roundtable of responses to that article, which aimed to reflect a diversity of views among people concerned with women's health. That diversity is not found in the 'Call for a Stop' campaign. Denese Shervington, then director of the Women of Colour Reproductive Health Forum in New Orleans, was of the opinion that each woman will have to decide for herself if the contraceptive side effects are worth the risk.[34] Ruth Macklin, a professor of bioethics, argues: 'Those who would restrict women's options are being paternalistic in their attempt to curtail the freedom to choose.'[35] Faye Schrater distinguishes between the two types of anti-hCG vaccines in development. She considers the long-terms risks of the prototype developed by NII and the Population Council unacceptable, but she supports further development of the safer alternative developed by HRP.[36]

Also in response Marge Berer and Sundari Ravindran sent an open letter to the *WGNRR Newsletter*:

'We believe that this campaign does not serve women's interests or needs because it is about narrowing women's choices, not increasing them .... We believe that research to develop new, safer and higher quality contraceptive methods is in the interest of women....If even one type of contraceptive vaccine fulfils what is aimed for, that is, a highly effective, convenient-to-use method that works for 12-18 months and that has fewer adverse effects than any hormonal method, we believe that the research will have been worth it.'[37]

Clinical trials continue

As the controversy intensified in the early 1990s, the scientists continued to plan and conduct phase II trials on efficacy of the new contraceptives. Reporting on early results in 1993, Talwar and his colleagues at NII were the first to show the efficacy of their prototype, though the need to give booster injections on average every three months indicated that duration of efficacy was still limited. In the 88 women who used the prototype as their only method of contraception during a total of approximately 1000 months, only one pregnancy was reported in those with more than the level of antibody titres considered necessary for the vaccine to be effective.[38] However, 26 pregnancies occurred in women whose antibody titres were (temporarily) low. Four of the 26 women took their pregnancies to term and reportedly delivered normal babies. These children are being followed up for long-term effects.[39]

Variation in immune response and resulting pregnancy risk was a problem that emerged clearly in the phase II clinical trials in India. As Talwar told me in August 1996:

'The main disadvantage of the method, as I see it, is that you have to be a "responder". Around 20 per cent of the women were poor responders [they did not produce sufficient amounts of antibodies]. This is something one has to improve.'[21]

Early in 1994, HRP initiated a phase II clinical trial on its prototype at two hospitals in Sweden. Of the 25 volunteers selected to participate, the first seven to receive the vaccine all experienced unexpected side effects, including pain at the injection site, fever and in two cases, sterile abscess formation. No further women were

enrolled and the trial was stopped in mid-1995. Various hypotheses were put forward to try to explain these effects. Far from giving up, the researchers decided to try to find ways to eliminate these effects or 'reduce them to a level acceptable to the volunteers and clinical investigators'.[40]

The Task Force on Vaccines for Fertility Regulation of WHO continues to support the development of 'advanced prototype' and 'optimised' vaccines in the meantime. The advanced prototype is a single injection, biocompatible/biodegradable, microsphere formulation. An optimised vaccine is being developed in the USA that is totally synthetic. It has a controlled-release system designed to provide immunity of a predictable and controlled duration. An orally active formulation of this 'optimised vaccine' is also being investigated.[41]

The Population Council had been involved in phase I clinical trials with NII. They were unable to get involved in phase II trials – US funding was refused because of anti-abortion pressures. The anti-hCG vaccine works just after implantation, and was condemned as an abortifacient.[42]

Influencing funders

In mid-1995, the women's health advocates involved in the 'Call for a Stop' campaign met again in Canada. They also aimed to negotiate with representatives of the International Development Research Centre (IDRC), who were supporting the development of the anti-fertility vaccine at NII in India and held the patent on the anti-HCG vaccine developed there. IDRC defended its support for NII's work by quoting Talwar and his colleagues:

'Phase II clinical trials showed that the vaccine could prevent pregnancy and continued to confirm the absence of adverse effects.'[43]

Given this apparent expression of support for NII's work, I was surprised to hear from Dr Talwar (who had since retired as NII's director) in August 1996, that IDRC had decided to stop funding NII's work on anti-fertility vaccines:

'Our research has been stopped by the women dictating....because they were so persistent I got a low priority.'[21]

In January 1997 the president of IDRC confirmed that funding had been stopped, but said it was because NII officials did not intend to seek further funding.[44]

Nature Medicine reported in May 1997 that India was indeed downgrading research on contraceptive vaccines. The Indian Department of Biotechnology is said to have decided to halve the project's annual grant, and to downgrade the vaccines from one of 16 high priority 'missions' to a regular 'research mode'. The current director of the NII, Dr Basu, is quoted as saying:

'We cannot allow this vaccine to enter phase III trials until its long-term safety is established'.[45]

It is difficult, if not impossible, to assess how important the 'Call for a Stop' campaign was in lowering the priority of anti-fertility vaccine research in India. Talwar was a committed proponent of this method and able to generate a lot of support for the research. The campaign coincided with his retirement and he also had powerful critics in India. The former director-general of the Indian Council for Medical Research, for example, is of the opinion that if a vaccine produces a cross-reaction with other hormones, it must not be developed.[46] Perhaps this is why Dr Basu, the new director of NII, seems not to want to take the same pro-active role, but there may be other reasons as well. It can perhaps best be said that international and national concern about the development of the whole beta sub-unit anti-hCG vaccine contributed to an environment in which research and funding priorities were re-assessed.

WHO reflects on research priorities

In 1995 and 1996, reflection on research priorities was also taking place at HRP. A discussion paper on criteria for these said:

'The views, needs and preferences for fertility-regulating methods as expressed by men and women, past, current or potential users, should guide the selection of new methods for development.'[47]

In line with this view, HRP organised a meeting in November 1995 on 'Women's and men's perspectives on fertility regulation meth-

ods and services' where researchers presented studies on the acceptability of different contraceptive methods. It became clear that individual preferences and perspectives vary widely, and the expression of these is sensitive to the methodology used to elicit those perspectives.[48] One paper presenting results of focus group discussions with married women mostly in their 30s with several children in seven countries revealed two striking similarities across countries: overall dissatisfaction with existing methods and a strongly expressed need for long-acting, highly effective yet reversible methods of contraception.[49]

HRP also set up a Gender Advisory Panel consisting of scientists, women's health advocates and health professionals working in reproductive health, who were asked in their first meeting in January 1996 for their views on the future of HRP's research priorities in the field of contraception, and specifically on anti-fertility vaccines. After reviewing the work done to date, the Panel said that:

'This method could fill a need for future generations, provided that some of the unanswered questions... were satisfactorily answered by continued research.'[50]

The Panel also recommended that the Programme conduct follow-up studies with women who have participated in clinical trials of the anti-hCG vaccine, and that social science research be done to elucidate different population groups' responses to a potential vaccine, including questions about possible fears, social consequences, service problems, mode of delivery, and mode of action. When asked about the terminology used for fertility-regulating vaccines, the Panel expressed the opinion that the term 'vaccine' should be avoided and that a new term be found, possibly 'immunocontraceptive'. This term has since been endorsed by HRP's Scientific and Technical Advisory Group and Policy and Coordination Committee.[51]

Women's health advocates present themselves as users

In early 1996, an informal telephone conversation took place between Beatrys Stemerding at WGNRR and Griffin at HRP, in which he reportedly said that the Human Reproduction Programme would consider stopping research on the anti-hCG vaccine if it were shown in an unbiased manner that 'the majority of potential users would not want the method'.[52] In response, the 'Call for a Stop' campaign launched an international postcard action. The postcards were addressed personally to Griffin at HRP, and state:

'I do not support the development of immunological contraceptives. Women and men alike need contraceptives that enable them to exercise greater control over their own fertility, without sacrificing their integrity, their health, or their wellbeing. In addition, the potential for abuse is simply too great with immunological contraceptives, which could easily become tools for population control.'

This raised questions for me about whether women's health activists can claim that they represent the majority of potential users in an unbiased manner.

Reflections

The development of anti-fertility vaccines has been accompanied by not one, but multiple controversies. Firstly, there was a discrete controversy among scientists on the safety of the anti-hCG vaccine which used the whole beta sub-unit as an antigen. Secondly, controversy emerged between a vocal group of women's health advocates and the whole scientific community involved in the development of anti-fertility vaccines. Thirdly, less apparent, there were debates within the women's health movement on the radical position taken by the campaign to stop further research on anti-fertility vaccines.[53]

The controversy among scientists has to do with the risks related to the cross-reactions with LH observed in the trials with the vaccine prototype based on the whole beta sub-unit of hCG. Both in the scientific literature and during interviews with scientists at WHO, I have been surprised by the cautious manner in which concerns about safety and long-terms effects are expressed. The different researchers do not seem to want to disagree openly with each other. This caution may be because open disagreement might increase the distrust among non-scientists

about the conduct of clinical research on new contraceptive methods. Another reason could be that despite theoretical concerns, researchers do benefit from the knowledge gained from others' clinical trials. Indeed, scientists share the point of view that theoretical risks have to be proven with 'uncontroversial facts' derived from studies.

Throughout the controversy, the researchers at WHO and NII have asserted that anti-hCG vaccines would be free of the kinds of adverse effects that women experience with hormone-dependent methods. It is surprising that the women's health advocates who call for a stop to this research do not acknowledge this possible advantage of anti-fertility vaccines. Instead, they appear to consider anti-fertility vaccines to be more dangerous than hormonal contraceptives. I have often pointed out in debates that opposing the principle of immunocontraception on the grounds of possible health risks due to manipulation of the immune system, implies also opposing hormonal contraception because of the possible risks due to manipulation of the endocrine system.[34] Despite decades of research and development, unexpected effects of the contraceptive pill continue to emerge, such as recent reports of increased risks of thrombosis with third-generation progestogens.

From the user's perspective anti-fertility vaccines may in fact turn out to be more acceptable than hormonal methods. Women all over the world discontinue hormonal methods because of side effects such as menstrual disturbances and weight changes. A method with no such adverse effects might well prove to be attractive to many users in diverse socio-cultural settings.[49,54]

The question remains, of course, whether the promise that anti-hCG methods will not cause menstrual disturbances or other adverse effects will prove to be true. The anti-hCG vaccine developed in India could theoretically cause such disturbances, because of its cross-reactions with LH. In the clinical trials conducted by Talwar and his colleagues, these menstrual disturbances did not occur in practice, an outcome often quoted by other scientists.

For me, the answer is not yet clear. In the first place, data in larger numbers of women is needed. In the second place, in the NII phase II trials, 85 per cent of the women are said to have had normal cycles (defined as between 22-35 days) using the prototype vaccine.[39] The results do not show, however, that the women experienced no change in their menstrual pattern. Rather, their menstruation, even if it did change, was still in the range considered normal by scientists. It would have been better to record the menstrual pattern of each participating woman in the months preceding vaccine use and the months during vaccine use. Only then would the actual effect on each woman's cycle be shown.[55]

Strategically, it has been surprising to me that the women's health advocates who call for a stop to research on anti-fertility vaccines have not distinguished between the various prototypes being developed. Because of this, they have missed an opportunity to establish an alliance with those researchers who have pursued maximum safety for this method. Such an alliance could have increased their credibility and impact in terms of their longer-term goal – redirecting the contraceptive development process.

Based on longstanding concerns about the history of eugenic abuse and coercive population programmes, and coming largely from positions of opposition to all long-acting contraceptives which depend on provider delivery, the views of the women's health advocates calling for a stop to the research will not easily be changed. Their radical opposition has had adverse effects, in my view, as it has also prevented more constructive dialogue between these women's health advocates and researchers on the design of clinical trials of safety and efficacy, and criteria used to determine acceptability to users.

Other women's health advocates have taken a less radical position. Instead of opposing the development of such new methods altogether, they have put forward questions that need to be addressed in further research, and become involved in the scientific assessment of safety, efficacy and acceptability of the method.

The point of view of some scientists is changing and they have shown themselves to be open to constructive dialogue. Major research institutions have responded to the critiques of women's health advocates and seem to have begun to reassess the safety, efficacy and acceptability issues at hand. HRP's mission has been reframed to espouse reproductive choice, and new research questions have been taken on – to make the effect of the vaccines reversible if required by the user, and develop an oral vaccine

in order to reduce the possibility of abuse connected with an injectable. These shifts towards a reproductive choice approach are occurring at a time when reproductive health and rights (as opposed to population control) have also moved to the forefront of the policy agenda internationally.

Constructive dialogue on issues of safety, efficacy, acceptability and possible abuse of anti-fertility vaccines is urgently needed. The position taken by the newly appointed Gender Advisory Panel of HRP should be viewed in this light. However, advisory bodies have always to keep in mind the diversity in women's and men's fertility-regulating needs and the differences in views on acceptable risks. How to deal with this diversity in setting priorities for future contraceptive technology development, in an environment where resources for innovative work are limited, is the biggest challenge for the future.

Women's health advocates who sit on committees such as the Gender Advisory Panel may be expected to represent potential users of the new technologies, which they cannot do. The most important role for women's health advocates on these bodies is, in my view, not to represent users, but to make sure that diverse women's health concerns are considered by scientists at an early stage in the development of new contraceptive technologies. The necessity of long-term follow-up of users appropriate to an immunocontraceptive, the need to develop more appropriate measures of menstrual disturbance and any other potential cross-reactions, the need to do follow-up studies of children born to women who had been on the method during pregnancy, and the need to diminish variation in immune response are examples of such issues in relation to anti-fertility vaccines.

Users' perspectives research on anti-hCG vaccines can provide additional input. As anti-hCG vaccines are not yet on the market, it is essential that users' views, fears, experiences and preferences for mode of delivery are studied in the context of future clinical trials. Such research can also make clear why, in diverse settings, some women decide to participate in a trial and others do not, and identify how women-users themselves evaluate safety, efficacy and acceptability of this new form of contraception.

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Résumé

L'auteur retrace la controverse suscitée par les vaccins anti-fécondité, et plus particulièrement par le vaccin anti-hCG. Il évoque d'abord la raison qui a conduit des chercheurs à travailler sur ce genre de produits, et les conditions spécifiques déterminées pour cette nouvelle méthode de contraception. Deux prototypes de vaccins anti-hCG se dégagent, dont l'un privilègie la sécurité d'emploi et l'autre l'efficacité. Un groupe de "défenseurs de la santé des femmes" s'est bruyamment opposé au développement des deux types de vaccins, faisant ressortir leurs risques théoriques pour la santé ainsi que les possibilités d'abus, et a demandé l'arrêt des recherches en ce domaine. L'article montre comment le discours des scientifiques sur l'acceptabilité et la sécurité d'emploi des technologies nouvelles pour les utilisatrices a évolué en réponse aux critiques des défenseurs de la santé des femmes. Il se termine par une réflexion sur le rôle joué par ces défenseurs dans le développement des technologies de contraception, et sur la réponse des chercheurs à leurs interventions.

Resumen

Este ensayo explora la controversia que rodea a las vacunas contra el embarazo, concentrándose principalmente en la vacuna anti-GCh (gonadotrofina coriónica humana). Examina, primero que nada, el razonamiento utilizado por los investigadores para justificar el desarrollo de vacunas contra el embarazo, así como los requisitos específicos que han establecido para ese nuevo método anticonceptivo. Dos prototipos distintos de vacunas anti-GCh están emergiendo: uno de ellos busca la máxima seguridad y el otro la máxima eficacia. Una agrupación que ha hecho valer su posición en pro de la salud de la mujer se opone al desarrollo de ambos prototipos de vacuna, recalcando los riesgos que teóricamente presentan para la salud, además del potencial que ofrecen para el abuso. La agrupación ha exhortado a que se detengan las investigaciones clínicas. Este trabajo muestra cómo ha cambiado el enfoque científico en relación a la seguridad y aceptabilidad de ese método para las futuras usuarias, como resultado de las críticas de quienes abogan la salud femenina. El ensayo concluye con una reflexión sobre el papel de esos activistas en el desarrollo de nuevos métodos anticonceptivos, y la reacción de los investigadores a sus actividades.