UNDP/UNFPA/WHO/WORLD BANK SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION

Challenges in reproductive health research

Biennial Report 1992–1993

WORLD HEALTH ORGANIZATION
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Edited by

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Preface

As the new Director, it gives me great pleasure to present this 1992–1993 Biennial Report of the Programme—the oldest programme of its kind in the United Nations family of organizations. This Programme of great stature is passing through a period of major challenges, most importantly that funding is declining at a time when the expectations of the world for better reproductive health knowledge and technology are continuing to rise. This Report documents the Programme's endeavours towards making sound reproductive health a reality for all.

During the biennium a particularly momentous event was the joint organization of a symposium with the Government of Mexico in Mexico City. Entitled Contraceptive Research and Development for the Year 2000 and Beyond, the Symposium brought together senior managers of all the international and some national public sector agencies that undertake contraceptive research, as well as programme directors and senior staff of certain international and national agencies that support or are otherwise involved in the field of fertility regulation research. The main objective of the Symposium was to review the progress made in the field of contraceptive research since 1984 (when Mexico City hosted the International Conference on Population) and to identify the challenges ahead in preparation for the next International Conference on Population and Development scheduled to be held in Cairo in 1994. The participants in the Symposium prepared a Declaration, which was sent by the WHO Director-General to the Executive Director of the United Nations Population Fund for consideration as a background document during preparatory meetings for the Cairo Conference. This Biennial Report is the Programme's contribution to the ongoing debate on the challenges in reproductive health research in preparation for the Cairo Conference.

Drawing from, and elaborating on, the deliberations of the Mexico Symposium, the first part of the Report highlights the major challenges in reproductive health research as this century draws to a close. On behalf of the Programme, I should like to thank Dr N. J. Alexander, Dr G. Bialy, Ms A. Germain, Dr A. Faundes, and Dr M. F. Fathalla for contributing chapters to this part of the Report.

The second part of the Report presents highlights of the Programme's work during 1992–1993. More detailed technical information on the activities mentioned in this Report can be found in the Programme's Annual Technical Reports.

The third, and final, part contains annexes on the financial situation of the Programme in 1992–1993, a list of institutions that collaborated with the Programme during the biennium, and a list of staff of the Programme.

Giuseppe Benagiano
Director

Executive summary

FROM CONTRACEPTIVE TECHNOLOGY TO REPRODUCTIVE HEALTH

At its inception in 1972, the objectives of the Programme were limited to the development of a variety of safe, acceptable, and effective methods for fertility regulation and the monitoring of the long-term safety and efficacy of existing methods; an additional but important objective was to provide support to institutions in developing countries so that they could conduct research relevant to their own needs. By 1979 the scope of the Programme had been broadened to include research on the acceptability of various contraceptive methods and on the prevention, diagnosis, and treatment of infertility. In 1986 the Programme's Policy Coordination and Advisory Committee further broadened the scope of activities with the recommendation that the Programme should collaborate closely with the WHO Global Programme on AIDS in conducting research on such issues as the transmission of human immunodeficiency virus (HIV) from mother to infant. And in 1988 the World Health Assembly, endorsing the policy guidelines of the Programme, reaffirmed the close relationship between family planning, health, and development, and the necessity to integrate family planning activities with those of maternal and child health. It was at this stage in the history of the Programme that its mandate was further expanded to include the coordination of the global research effort in the field of reproductive health.

What is reproductive health?

Within the framework of WHO's definition of health as a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity, reproductive health addresses the reproductive processes, functions, and system at all stages of life. Reproductive health therefore implies that people are able to have a responsible, satisfying, and safe sex life and that they have the capability to reproduce and the freedom to decide if, when, and how often to do so. Implicit in this last condition are the right of men and women to be informed of and to have access to safe, effective, affordable, and acceptable methods of fertility regulation of their choice, and the right of access to appropriate health care services that will enable women to go safely through pregnancy and childbirth and provide couples with the best chance of having a healthy infant.

The concept of reproductive health

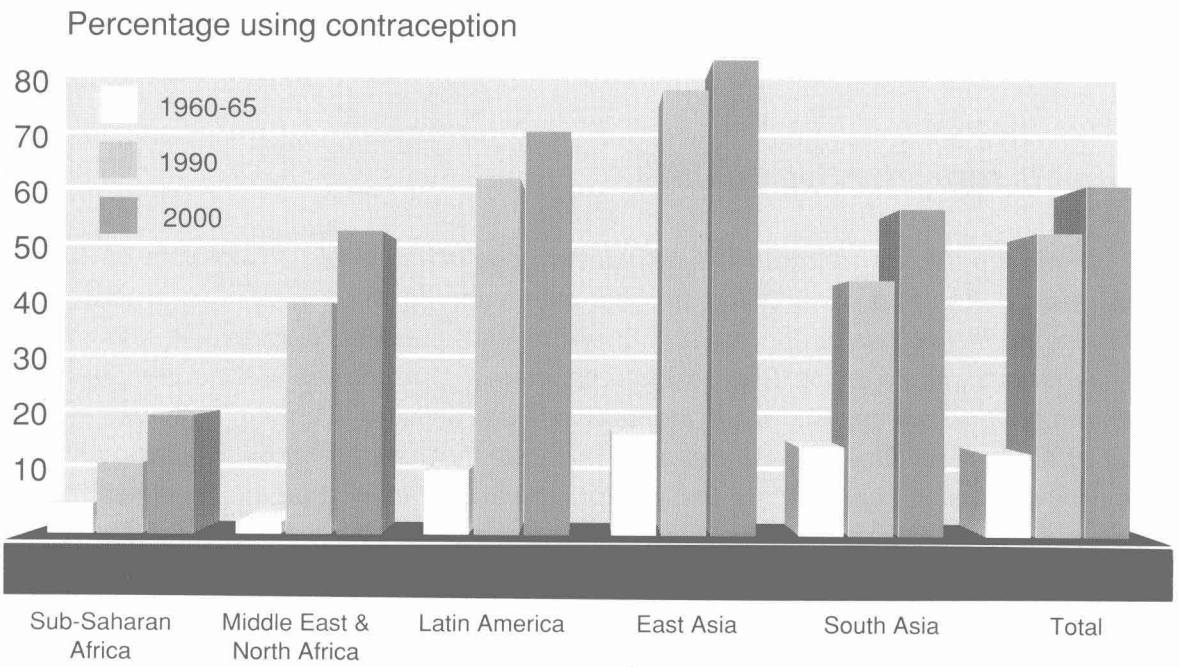
The basic elements of reproductive health are: responsible reproductive/sexual behaviour, widely available family planning services, effective maternal care and safe motherhood, effective control of reproductive tract infections (including sexually transmitted diseases (STDs)), prevention and management of infertility, elimination of unsafe abortion, and prevention and treatment of malignancies of reproductive organs. Furthermore, reproductive health affects, and is affected by, other aspects of health, most particularly human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), nutrition, infant and child health, adolescent health and sexuality, lifestyle, and environmental factors. Pervading and affecting all aspects of reproductive health are various social, cultural, and behavioural factors.

The Programme, with its limited resources, cannot involve itself in all areas of reproductive health research. Within WHO, work in the area of reproductive health is shared by various Divisions and Units. Two major players, apart from the Programme, are the Division of Family Health and the Global Programme on AIDS.

CHALLENGES IN FERTILITY REGULATION RESEARCH

Over the last three decades there has been an impressive rise in the use of contraceptives all over the world, which is expected to continue up to the year 2000 (Fig. 1). In 1990 up to 57% of all married

Fig. 1. Trends in contraceptive use in different developing regions of the world



women of reproductive age or their husbands were using a method of contraception. This represents an increase of 6% over the prevalence in 1983 (Table 1).

These figures, however, do not tell the whole story. For example, in the least developed countries, which represent some 540 million people, the total fertility rate was still 6.1 births per woman in 1992, which corresponds to an estimated prevalence of contraceptive use of only 14%.

It is estimated that there are some 120 million women in developing countries who are not practising family planning even though they say that they do not want to become pregnant. The United Nations Population Fund (UNFPA) estimates that during the 1990s the number of married women of reproductive age in developing countries will increase by about 212 million (28%)—from 747 million in 1990 to 959 million in 2000. If the world is to achieve the United Nations medium-variant population projection of 6.2 billion by the year 2000, it is imperative that fertility in developing countries drops to 3.3 births per woman (from 3.9 in 1985–90) and contraceptive prevalence rises to 59%, from the 1990 figure of 53%. If these levels are to be achieved, the number of contraceptive users in developing countries must increase by 186 million by the year 2000—from 381 million in 1990 to 567 million by the year 2000.

The reproductive health perspective

Among all the factors that influence reproductive health, fertility regulation is undoubtedly one of the most important as it has a bearing on, among others, the prevention of unwanted pregnancy (and its consequences), the prevention of STDs and infertility, sexuality, infant survival and well-being, and safe motherhood.

Unwanted pregnancy and fertility regulation

Half of all pregnancies are unplanned and a quarter certainly unwanted. Unwanted pregnancy is a major public health problem with potentially serious consequences for the health of the girl or woman. Not only is it a denial of a wom-

Table 1. Percentage of couples with wife in reproductive age using a contraceptive method

	World			More developed regions			Less developed regions		
	1983	1987	1990	1983	1987	1990	1983	1987	1990
All methods	51	53	57	70	71	72	45	48	53
Modern methods	42	44	49	46	47	49	40	44	48

Modern methods in this table include: female and male sterilization, oral pills, injectable methods, intrauterine devices, vaginal barrier methods (cervical cap, diaphragm), and the condom.

an's fundamental right to control her fertility, it also exposes her to the hazards of pregnancy and childbirth, or possibly an abortion done under unsafe conditions. In developing countries one in 50 women dies from complications of pregnancy and childbirth, compared to only one in 2700 in developed countries. Also, when a mother dies, the chances of death for her children under five years of age increase by 50%.

Many unwanted pregnancies result in abortion. Around 50 million abortions are performed each year around the world. In developing countries many a pregnancy is terminated in clandestine or otherwise unsafe conditions. This exposes women to a high risk of mortality and morbidity. The estimated annual number of unsafe abortions in the world is 21 million. At least 180 women die every day from unsafe abortions.

Fertility regulation and birth spacing

In many developing countries the traditional practice of prolonged breast-feeding, which helps to achieve longer birth intervals, is gradually eroding. But fortunately contraceptive use is rising and helping to maintain adequate birth intervals. However, where the use of modern contraceptives is not rising as fast as the decline in breast-feeding, many women and their children are being exposed to avoidable health risks, which can lead to death.

With regard to delaying the next birth, two major challenges for policy-makers and scientists are: (*a*) the maintenance of the practice of prolonged breast-feeding but at the same time promoting the timely introduction and use of appropriate contraceptives to achieve adequate birth intervals; and (*b*) the development of suitable and more acceptable methods of birth spacing for lactating women.

The biomedical perspective

Expanding contraceptive choice

Although contraceptive use continues to rise in the world, the currently available methods, however good, do not meet all the different requirements of all the current and potential users. New methods are needed therefore so that the needs of a maximum number of individuals and couples can be satisfied.

Vaginal methods

Vaginal methods include: the barrier methods (condom, diaphragm, and cervical caps) and spermicides (foams, jellies, etc.) or a combination of the two. While other methods have been improved (e.g., oral pills and IUDs), vaginal methods have remained essentially unchanged over the past three decades. Hence, their use-effectiveness and acceptability remain low.

Women's health advocates have been demanding that scientists develop methods of fertility regulation that: (*a*) are under the control of the user; (*b*) are not systemic in action; and (*c*) protect the user against sexually transmitted disease (STD). Many scientists regard this a tall order given the limitations of currently available technology. However, some scientists feel that vaginal methods, which come closer than other methods to meeting these requirements, have not

received due attention. While the current systemic and service-dependent methods have their own advantages and have proven to be safe and effective, in the coming years improving vaginal methods will be a major challenge.

Male methods

The Programme's own research has demonstrated that, on the one hand, it is possible to suppress spermatogenesis by hormonal means. On the other hand, once spermatogenesis is suppressed and the semen is free of spermatozoa, a high contraceptive efficacy can be maintained for the duration of drug administration (one year in the study conducted by the Programme). Upon withdrawal of the drug, the contraceptive effects are completely reversible. While this represents a major milestone in the history of male contraceptive research, a great amount of further work will be needed to turn this lead into a veritable product.

Fertility regulating vaccines

Fertility regulating vaccines hold the promise of a major breakthrough in contraceptive research. They are expected to be usable by women at all stages of their reproductive life, they would be able to provide long-term, but not permanent, contraceptive protection after a single administration, and they would not produce the disturbances in the menstrual cycle and the metabolic side-effects associated with the hormonal methods. While the whole area of fertility regulating vaccines is full of challenges, one especially formidable challenge would be to develop vaccines for men.

Post-ovulatory contraception

The advent of antiprogestogens has provided some of the most exciting, and sometimes controversial, developments in antifertility research in recent years. Mifepristone (in combination with a low dose of a prostaglandin analogue) has been developed into a non-surgical method of early pregnancy termination. Furthermore, mifepristone is already showing great promise for use as a method of menstrual regulation and in emergency contraception. It may also be possible to use mifepristone (alone or in combination with a prostaglandin) in a once-a-month, menses-inducing pill. Such a pill may prove to be a more attractive alternative to the daily pill. Some scientists regard the developments in this field as a precursor to the development of a post- or peri-coital contraceptive pill.

The epidemiology of contraceptive use

Although the clinical and epidemiological methods currently available for ensuring safety of contraceptives are quite adequate, the "translation" of epidemiological findings into sound advice for consumers is not always easy. A challenge for scientists is to formulate public health advice on the basis of epidemiological studies such that service providers can give the users and potential users of contraceptives reliable and meaningful information on the health implications of the epidemiological findings for them.

Involving the private sector in contraceptive development

Over the last 15 years the pharmaceutical industry has retrenched from the field

of fertility regulation. Originally the industry began to withdraw from the field for reasons such as an unfavourable political climate with regard to contraceptives, problems of liability, and stringent regulatory requirements that prolonged the product development process.

These issues are no longer regarded as the main impediments by industry. Today, the concerns are largely economic. Industrial enterprises see the current profit-making markets, which are mainly in developed countries, already saturated with effective products (Fig 2.). They fear that the cost of developing new products may be too high in relation to the paying capacity of the people in developing countries and thus there may not be sufficient returns on investment.

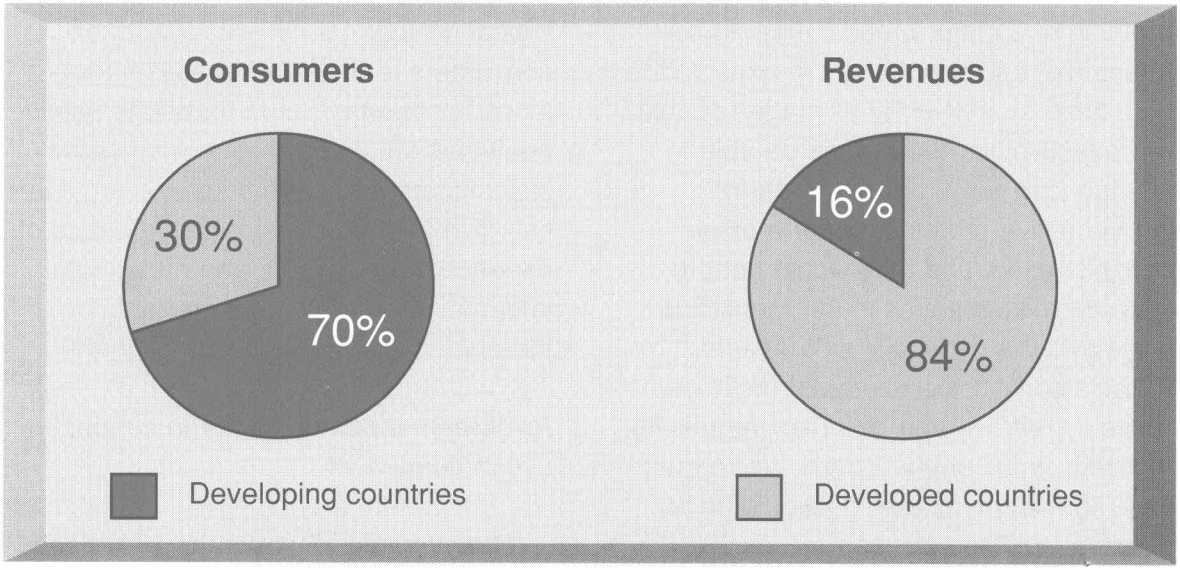
However, a favourable climate now appears to be emerging for the public and private sectors to work together more closely. It is now believed that the two sectors will need to collaborate in research in order to develop the contraceptives that meet people's needs and expectations beyond this decade.

The social perspective

Contraceptive use behaviour

A question often asked is why women who say they do not want more children do not practice contraception, especially when it is known that in most countries almost all of married women know about contraception. Social science research has generated a wealth of information about the various factors that affect contraceptive use. While there are certain factors that appear to influence contraceptive use in most societies (e.g., women's education, access to services and

Fig. 2. The global contraceptive market



information, and urban residence), it is difficult and unwise to make generalizations. A particularly important challenge is to discover quickly which factors are more important than others in different societies, and to translate this understanding into effective policies and action.

Adolescents and contraceptives

In most developing countries there is a large, and growing, population of adolescents. The last decades have witnessed a changing pattern of sexuality among this population group. It has been found that economic progress and urbanization have been accompanied by a shift in the traditional values associated with sexuality, with the result that many more young people are having sexual relations prior to marriage. In many societies this change has occurred against the backdrop of strict traditional customs, and the society and family planning services are as yet often unprepared in terms of providing information on, and methods of, fertility regulation to the adolescents. Understanding and meeting the information and contraceptive needs of adolescents is a growing area of challenge for scientists and policy-makers.

Sexual behaviour, fertility regulation, and STDs

Sexual behaviour has a bearing on the risk of unwanted pregnancy and of contracting an STD (and possible infertility). It may also influence contraceptive choice. With STDs and unwanted pregnancies on the rise around the world, especially among adolescents, the study of sexual behaviour, particularly in developing countries, has acquired a certain urgency. A major problem is that sexuality is often surrounded by strict social, moral, and religious beliefs and these make an objective study of the subject difficult. But such knowledge is essential not only in developing sound advice for people but also in deciding which types of contraceptive will most suit people's needs.

The women's perspective

In March 1993 the Government of Mexico and the Programme jointly organized a Symposium in Mexico City entitled Contraceptive Research and Development for the Year 2000 and Beyond. The Declaration of the Symposium (see pages 53–57) calls for the inclusion of women's health advocates and potential users in "all decision-making mechanisms and advisory bodies that are established to guide the research process...". Scientists should welcome this call as the representation of the views of the ultimate users in the contraceptive development process can help to focus scarce resources on methods that are likely to be most acceptable. A major challenge for scientists will be to make adjustments in the current research culture in order to incorporate the viewpoints of potential users and their representatives. On the other hand, the women's health movement will need to be better informed about scientific issues related to fertility regulation research.

The challenge for governments

The importance of the need to continue and expand research on fertility regulation methods cannot be overemphasized. The Mexico Symposium calls on governments in developing countries to "establish programmes for the conduct

of reproductive and sexual health research as a priority component of their national health research agendas, and allocate the funds and develop the human and institutional resources required for carrying out such research". A call was also addressed to donor governments and agencies to: (*a*) "provide greater financial resources as a priority in order to strengthen further the human and institutional capabilities of developing countries"; and (*b*) "increase support for basic biomedical, technological, clinical, epidemiological, and social science research to improve existing and to develop new fertility regulation methods that are safe, effective, affordable, suitable for different age groups, and designed in response to users' needs".

LAUNCHING A SECOND CONTRACEPTIVE REVOLUTION

The advances in contraceptive technology over the past few decades can only be described as a revolution. The methods resulting from this revolution have produced a dramatic decline in fertility in many parts of the world. However, the currently available contraceptive "hardware", though still usable, is inadeqaute to meet the present requirements and the rapidly expanding future needs. A second contraceptive revolution is urgently needed, and the agenda for the contraceptives of the 21st century must be set now.

For the successful launching of a second contraceptive technology revolution, the field needs a clear and appealing mission, a strong scientific base, and a private industry ready to seize the opportunity. There are indications that these criteria can now be met. For instance, the mission is now becoming clear and compelling, with women increasingly articulating their unmet needs. Science is again becoming ripe with fascinating advances. New frontiers are opening up with research on cell and molecular biology and with the advent of biotechnology. There are also signs that private industry may be ready to work jointly with public sector programmes to develop new methods of fertility regulation.

THE CHALLENGE OF SEXUALLY TRANSMITTED DISEASES

Sexually transmitted diseases (STDs) are a major public health problem in all countries, but especially so in developing countries. Table 2 shows the global

Table 2. Global incidence of STDs

Disease	Minimum estimates of yearly incidence
Trichomoniasis	120 million
Chlamydial infections	50 million
Human papilloma virus (HPV)	30 million
Gonorrhoea	25 million
Herpes simplex virus (HSV)	20 million
Syphilis	3.5 million

incidence of STDs.

STDs can cause a number of serious clinical conditions and are the most important preventable cause of infertility (see Table 3). The consequences of STDs are particularly severe for women as they are more susceptible to infection and experience symptoms, complications and secondary ascending infection much more often than men.

Genital infection with *Chlamydia trachomatis* is estimated to be the most common bacterial STD with a minimum estimate of 50 million new infections worldwide each year. Chlamydial lower genital tract infection is asymptomatic in the majority of infected men and women.

Only in some countries (such as Sweden) can it be claimed that the public health problem of STDs is diminishing. As more data become available from developing countries, it is clear that reproductive tract infections including STDs and HIV infection are a major concern with substantial social and economic implications. The challenges for the remainder of this century include improved health education for both sexes especially male adolescents, dramatic changes in the status of women and their enfranchisement, and the creation of equal opportunities for adequate reproductive health care and education.

The principal constraints to effective STD control especially in developing

Table 3. Major STD microbial agents and the conditions they produce

Agent	Acute disease	Pregnancy-associated conditions	Chronic conditions
Neisseria gonorrhoeae	Urethritis Cervicitis Salpingitis	Premature birth Septic abortion Ophthalmia of neonate Postpartum endometritis	Infertility Ectopic pregnancy
Chlamydia trachomatis	Urethritis Cervicitis Salpingitis	Septic abortion Ophthalmia of neonate Postpartum endometritis	Infertility Ectopic pregnancy
Treponema pallidum	Primary and secondary syphilis	Spontaneous abortion Stillbirth Congenital syphilis	Neurosyphilis Cardiovascular syphilis Gumma
Human papilloma virus	Genital warts	Neonatal laryngeal papillomatosis	Genital cancer
Herpes simplex virus-2	Genital ulcer	Neonatal herpes Premature birth	Possibly genital cancer

countries include the absence of simple, inexpensive, and accurate diagnostic kits and little or no epidemiological research on the incidence or prevalence of the disease. These deficiencies coupled with the enormous problem of health education and the continued provision of male condoms free of charge or for a nominal cost at all contact points between the subject at risk of STDs and the health care system, pose formidable challenges.

The extent and microbiological nature of reproductive tract infections in developing countries, especially in rural communities with restricted access to health care, need to be quantified. While *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are well established as a cause of salpingitis there remain some 30-40% of cases in which neither organism can be identified. Research is needed on the role of other organisms (including the mycoplasmas) in lower genital tract infection, and on bacterial vaginosis in the genesis of female upper genital tract infection. Vaccines against chlamydial and gonococcal infection have great potential in the long-term for STD control, but much more research and development work is still required. New and continuous advances in immunotherapy have increased the probability of success in this area.

HIGHLIGHTS OF 1992–1993

Epidemiological research

Hormonal contraceptives and cancer

In 1979 the Programme started a major multinational case–control study to investigate the possible relationship between the use of hormonal contraceptives and neoplastic diseases of the breast, cervix, endometrium, gallbladder, liver, and ovary. An important finding from this study has been that most results from the studies in developed countries of hormonal contraceptives and risk of cancer are also likely to be applicable to women in developing countries. The main results from the study relating to depot-medroxyprogesterone acetate (DMPA) were reviewed in 1993 by a meeting of experts. The participants concluded that among DMPA users there was no evidence for an overall increase in the risk of cancer at any of the four sites reviewed (breast, cervix, endometrium, and ovary). It was also concluded that DMPA had a protective effect with regard to endometrial cancer. Thus, it was recommended not to restrict the use of DMPA as a contraceptive on the grounds of risk of neoplasia.

Vasectomy and cancer

In 1993 two studies were published in the USA which showed an increased risk of prostate cancer 20 years after vasectomy. Although these studies do not establish a causal link between vasectomy and prostate cancer, they may affect the acceptability of vasectomy not only in developed countries but also in developing countries where this method of family planning is quite prevalent. In 1993 the Programme initiated the pilot phase of a multicentre case–control study on the relationship of prostate cancer and vasectomy in four developing countries where this family planning method is common (China, India, Nepal, Republic of Korea).