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

Reproductive health research at WHO: a new beginning

Biennial Report 1998 - 1999

World Health Organization
Geneva

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PREFACE

"There will be a change. A change in focus. A change in the way we organize our work. A change in the way we work as a team." These words of Dr Gro Harlem Brundtland addressed to the staff on her first day in office as WHO's new Director-General, on 21 July 1998, very much typify the developments in the Programme during the biennium 1998-1999. So much so that I believe that this biennium can best be described as "A new beginning". Let me briefly explain some of the reasons why I believe that the Programme has indeed embarked upon a new, exciting phase in its distinguished history. Three main reasons come to mind.

First, in June 1998, the Policy and Coordination Committee (PCC), which is the Programme's most senior governing body, agreed after several years of debating the pros and cons that the Programme should expand its research agenda in line with the broader concept of sexual and reproductive health as adopted at the International Conference on Population and Development (ICPD) in Cairo, Egypt, in 1994. Specifically, PCC agreed that the research agenda would encompass, in addition to fertility regulation, high-priority research on unsafe abortion, maternal health, reproductive tract infections (including cervical cancer), and planning and programming in reproductive health. Aspects of research on adolescent reproductive health, female genital mutilation and other harmful practices, which are relevant to the Programme's mandate, would also be incorporated.

This decision of PCC has created a unique opportunity for the Programme to expand in areas of reproductive health research where its expertise and worldwide network of collaborating scientists and institutions can make a major impact. Take maternal health research, for instance. We know that postpartum haemorrhage is the main cause of maternal mortality, with about 25 per cent of deaths worldwide due to this tragic complication. Fortunately, in any given hospital, a maternal death is a relatively rare event and, obviously, a maternal death caused by haemorrhage is even rarer. It follows from this that, in order to study a new drug to prevent postpartum haemorrhage, for example, a large number of hospitals need to be involved and tens of thousands of deliveries observed. Few, if any, international organizations apart from the Programme has the know-how and experience to design, set up, and manage such multisite, usually multinational, trials.

Second, in November 1998, the new WHO Administration under Dr Brundtland's leadership decided to bring the Programme together with the former WHO Division of Reproductive Health (Technical Support) into a newly created Department - the Department of Reproductive Health and Research. In a sense, this move represented the formal consolidation of a close partnership that had been growing between these two entities over a number of years and particularly since 1995 when the World Health Assembly in it resolution WHA48.10 called upon WHO's Director-General:

"to develop a coherent programmatic approach for research and action in reproductive health and reproductive health care within WHO to overcome present structural barriers to efficient planning and implementation....."

The joining of the Programme and the Reproductive Health (Technical Support) Division has created the enabling environment to exploit fully the complementary - and frequently synergistic - experience and skills available in these two groups to the benefit of countries and of the sexual and reproductive health of their peoples. Signs of this synergism can be discerned already in all areas of the Department's work - in the research we support, the norms and guidelines we develop, the technical support to countries we provide, and in the work we do in the areas of advocacy and human rights, especially reproductive rights.

In the years to come I expect this complementarity and synergism to grow even stronger as the Programme becomes more closely involved with the development and field-testing of new interventions and, by doing so, identifies new and unmet research needs in the countries we serve. This close association of the research enterprise with the realities on the ground will almost certainly be a determining influence in shaping the Programme's research agenda in future biennia.

Third, the establishment of the Department of Reproductive Health and Research also created opportunities for effecting changes "in the way we do things", "in the way we

work as a team". Specifically, the restructuring provided staff with the "space" to review existing structures and design new, more flexible working arrangements based on the team concept. There are currently four major teams in the Department devoted to "research and evidence", "development of norms and tools", technical support to countries", and "advocacy and human rights". While, by definition, the composition of teams is flexible and varies, the "research and evidence team" consists mainly of Programme staff whereas the "development of normals and tools" team is mostly composed of staff members from the former Reproductive Health (Technical Support) Division. The other two teams have a mixed composition. These new arrangements should facilitate providing a comprehensive and integrated response to a country's reproductive health needs. For instance, the diversity of skills in the team providing technical support to countries facilitates linking research and research capacity building to a country's needs in planning, design and implementation of reproductive health programmes.

Creating the necessary changes and adapting to them can be time-consuming and carries a serious risk that the "real", technical work will suffer. I am pleased to report that this certainly has not been the case in the Programme, as the pages that follow will amply demonstrate.

The recently completed five-year review of progress in the implementation of the ICPD Programme of Action and the similar review now under way of the Plan for Action of the Fourth World Conference on Women (Beijing, China, 1995) have identified many areas where achievements are falling short of targets and increased efforts are needed. The changes that have taken place during the biennium 1998-1999 within the Programme and in its immediate environment should enable us to deal effectively with these new demands. For the Programme, the biennium 2000-2001 is not just the start of a new millennium but a truly new beginning in many exciting ways.

Paul F.A. Van Look, MD, PhD, MFFP
Director

EXECUTIVE SUMMARY

UNDERSTANDING PEOPLE'S REPRODUCTIVE HEALTH NEEDS AND PERSPECTIVES

Men's involvement in reproductive health

The paucity of information in developing countries on men's roles in and perspectives towards reproductive health led the Programme to launch, in 1995, a social science research initiative to address this problem. A total of 17 studies were supported. In general, the studies have shown that, while there may be high levels of awareness and approval of contraception among men, in practice prevailing attitudes conspire to reduce contraceptive use. For example, a study of 714 Jamaican men between the ages of 15-40 years indicated that there were high overall levels of awareness, approval and use of contraception. Yet study participants expressed concerns about the side-effects and low effectiveness of certain female contraceptive methods. And while 30% of the men in the study favoured condom use for disease prevention, they considered female contraception more appropriate when they were in a "bona fide" relationship with a trusted partner. On the other hand, men were strongly opposed to permanent methods. Eighty-nine per cent of the men disapproved of tubal ligations for their partners and 96% would not consider a vasectomy for themselves. For many men, the uncertainty of relationships made vasectomy too final an option.

A study of 200 Mexican men examined which factors influenced men's choice of vasectomy as a method of

contraception. Factors supporting the use of vasectomy included: having three or more children; prior experience with withdrawal; predominant use of traditional methods; and a high level of communication with partners on contraception. Men who had no intention of getting a vasectomy reported either that it was not easily accessible or that they were opposed to family planning. Based on the results of the study, the authors suggested that family planning programmes should emphasize that vasectomy had no impact on virility or pleasure during sexual intercourse.

Ten focus group discussions with married men and women were conducted in Umraniye, one of the most densely populated districts in Istanbul, Turkey, to determine their attitudes towards contraception. There was a sustained willingness among the men to use certain types of male contraceptive methods, withdrawal being the most common (25% of participants); far fewer used condoms (7-8%). Men favoured withdrawal because of poor knowledge of other methods, negative experiences with modern contraceptive methods, and rumours about the side-effects of modern methods.

Several factors appeared to contribute to the reluctance of men to use condoms. Almost all study participants said they would be embarrassed to buy condoms in public. There was also the perception that condoms are intended for disease prevention.

Four other studies also examined men's attitudes towards condom use. In two studies in Shanghai, China, 2266 male clinic attendees diagnosed with a sexually transmitted infection (STI) were randomly assigned to three groups and received: routine clinical services; routine services and an educational video about STIs; or routine services, educational video plus opportunity to participate in a discussion group. Knowledge and attitudes were determined 2-3 weeks later in a follow-up interview. Men in the video and video-plus-discussion groups correctly answered questions about condoms more frequently, and had more a positive attitude towards condoms, than men in the group that obtained standard clinical services only. The results of this study underscore the need for education to improve the chances of successfully introducing condoms, and other contraceptive methods, into a culture.

Another study in China was designed to understand providers' perspectives of clients, counselling and condom promotion in STI clinics. Clinic attendees were also interviewed in-depth to ascertain their attitudes towards condom use. Embarrassment about telling one's spouse about the STI was the main reason for not using a condom. The results also revealed

that 80% of the clients feared visiting public STI clinics because they expected providers to express negative attitudes. The physicians on the other hand, did not always understand clients' fears and perceived themselves as having good attitudes towards clients. Moreover, while most physicians recognized the importance of counselling for prevention of STIs and human immunodeficiency virus (HIV) infection, doctors lacked the time to provide adequate consultations.

The Programme is also supporting studies in South Africa and Thailand on the acceptability of a non-latex male condom. The results will provide information about the background characteristics of men and women who are likely to accept the latex or non-latex condom, and ascertain reasons for discontinuing condom use.

Family planning and sexual behaviour in the era of HIV/STIs

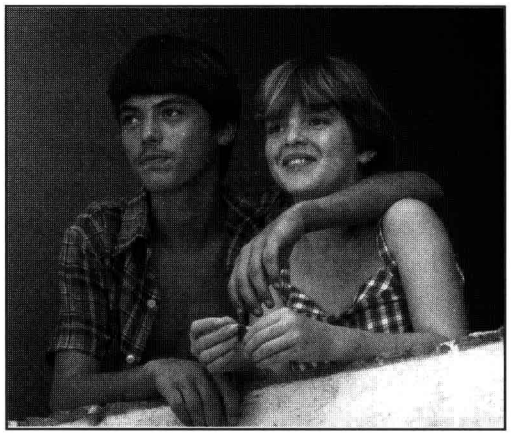
The Programme's six-country study, entitled Family Planning and Sexual Behaviour in the Era of HIV/AIDS, was launched to ascertain the perspectives of sexually active individuals on the dual risks of unwanted pregnancy and HIV/STIs. In addition, the study also investigated practical and effective ways of coping with these risks, and explored opportunities for changing people's behaviour, with particular emphasis on communication between partners. In Phase I of the study, focus groups collected qualitative data on community attitudes towards family planning and sexual health.

The Phase I findings showed that the focus group participants had high levels of knowledge about STIs and HIV/AIDS, and many felt that using methods for preventing both STIs and unwanted pregnancy made sense. However, male opposition to family planning was a major barrier not just to the use of condoms for dual protection, but to contraceptive methods generally. Many participants in the study felt that attitudes towards condom use would have to change, particularly among men, before condom use would be more widely taken up. Misconceptions regarding AIDS were also noted by the study, such as the belief that AIDS could be cured by sleeping with a child under 10 years of age. The Phase I results are being used in Phase II as the basis of a survey to quantify people's perspectives on reproductive health.

Sexual and reproductive health needs and perspectives of adolescents

Over one billion young people live in developing countries and yet there is insufficient information to develop evidence-based strategies for meeting their sexual and reproductive health needs. To help combat this knowledge gap, since 1990 the Programme has supported 34 studies in 20 developing countries on the reproductive health needs of young people. In 1999, the Programme reviewed the findings from these studies and found that, while substantial numbers of youth in all regions were sexually active, there were major gender differences in attitudes towards sex and this influenced risk perception and behaviour. Males, in particular, were consistently more likely to engage in risky sexual practices and consistently less likely to use condoms with regular partners. Compounding this problem was the fact that sexually active females usually deferred to male partners for contraceptive decisions. Not surprisingly, the

use of contraception in general, and condoms in particular, condoms was inconsistent. These and other findings underscore the need for youth-friendly reproductive health services, with counselling on sexuality, pregnancy, post-abortion issues and family planning.



The Programme also launched a major initiative to identify factors that contribute to positive sexual and reproductive health among adolescents. Three regional workshops, designed to develop research proposals, were held in Brazil, Kenya and Thailand during 1998-1999, and 27 studies were selected for support. In addition, two Programme-supported multicentre studies are under way in China. The first is an exploratory study that has been examining the reproductive health needs of young female migrant workers. The study found that, despite widespread sexual activity, the women lacked knowledge about their bodies, reproduction and reproductive health. The second study investigated the unmet needs of sexually active, unmarried, young adults and the barriers that inhibited them from obtaining sexual and reproductive health services. The investigators found that unmarried youth generally lack knowledge of safe sex, contraceptives and reproductive health. All involved in the study, that is the young people themselves, their families and family planning providers, agreed on the need for systematic sex education. Condoms, pills and spermicides were identified as suitable contraceptive methods for young adults.

The Programme is also supporting projects to evaluate and improve reproductive health services for adolescents, including an ongoing study in six sub-Saharan countries Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Guinea and Senegal. In 1999, the first phase of the study, to profile adolescent users, was completed in Côte d'Ivoire. Results showed that half of all adolescents attending general health facilities were sexually experienced, with their sexual debut occurring at an average age of 15 years; and one-third of all women requiring delivery services were adolescents. The study identified four priority areas for intervention. First, parents and influential community members need to be provided with information and communication skills. Second, fees for reproductive health services should be reduced or waived for adolescents. Third, youth-friendly health services need to be developed, including reorientation training for existing providers, separate waiting areas for adolescents and ensuring the availability of supplies, including contraceptives. Finally, the mass media should also be involved in providing useful and acceptable messages about sex to adolescents.

Gender and human rights issues in reproductive health

Initiative in gender and reproductive health

This is an innovative training project, initiated in 1996, to help programme managers understand and implement a gender-equality and rights-based

approach to reproductive health planning. Following a 1997 pilot course in South Africa, the curriculum was run in 1999 in four regional centres in Argentina, Australia, China and Kenya. The final curriculum will be published in 2001.

Understanding the informed consent process in human reproduction research

Guidelines by which potential research subjects are informed about a study and give their consent to participate are well-developed and accepted. How these guidelines are translated into practice is less well understood, however. In 1997, the Programme launched a pilot initiative to examine this issue. Two studies, in Brazil and Chile, were completed in 1998; the third is ongoing in Mexico. The results of the two completed studies indicated that research subjects and investigators had very different understandings about the research process and the information given, as well as about the rights and obligations of the two groups.

Discriminatory laws and policies that affect women's reproductive health

During 1999, the Programme began a process of consultation to understand how existing laws and regulations could be reviewed, with the aim of understanding which laws or policies adversely affect women's reproductive health. With the help of advice from outside experts it was concluded that it would not be useful to create an inventory of laws, since this would duplicate previous and ongoing efforts by other organizations. Instead, it was decided that existing information in this area should be utilized. It was also decided that a detailed analysis was needed to determine what would be feasible and appropriate in this area; what the purpose of such an undertaking would be; and what the comparative advantage of WHO would be for undertaking this work. The Department of Reproductive Health and Research has therefore begun drafting a strategy for work on human rights, which would include attention to discriminatory laws and policies, and which can serve as a basis for consultation.

DEVELOPING NEW METHODS OF FERTILITY REGULATION

To meet the need for a wider range of fertility regulation methods, the Programme has supported the development of improved versions of existing technologies, to make them safer and more effective, as well as the development of new methods.

New and improved contraceptive methods for women

A three-monthly injectable contraceptive –levonorgestrel butanoate

Working with the Contraceptive Development Branch of the US National Institute of Child Health and Human Development, the Programme identified levonorgestrel butanoate for further development, as a better alternative to the existing three-monthly injectable, depot medroxyprogesterone acetate (DMPA). Studies over the past two years have focused on improving the formulation of a clinically-acceptable preparation of the compound. Once such a formulation is developed, pharmacokinetic and tolerance studies in animal models will

be carried out, as well as Phase I and II clinical trials in humans.

A six/twelve-monthly immunocontraceptive

In this area, the Programme has focused on a contraceptive directed against human chorionic gonadotrophin (hCG). A prototype hCG immunocontraceptive entered Phase II clinical trials in 1994, but the study was stopped when the first few volunteers developed unexpected injection-site pain and tissue reactions. Research in 1997-1998 led to the development of an advanced prototype which did not produce the unacceptable injection-site reactions in animal models. In 1999, a batch of this prototype was produced according to Good Manufacturing Practice and used in pre-Phase I toxicity studies in rabbits to determine the highest dose of the standard immunocontraceptive formulation that would not produce muscle irritation at the site of injection. These studies are ongoing and, if successful, a new Phase I clinical trial application will be made.

Emergency contraception

In 1992, the Programme showed that a single 600 mg dose of *mifepristone* was effective as an emergency contraceptive. Based on subsequent work indicating that lower doses of mifepristone might also be effective, the Programme compared the efficacy of 50 mg and 10 mg doses of mifepristone with the 600 mg dose in women within five days of unprotected coitus. The results showed that the failure rates in the three groups were comparable, ranging from 1.1% to 1.3% for all groups. A comparison of the number of expected and actually observed pregnancies indicated that each dose prevented 85% of the pregnancies. A common side-effect was delay in onset of the next menses, which increased with increasing mifepristone dose. These results have practical implications since the lower dose of mifepristone will be cheaper, a significant consideration particularly in developing countries.

In 1993, Programme-supported research suggested that levonorgestrel was as effective as the Yuzpe regimen of emergency contraception, but had fewer side-effects. To confirm this, the Programme supported a double-blind, randomized study that included 1998 women in 14 countries. The results showed that levonorgestrel treatment was more effective than the Yuzpe regimen, and that fewer women receiving levonorgestrel reported side-effects, such as nausea, vomiting, dizziness and fatigue. Another important finding was that pregnancy rates for both treatment regimens increased with increasing time between unprotected coitus and receiving treatment. These findings, which were published in 1998, have had a major impact on emergency contraception services, with authorities in several countries expressing interest in registering the levonorgestrel method.

An important question remaining is whether mifepristone is a better emergency contraceptive than levonorgestrel. A trial to answer this question is under way.

Natural family planning

The "rhythm" or "calendar" method is the most commonly used method of natural family planning worldwide. The Institute for Reproductive Health (IRH) at Georgetown University, Washington, DC, USA has derived a blanket rule by which women with regular cycles abstain on days 8-19 of the menstrual cycle; a bead collar is used to help the women keep track of cycle days. IRH is initiating a

multicentre project to study the effectiveness and acceptability of the 8-19 day rule method, and the Programme is considering potential support to save centres in sub-Saharan Africa.

Lactational amenorrhoea

In the past two years, several papers were published reporting the results from a large multinational programme study that investigated the relationship between lactational amenorrhoea and breastfeeding practices and whether there were significant differences in the period of lactational amenorrhoea between different populations with similar breastfeeding practices. Ten factors were found to be related to the duration of amenorrhoea, seven of which had to do with infant breastfeeding characteristics. Among other factors, the risk that menses would return was reduced by: a shorter interval between birth and the first breastfeed; delaying supplementation of breastfeeding with food or drink; and by increasing the duration and frequency of breastfeeds. The results supported the Bellagio Consensus and confirmed that the lactational amenorrhoea method is a viable approach to postpartum contraception.

Non-surgical abortion with mifepristone plus misoprostol

There is a need to improve the efficacy of the sequential regimen for non-surgical abortion (mifepristone followed by a prostaglandin such as misoprostol or gemeprost), and to reduce the post-abortion bleeding associated with its use. A study of 1589 women in the first trimester of pregnancy was carried out to compare the efficacy of a single dose of either 200 mg or 600 mg of mifepristone followed, 48 h later, by a 0.4 mg oral dose of misoprostol. The results showed that the lower dose was as effective as the higher dose. This finding is important because the costs of 600 mg of mifepristone may be prohibitive in developing countries.

A problem with the above regimen is that the effectiveness of the mifepristone-misoprostol combination is too low to justify its use by women with menstrual delays of more than 21 days (49 days' gestation). Higher doses of mifepristone do not increase efficacy in this regard. Hence, the Programme is focusing on the prostaglandin component to see if a regimen can be identified that would be suitable for pregnancies of up to 63 days' gestation. For example, an ongoing study is comparing the efficacy and side-effects of repeated doses of misoprostol, given after 200 mg of mifepristone.

Hormonal contraceptives for men

Testosterone buciclate

Testosterone buciclate shows promise as a three-monthly injectable contraceptive for men. In 1998, Programme-supported research led to the formulation of a stable, 400 mg/ml suspension of the compound, that would be suitable for preclinical and clinical trials. Meanwhile, discussions have been held with the US National Institutes of Health and a potential industrial partner concerning the licensing of testosterone buciclate, both as a male contraceptive and for androgen replacement therapy in hypogonadal men.

Testosterone undecanoate

Testosterone undecanoate has shown promise as a six-weekly injectable contraceptive for men. During the biennium, the Programme has been supporting a multicentre study in

China to see how quickly and to what extent this androgen suppresses spermatogenesis, and for how long sperm production remains suppressed. This study is still ongoing. A concurrent study, to assess the acceptability of testosterone undecanoate as a male contraceptive, is also ongoing and involves the participants of the efficacy study and their partners.

Basic research into human reproduction

The Programme continues to support basic research to identify new leads for regulating male fertility; for contraceptive methods that could be used once a month by women; and for improving the performance and acceptability of progestogen-based methods of fertility regulation.

Endometrial bleeding

Many of the approximately 20 million women who use progestogen-only methods of contraception endure irregularities in vaginal bleeding caused by these methods, but options to alleviate this problem are few. Thus, the Programme has supported research into the mechanism of normal menstruation, and particularly into understanding how contraceptive steroids, such as progestogens, affect this process.

Results of this work suggest that normal menstruation is an inflammatory response to the withdrawal of progesterone, rather than a vasoconstrictive event as had previously been thought, and that this leads to destruction of the endometrial tissue by cells of the immune system. On the other hand, progestogen-induced endometrial bleeding is intermittent, unpredictable and occurs from superficial veins and capillaries. Work supported by the Programme confirmed that progestogen-induced bleeding was associated with vascular frailty and abnormal angiogenesis, and provided further evidence that progestogen-induced bleeding was associated with abnormal levels of enzymes involved in the destruction of connective tissue.

In 1998, two studies were launched to see if different treatments could ameliorate the effects of progestogen-induced bleeding. These studies are expected to be completed by mid-2001.

Male reproductive physiology

Triptolide is a compound isolated from the roots of the Chinese medicinal plant, Tripterygium wilfordii, that causes infertility in male rats and mice and in men. Programme-supported research during the biennium found that triptolide induced no signs of clinical toxicity or mortality in the test animals and no alterations in chromosome structure or number. Studies are ongoing to examine the mechanisms underlying the antifertility effects of this compound.

In 1998, a three-year project to study the mechanisms of spermatogenesis was completed. The results show that a truncated form of the receptor, c-kit, is able to activate oocytes to undergo parthenogenetic cell division. The normal protein receptor is found in sperm cytoplasm, and the research suggests it may be involved in oocyte activation and subsequent egg development. Thus, it may offer a novel target for male contraception. Research is ongoing in mice to see if animals lacking the truncated version of the receptor exhibit normal spermatogenesis and whether the spermatozoa they produce are capable of fertilization and egg activation.