

Safety and efficacy of fertility-regulating methods: a decade of research^{*}

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An international venture was launched in 1985 to fill a recognized gap in post-marketing surveillance of fertility-regulating methods. For this purpose a new task force was set up by the Special Programme of Research, Development, and Research Training in Human Reproduction, which is cosponsored by the United Nations Development Programme, the United Nations Population Fund, the World Bank, and WHO. Research priorities were chosen and epidemiological studies inaugurated, involving a total of 47 countries — mostly from the developing world. Important progress has been made, especially in helping to define the beneficial and possible adverse effects of oral contraceptives on the risk of neoplasia; in showing that the injectable contraceptive depot-medroxyprogesterone acetate protects against endometrial cancer and does not increase the overall risk of breast cancer; in clarifying which groups of women are susceptible to the rare cardiovascular complications of oral contraceptives (myocardial infarction, stroke, and venous thromboembolism); and in establishing the long-term effectiveness and safety of intrauterine devices. The research has already made a significant impact on family planning policies and practice. Critical appraisal of this venture, which has been modestly funded, confirms the value of mission-oriented research. It also illustrates the potential of collaboration that bridges the global divide between developing and developed countries.

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Introduction

In 1984 an international conference on population in Mexico urged governments and funding agencies to allocate increased resources for research in human reproduction and fertility regulation. One of the needs highlighted was for “epidemiological research on the short- and long-term adverse and beneficial medical effects of fertility regulating agents” (1). This led to action by the Special Programme of Research, Development, and Research Training in Human Reproduction, established by WHO and now cosponsored by the United Nations Development Programme, the United Nations Population Fund, the World Bank, and WHO. The Special Programme formed a new Task Force on the Safety and Efficacy of Fertility Regulating Methods. Research on such matters had previously been conducted by task forces concerned with specific methods (2), but it was decided to increase epidemiological and biostatistical input to evaluate the issues of safety and effectiveness that arise after a method has been approved for marketing (3).

Statements about gaps in knowledge and research strategies in population studies are often published, but there is seldom critical review of the outputs of programmes — including their successes and failures. In the decade since its research programme was launched, the new task force (renamed twice) has been responsible for the publication of over 200 scientific papers. The purpose of this review is not to document all this research, but to describe the process that was followed and the most important findings. An attempt is also made to assess the impact of the research on family planning policies and practice. It is sometimes alleged that mission-oriented research is doomed to failure, and that significant advances in knowledge nearly always result from investigator-initiated research. To what extent has this venture fulfilled its aims?

Selection of priorities

A steering committee for the new task force met for the first time in February 1985. It included 13 scientists from developing and developed countries, together with representatives of other agencies which support and conduct research in human reproduction. After reviewing published information and research in progress, the committee listed more than 100 questions about the safety or effectiveness of currently used fertility-regulating methods.

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Priority was given to research relevant to developing countries, because most previous research had been conducted in Western Europe or the USA. Other criteria for selection included the feasibility and expected cost of suitable projects, and the likelihood that these might be undertaken by other agencies. Members of the committee presented their views on which topics deserved immediate attention. Following further discussion and debate about possible projects, the committee identified nine priority areas for research, as shown in Table 1.

Table 1. **Research priorities identified in 1985**

1. Contraceptive use during lactation — effects on infant health
2. Pelvic inflammatory disease and contraception
3. Cardiovascular disease and hormonal contraception
4. Cancer and hormonal contraception
5. Interactions between contraceptive use and disease
6. Morbidity due to female sterilization
7. Morbidity due to induced abortion
8. Safety of Norplant
9. Safety and efficacy of IUDs

Implementation of research strategy

Several different approaches were used for attacking research priorities. To answer questions about hormonal contraceptives and risk of cancer, particularly in developing countries, the task force assumed responsibility for an ongoing multicentre case-control study: the WHO Collaborative Study of Neoplasia and Steroid Contraceptives (4). In other instances, pilot projects were conducted before the launching of new multicentre studies, such as the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (5). Most of these studies involved centres in both developing and developed countries, and many used the established network of collaborating centres, a feature of the Special Programme. Funding was awarded in other cases to research groups not previously associated with the Special Programme, who had opportunities to answer relevant questions. It was realized that some important issues, such as the occurrence of pelvic inflammatory disease in users of intrauterine devices (IUDs), could be elucidated by analysing existing databases from clinical trials (6).

There has been collaboration with other agencies involved in research in human reproduction. For example, a major post-marketing surveillance study of the new implantable contraceptive, Norplant, was developed and funded in collaboration with Family Health International and the Population Council. The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contra-

ception received partial funding from the US National Institutes of Health.

The research strategy has been reviewed at regular intervals and modified — either because lines of research proved not to be fruitful or because of the emergence of new problems. For example, studies were initiated following a special meeting held in 1987 to consider possible interactions between contraceptive methods and human immunodeficiency virus (HIV) infection (7). Concern about a possible link between vasectomy and prostate cancer, following publication of reports from the USA (8), led the task force to support new epidemiological studies which are still in progress.

Review of findings

Some of the main achievements of the task force will be summarized, starting with the research areas that were identified as priorities (Table 1).

- The growth and development of infants whose mothers used progestogen-only contraceptives during lactation were examined in a large cohort study in seven centres in five countries. The infants of breastfeeding women who chose progestogen-only pills, injections, or implants were compared with the infants of breastfeeding mothers who chose nonhormonal methods of contraception. The results from 2466 mother-infant pairs, involving follow-up until 1 year of age, showed no adverse effects of the progestogen-only contraceptives on infant growth or development (9, 10).
- To clarify the relationship between IUDs and pelvic inflammatory disease, data were analysed from 12 randomized controlled trials and one nonrandomized pilot study — which had all been conducted by WHO since 1975 (6). The overall incidence of pelvic inflammatory disease following 22 908 IUD insertions was only 1.6 per 1000 woman-years. The risk was mainly during the first 20 days after insertion, and was then low and constant for up to 8 years of follow-up.
- The WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was designed to assess whether modern oral contraceptives (containing lower doses of estrogens and progestogens than those originally studied), when used according to current prescribing practices, confer any increased risk of myocardial infarction, stroke, or venous thromboembolism. Another primary aim was to determine whether any risks identified in Europe were also present in developing countries. By interviewing large numbers of women, it was also hoped to define risks in subgroups, such as past users of oral contraceptives and those with other risk factors for cardiovascular disease, and to see whether risks varied with the composition of oral contraceptives. This hospital-based case-control study was

conducted in 21 centres in Africa, Asia, Europe, and Latin America.

The reports published on myocardial infarction (11), ischaemic stroke (12), haemorrhagic stroke (13), and venous thromboembolism (14) provide the most extensive data that are available about these rare complications of oral contraception. Overall estimates of relative risks were similar for the developing countries and Europe. The increased risks of myocardial infarction and stroke were mainly seen in older women who smoked, and were also greater among women with a history of hypertension or whose blood pressure had not been checked before oral contraceptive use (11–13). A new observation concerning venous thromboembolism was that the risk was higher among women using oral contraceptives containing the third-generation progestogens desogestrel or gestodene, rather than levonorgestrel (15).

- The WHO Collaborative Study of Neoplasia and Steroid Contraceptives was a hospital-based case-control study conducted in eight developing and three developed countries, with the aim of determining whether various steroid contraceptives alter the risk of cancers of the breast, uterus (corpus and cervix), ovary, and hepatobiliary system (4). The study involved interviews with nearly 10 000 women with cancer and nearly 20 000 controls. More than 50 published reports from this study have provided information about the safety of oral and injectable contraceptives, as well as about other factors influencing cancer risk such as parity, lactation, and sexual behaviour. A few key findings are mentioned here.

Combined oral contraceptives were found to have a protective effect against cancers of the ovary (16) and endometrium (17). The relative risk of breast cancer in women who had ever used oral contraceptives was close to 1.0, but there appeared to be some increase in risk among current and recent users (18). Risks of both squamous cell carcinoma (19) and adenocarcinoma (20) of the cervix were found to increase with duration of oral contraception: it was concluded that there may be a causal relationship between use of oral contraceptives and risk of cervical cancer. There was no evidence that oral contraceptives increase the risk of liver cancer (21) or cancer of the gall-bladder (22). Apart from liver cancer, the results obtained suggested that oral contraceptives have similar effects on the risk of neoplasia in developing and developed countries (4).

This study also provided the most extensive information that is available about the relationship of the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) to cancer risk in women (23). DMPA was found to have a protective effect against endometrial cancer (24), which appeared to be at least as strong as that of combined oral contraceptives. There was no evidence that DMPA altered the risks of invasive cervical cancer (25) or cancers of the ovary (26) or

liver (27). While there was some evidence of an increased risk of breast cancer in recent (or current) users of DMPA, the overall risk of this disease was not significantly increased (28, 29).

- The task force identified a number of diseases prevalent in developing countries that might be affected by contraceptive use. Priority was given to anaemia, a condition that is very common in developing countries. Contraception is believed to lower the risk of iron-deficiency anaemia by reducing the number of pregnancies and increasing the interval of time between them, but individual methods of fertility regulation may also modify iron status through effects on menstrual blood loss. This issue was examined in a study of 2507 women in seven countries, in which haemoglobin and ferritin levels were measured in groups of women using several types of contraceptive or initiating contraception (30). The results suggested that hormonal contraceptives had more beneficial effects on haemoglobin levels than did IUDs. The task force has also supported research on oral contraception in women with schistosomiasis (31), and other studies are in progress on hepatitis B, systemic lupus erythematosus, and glucose intolerance (32).
- Female sterilization is a common method of fertility regulation, but its effectiveness and risks depend on the health service setting in which the procedure is performed. The task force collaborated with the World Federation for Voluntary Surgical Contraception in evaluating a surveillance scheme for identifying preventable causes of morbidity and mortality following surgical sterilization in different settings. An alternative method of sterilization, involving blind transcervical instillation of phenol-atrabrine paste, was assessed by a follow-up study in China: the method was found to have an appreciable failure rate (33).
- To define the consequences of unsafe abortions, a protocol and questionnaire were developed for hospital-based descriptive studies of morbidity and mortality related to induced abortion (and of associated costs to the health system). The general method had been developed previously by the Special Programme (34). Studies were completed in 10 countries (47 hospitals) in Africa, Asia, and Latin America, and the results reported in individual countries (35).
- The post-marketing surveillance of Norplant, a new implantable contraceptive, was designed to detect any major short- to medium-term side-effects that might not have been discovered in clinical trials. In 32 family planning clinics in eight developing countries, about 8000 Norplant users and 8000 controls (women choosing an IUD or sterilization) were followed up for 5 years, irrespective of changes in contraceptive method. The aim of accumulating 25 000 woman-years of observation of current Norplant users was achieved, with an overall follow-up rate of about 96% (32). The study confirmed the very

high effectiveness of Norplant and provided considerable evidence of safety (36).

- Several new IUDs were assessed in randomized controlled trials. Of particular importance was the extended observation of women using two copper-bearing IUDs — TCU380A and TCU220C (37). After 12 years, the cumulative rates of pregnancy (intrauterine or ectopic) for these devices were only 2.2 and 7.6 per 100 women, respectively. Total medical removals (mostly for pain and/or bleeding) were about 6% in the first year and decreased to about 4% per year for each device up to 12 years. It was concluded that both devices are safe and effective for at least 12 years of use, with the low pregnancy rate with the TCU380A being comparable to that reported from the USA for women who had undergone sterilization (38).

Apart from the initial priority areas, completed research includes a record linkage study showing no increased risk of testicular cancer after vasectomy (39), a study providing the first evidence that DMPA protects against the development of uterine fibroids (40), and a controlled trial of the hormonal effects of oral contraceptives on well-being and sexuality (41).

Impact on family planning policies and practice

A programme of research on fertility regulation can be assessed not only by its contributions to scientific knowledge, but also — and more importantly — by the extent to which it has influenced policy and improved the choices available to individual women and men. Because the research undertaken by the task force was aimed at providing answers to unresolved questions, it is reasonable to ask what its practical impact has been.

In some cases, the main outcome of the research has been to confirm the safety of existing methods of fertility regulation. For example, the very large follow-up study of breastfed infants showed that there is no apparent reason to deny lactating women the use of progestogen-only contraceptives (9, 10). During the 1980s there was much concern about the possible influence of oral contraceptives on the risk of malignant disease, especially breast cancer. The new information provided by the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, particularly from developing countries, enabled a WHO Scientific Group to recommend that no changes to family planning policies are needed (42). The post-marketing surveillance of Norplant has provided reassurance about the safety of this new contraceptive method (36).

The descriptive studies of morbidity and mortality due to unsafe abortions were presented at national workshops at which government officials participated. The information presented may assist in advocacy for development of social and legal policies

that could reduce the burden of unsafe abortions. So far the most tangible effect of the research has been to focus attention on the need for better post-abortion care (including family planning advice) in several countries.

The research on DMPA and cancer has already led to important regulatory action. Although this injectable contraceptive was introduced in many countries from the 1960s, it was withheld in others because it had not been approved in the country responsible for its manufacture, the USA. This was mainly because experiments with beagle dogs had raised concerns that DMPA might increase the risk of breast cancer (23). In 1992 the Fertility and Maternal Health Drugs Advisory Committee of the Food and Drug Administration (FDA) examined the reassuring results from the WHO study (28), together with those from another study in New Zealand which was partially funded by the task force (43). The FDA subsequently approved the use of DMPA for contraception in the USA.

The research on IUDs also has had profound effects on policy and practice. In the 1980s, concern about the relationship between IUDs and pelvic inflammatory disease led to a major decline in use of IUDs in some countries. In the USA, where two manufacturers stopped marketing IUDs (44), use of this method declined from 2.2 million women in 1982 to 0.7 million in 1988 (45). Analysis of the extensive data from WHO clinical trials showed that, with appropriate selection of IUD users, the incidence of pelvic inflammatory disease was very low (6). Moreover, because the small risk was mainly confined to the first 20 days after insertion, it became clear that the common practice of replacing IUDs at regular intervals should be abandoned.

The continued follow-up of women in the WHO randomized controlled trials of copper-bearing IUDs established the effectiveness and safety of these devices over long periods. Their life span approved by regulatory authorities, which had earlier been only 2 years, was progressively increased. In 1994 the FDA approved a 10-year claim of efficacy and safety for the TCU380A device.

The evidence that the newer copper-bearing IUDs were more effective than older devices led to a major change in China, the world's biggest market for IUDs. The State Family Planning Commission decided to stop purchasing steel IUDs, despite their much lower production costs, and to advise factories to cease producing them from January 1993 (46). This followed a cost-benefit analysis which took account of the direct costs to individuals (or families) and to society of the unplanned pregnancies due to contraceptive failure with the stainless steel ring IUDs that were used in China. It was estimated that, if all IUDs inserted from 1993 onwards were the newer copper-bearing devices rather than stainless steel rings, the net effect over the next 10 years would be to avert 41 million pregnancies — leading to 26 million induced abortions, 1 million miscarriages or stillbirths, and 14 million live births (46).

The results of the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception also have important practical implications. The new finding that oral contraceptives containing the third-generation progestogens desogestrel or gestodene carry a higher risk of venous thromboembolism (15) has generated much controversy. Nevertheless, the observation has been confirmed in several other studies and has led to the issuing of advice by regulatory authorities in some countries (47, 48).

The findings concerning myocardial infarction (11) and stroke (12, 13) are likely to be more important from a public health perspective. These show that previous precautions about the use of combined oral contraceptives, particularly by older women who smoke, are also relevant for women using low-dose preparations — including those in developing countries. A striking feature of the results concerning both myocardial infarction and ischaemic stroke was the increased risk among women whose blood pressure had not been checked before the current episode of oral contraception. This finding will require reappraisal of existing guidelines for provision of oral contraceptives in some countries.

Relative importance of research findings

To gauge the significance of this research, an informal survey was conducted. The approach was adapted from that used by Venning to establish a list of important adverse reactions to drugs (49). A letter was sent in June 1997 to representatives of 10 key organizations concerned with family planning (excluding WHO), as well as to another 10 international experts in developed and developing countries. The letter did not disclose the specific reason for the survey, but explained that its purpose was to identify the most important advances over the last decade in knowledge derived from epidemiological studies about the risks, benefits, and efficacy of fertility-regulating methods (contraception, male or female sterilization, and abortion). The 20 experts were asked to list what they considered to be the five most important advances in knowledge in this respect, relevant to family planning policy or practice, since 1985.

Responses were received from all 20 experts and Table 2 shows the advances listed by at least four respondents. Seven of the 10 subjects selected as most important are advances in which the Task Force on the Safety and Efficacy of Fertility Regulating Methods played a major role.

In referring to the improved knowledge about the relationship between oral contraceptives and risks of cancer and cardiovascular disease, some respondents mentioned the importance of new knowledge from developing countries. This came almost entirely from the collaborative studies conducted by WHO. In the case of cardiovascular disease, the WHO study

Table 2. Important advances in knowledge about safety or efficacy of fertility-regulating methods listed by panel of experts

| Subject | No. of respondents |
|---|--------------------|
| Oral contraceptives and cancer (benefits and risks) | 11 |
| Oral contraceptives and cardiovascular disease | 11 |
| Oral contraceptives and breast cancer (limited relationship) | 8 |
| DMPA and breast cancer (limited relationship) | 8 |
| Effectiveness of condoms against HIV transmission | 7 |
| Effectiveness of female sterilization (occurrence of failure) | 6 |
| Safety and efficacy of mifepristone | 6 |
| IUDs and pelvic inflammatory disease (clarification) | 4 |
| Suitability of copper-bearing IUDs for long-term use | 4 |
| Third-generation oral contraceptives and venous thromboembolism | 4 |

also provided the most extensive data so far available worldwide. Clarification of the limited relationship between oral contraceptives and breast cancer depended on many investigations (including the WHO study), and several respondents mentioned the collaborative re-analysis of these data (50). The new information about DMPA and breast cancer, which was linked to the FDA decision by several respondents, came entirely from the WHO study and one other investigation that was partially funded by the task force. The role of the task force in clarifying the relationship between IUDs and pelvic inflammatory disease, in establishing the effectiveness and safety of copper-bearing IUDs for long-term use, and in identifying the higher risk of venous thromboembolism with third-generation oral contraceptives has already been outlined.

In addition, it may be noted that another part of the Special Programme, the Task Force on Post-ovulatory Methods for Fertility Regulation, has contributed significantly to knowledge about safe and effective regimens for emergency contraception and abortion using mifepristone (51).

Discussion

Freedom from excessive fertility has been described as the fifth freedom, after freedom of speech and worship, and freedom from want and fear (52). In order to exercise this freedom, women and their partners need access to family planning services that are effective and safe. Risks that might be accepted in treating a serious disease are not acceptable for fertility regulation by healthy, young couples. The efficacy and common short-term side-effects of contraceptives are studied initially in clinical trials of new drugs and devices. Reliable information about effectiveness in the field and about rare or delayed hazards requires epidemiological research. Despite important work on oral contraceptives, particularly in the United Kingdom, there was far too little research before the mid-1980s. Thus, a public board of inquiry

established in the USA to advise on the safety of DMPA was scathing about the dearth of adequate research (53).

The research programme reviewed here was an attempt to fill this gap. Over a period of 10 years, the initiative has produced a wealth of scientific information which has already had a significant impact on family planning policies and practice. Particularly important contributions have been the work on hormonal contraceptives and cancer, on oral contraceptives and cardiovascular disease, and on the long-term effectiveness and safety of IUDs.

The success of this venture illustrates the potential of collaborative research that spans the "global divide" between developing and developed countries (54). The research reviewed here involved the participation of scientists in 47 countries. Previous work on the safety and efficacy of fertility-regulating methods had mostly been done within single countries, with the majority of studies being conducted in the USA or the United Kingdom. For example, of 19 case-control and cohort studies of oral contraceptives and myocardial infarction cited recently (11), 17 were carried out in these two countries; the others were from Italy and Yugoslavia (1983-86). In a review on vasectomy and risk of prostate cancer (8), all the 9 relevant studies were from one country (the USA).

While international studies pose organizational challenges, they offer several advantages. First, they enable recruitment of sufficiently large numbers of subjects to provide reliable information about uncommon effects. Second, involvement of developing countries means that the results are more likely to be relevant to people living outside Europe or the USA. Third, inclusion of people from different settings may be essential if studies are to detect some important effects. This advantage is illustrated by an excellent case-control study of stroke in American women (55), which could be interpreted as showing that low-estrogen oral contraceptives do not increase the risk of stroke. A more likely explanation for the reassuring result of this study is that oral contraceptives had been used almost exclusively by young women without hypertension or diabetes. In the WHO collaborative study, the increased risk of stroke in users of low-estrogen oral contraceptives was more apparent in developing countries than in Europe, and this probably reflected the use of oral contraceptives by women with other cardiovascular risk factors (12, 13).

WHO may be in a unique position to secure such global partnership in research. But this programme also illustrates the value of mission-oriented research. The priorities chosen in 1985 proved to be research topics capable of yielding information of high practical importance. The subsequent success of the initiative probably depended on several factors. First, there was a long-term institutional commitment. Whereas many funding bodies expect projects to be completed within 3-5 years, epidemiological research often

requires a longer period. Thus the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was planned in 1985; potential collaborating centres were visited, and a protocol and questionnaire were developed for a pilot study (lasting 9-18 months) by early 1987 (5); the main phase of data collection started in 1989; and major reports were published between 1995 and 1997 (11-15).

Another contributing factor was the close supervision of studies by a steering committee of independent scientists and a secretariat with expertise in the relevant scientific disciplines. Whereas a few studies were allocated funding but essentially conducted externally, most were coordinated by the secretariat in Geneva. For the large collaborative studies of cancer and cardiovascular disease, additional coordinating centres were established in Seattle, USA, and London, England, respectively. The fact that many studies involved the same network of collaborating centres must also have enhanced the quality of research.

The involvement of collaborating centres has contributed to the building of research capacity in many developing countries. Training posts have been provided for some individuals; for example, 10 trainees from six countries worked at the coordinating centre in Seattle. The Special Programme has also made other contributions, apart from the research projects conducted. It has provided technical advice to countries and organizations, and has arranged consensus meetings on important topics such as safety requirements for contraceptive steroids (56), HIV infection and contraception (7), oral contraceptives and neoplasia (42), DMPA and cancer (23), vasectomy and cancers of the prostate and testis (57), and new techniques for female sterilization (58). Courses on reproductive health epidemiology have been organized in developing countries. Between 1985 and 1994, the total expenditure on all activities of the task force (including research funding and central costs) was only about US\$ 1.5 million per year.

Not all the initiatives taken have been successful. For various reasons, less has been achieved in research on HIV/AIDS (acquired immunodeficiency syndrome) than was hoped. Important research questions identified included the possible influence of hormonal contraceptives or IUDs on susceptibility to HIV infection, on infectiousness of HIV-infected women, and on the development and course of HIV-related illness (7). To investigate any interaction between contraceptives and HIV transmission, pilot studies were launched in Kenya, Thailand, and Zambia. Full-scale projects were delayed — partly because of logistic problems, but mainly to avoid duplicating the efforts of other agencies. In the event, an opportunity was lost because the accrual of evidence that condoms can prevent HIV transmission (and that counselling to use condoms is beneficial) made an adequate study impractical. There is now an ethical obligation to

counsel people at risk of HIV infection to use condoms consistently. Such counselling should greatly reduce the risk of HIV transmission, and the low occurrence of seroconversion will then make a study uninformative.

The task force is now studying the effects of hormonal contraceptives on the shedding of HIV in cervical and vaginal secretions and on the natural history of HIV infection (32). Other research in progress includes a case-control study on vasectomy and prostate cancer, a major study of bone density in relation to hormonal contraception, and evaluation of condom regimens. The Special Programme has also expanded its activities beyond fertility-regulating methods, to issues such as antenatal care (32).

Future research on the safety and efficacy of fertility-regulating methods should be directed not

only at the discovery of new information, but also at ways of applying existing knowledge to improve the services available to women and their partners. The experience of the last decade suggests that collaborative research involving developing and developed countries has much to offer. ■

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Résumé

Sécurité et efficacité des méthodes de régulation de la fécondité : une décennie de recherche

Une initiative internationale a été lancée en 1985 pour combler un vide reconnu dans la surveillance post-marketing des méthodes de régulation de la fécondité. Un groupe spécial a été créé à cet effet par le Programme spécial de recherche, de développement et de formation à la recherche en reproduction humaine, qui est coparrainé par le Programme des Nations Unies pour le Développement, le Fonds des Nations Unies pour la Population, la Banque mondiale et l'OMS. Des recherches prioritaires ont été choisies et des études épidémiologiques associant 47 pays, principalement des pays en développement, ont été entamées. D'importants progrès ont été accomplis, ces travaux ayant notamment aidé à définir les effets bénéfiques et les effets indésirables potentiels des contraceptifs oraux, en particulier le risque de néoplasie; montré que l'acétate

de médroxyprogestérone retard injectable protège du cancer de l'endomètre et n'augmente pas le risque général de cancer du sein; précisé les groupes de femmes qui sont sujettes aux complications cardio-vasculaires rares liées à l'usage des contraceptifs oraux (infarctus du myocarde, accident vasculaire cérébral et thromboembolie veineuse) et, enfin, établi l'efficacité et l'innocuité à long terme des dispositifs intra-utérins. Les recherches ont déjà eu un impact significatif sur la pratique de la planification familiale et les politiques dans ce domaine. L'évaluation critique de cette initiative, dont le financement a été modeste, confirme l'utilité des recherches thématiques et illustre les liens qu'une action concertée peut tisser entre pays industrialisés et pays en développement.

Resumen

Seguridad y eficacia de los métodos de regulación de la fecundidad: un decenio de investigación

En 1985 se puso en marcha un proyecto internacional para llenar un vacío evidente en la vigilancia pos-comercialización de los métodos de regulación de la fecundidad. El Programa Especial de Investigaciones, Desarrollo y Formación de Investigadores sobre Reproducción Humana, copatrocinado por el Programa de las Naciones Unidas para el Desarrollo, el Fondo de Población de las Naciones Unidas, el Banco Mundial y la OMS, estableció un nuevo grupo de estudio con ese fin. Se determinaron temas prioritarios de investigación y se iniciaron estudios epidemiológicos, que abarcaron un total de 47 países, en su mayoría del mundo en desarrollo. Se han logrado avances importantes, especialmente en lo relativo a definir los efectos beneficiosos y los posibles efectos adversos de los anticonceptivos orales en cuanto al riesgo de neoplasia; demostrar que el anticonceptivo inyectable de medroxi-

progesterona de liberación retardada protege contra el cáncer endometrial y no aumenta el riesgo general de cáncer de mama; aclarar cuáles son los grupos de mujeres más propensas a sufrir las poco frecuentes complicaciones cardiovasculares asociadas a los anticonceptivos orales (infarto de miocardio, accidente cerebrovascular y tromboembolia venosa); y establecer la eficacia y la seguridad a largo plazo de los dispositivos intrauterinos. La investigación ya ha tenido una influencia significativa en las políticas y prácticas de planificación familiar. La valoración crítica de este proyecto, que ha contado con escasa financiación, confirma el valor de las investigaciones orientadas a objetivos precisos. También ilustra el potencial de una colaboración que tiende puentes sobre la división mundial entre países en desarrollo y países desarrollados.

References

1. *Report of the International Conference on Population, Mexico City, 6–14 August 1981*. New York, United Nations, 1984 (E/CONF 76/19 UN Publication Sales No. E84.XIII.8).
2. **Diczfalusy E**. WHO Special Programme of Research, Development, and Research Training in Human Reproduction. The first fifteen years: a review. *Contraception*, 1986, **34**: 1–119.
3. **WHO Special Programme of Research, Development, and Research Training in Human Reproduction**. *Thirteenth annual report*. Geneva, World Health Organization, 1984: 69–70.
4. **Thomas DB**. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives: the influence of combined oral contraceptives on risk of neoplasms in developing and developed countries. *Contraception*, 1991, **43**: 695–710.
5. **WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. A multinational case-control study of cardiovascular disease and steroid hormone contraceptives: description and validation of methods. *Journal of clinical epidemiology*, 1995, **48**: 1513–1547.
6. **Farley TMM et al**. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet*, 1992, **339**: 785–788.
7. Acquired immunodeficiency syndrome (AIDS). Contraceptive methods and human immunodeficiency virus (HIV). *Weekly epidemiological record*, 1987, **62** (33): 244.
8. **Farley TMM et al**. The safety of vasectomy: recent concerns. *Bulletin of the World Health Organization*, 1993, **71**: 413–419.
9. **World Health Organization Task Force for Epidemiological Research on Reproductive Health**. Progestogen-only contraceptives during lactation: I. Infant growth. *Contraception*, 1994, **50**: 35–53.
10. **World Health Organization Task Force for Epidemiological Research on Reproductive Health**. Progestogen-only contraceptives during lactation: II. Infant development. *Contraception*, 1994, **50**: 55–68.
11. **WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet*, 1997, **349**: 1202–1209.
12. **WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*, 1996, **348**: 498–505.
13. **WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet*, 1996, **348**: 505–510.
14. **World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet*, 1995, **346**: 1575–1582.
15. **World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception**. Effect of different progestogens in low oestrogen oral contraceptives on venous thromboembolic disease. *Lancet*, 1995, **346**: 1582–1588.
16. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Epithelial ovarian cancer and combined oral contraceptives. *International journal of epidemiology*, 1989, **18**: 538–545.
17. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Endometrial cancer and combined oral contraceptives. *International journal of epidemiology*, 1988, **17**: 263–269.
18. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Breast cancer and combined oral contraceptives: results from a multinational study. *British journal of cancer*, 1990, **61**: 110–119.
19. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Invasive squamous-cell cervical carcinoma and combined oral contraceptives: results from a multinational study. *International journal of cancer*, 1993, **55**: 228–236.
20. **Thomas DB, Ray RM, and the WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Oral contraceptives and invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. *American journal of epidemiology*, 1996, **144**: 281–289.
21. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Combined oral contraceptives and liver cancer. *International journal of cancer*, 1989, **43**: 254–259.
22. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Combined oral contraceptives and gallbladder cancer. *International journal of epidemiology*, 1989, **18**: 309–314.
23. Depot-medroxyprogesterone acetate (DMPA) and cancer. Memorandum from a WHO meeting. *Bulletin of the World Health Organization*, 1993, **71**: 669–676.
24. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. *International journal of cancer*, 1991, **49**: 186–190.
25. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. *Contraception*, 1992, **45**: 299–312.
26. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. *International journal of cancer*, 1991, **49**: 191–195.
27. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Depot-medroxyprogesterone acetate (DMPA) and risk of liver cancer. *International journal of cancer*, 1991, **49**: 182–185.
28. **WHO Collaborative Study of Neoplasia and Steroid Contraceptives**. Breast cancer and depot-medroxyprogesterone acetate: a multinational study. *Lancet*, 1991, **338**: 833–838.
29. **Skegg DCG et al**. Depot-medroxyprogesterone acetate and breast cancer. A pooled analysis of the World Health Organization and New Zealand studies. *Journal of the American Medical Association*, 1995, **273**: 799–804.
30. **Task Force for Epidemiological Research on Reproductive Health**. Effects of contraceptives on hemoglobin and ferritin. *Contraception*, 1998, **58**: 261–273.
31. **Sy FS et al**. Effect of oral contraceptives on liver function tests of women with schistosomiasis in the Philippines. *Contraception*, 1986, **34**: 283–294.
32. **Meirik O, Rowe PJ, Villar J**. Surveillance and evaluation. In: Van Look PFA, ed. *HRP annual technical report 1996*. Geneva, World Health Organization, 1997: 125–160.
33. **Kang XP et al**. Effectiveness of phenol–atrabrine paste (PAP) instillation for female sterilization. *International journal of gynecology and obstetrics*, 1990, **33**: 49–57.
34. **Figa-Talamanca I et al**. Illegal abortion: an attempt to assess its cost to the health services and its incidence in the community. *International journal of health services*, 1986, **16**: 375–389.
35. **Begum SF et al**. *Hospital-based descriptive study of illegally induced abortion-related mortality and morbidity, and its cost on health services*. Dhaka, Bangladesh Association for Prevention of Septic Abortion (BAPSA), 1991.
36. **Fraser IS et al**. Norplant consensus statement and background review. *Contraception*, 1998, **57**: 1–9.
37. **UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction**. Long-term reversible contraception: twelve years of experience with the TCu380A and TCu220C. *Contraception*, 1997, **56**: 341–352.

38. **Peterson HB et al.** The risk of pregnancy after tubal sterilization: findings from the US Collaborative Review of Sterilization. *American journal of obstetrics and gynecology*, 1996, **174**: 1161–1170.
39. **Moller H, Knudsen LB, Lyng E.** Risk of testicular cancer after vasectomy: cohort study of over 73,000 men. *British medical journal*, 1994, **309**: 295–299.
40. **Lumbiganon P et al.** Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. *British journal of obstetrics and gynaecology*, 1996, **103**: 909–914.
41. **Graham CA et al.** The effects of steroidal contraceptives on the well-being and sexuality of women: a double-blind, placebo-controlled, two-centre study of combined and progestogen-only methods. *Contraception*, 1995, **52**: 363–369.
42. *Oral contraceptives and neoplasia. Report of a WHO Scientific Group.* Geneva, World Health Organization, 1992 (WHO Technical Report Series, No. 817).
43. **Paul C, Skegg DCG, Spears GFS.** Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. *British medical journal*, 1989, **299**: 759–762.
44. **Forrest JD.** The end of IUD marketing in the United States: what does it mean for American women? *Family planning perspectives*, 1986, **18**: 52–57.
45. **Mosher WD, Pratt WF.** Use of contraception and family planning services in the United States, 1988. *American journal of public health*, 1990, **80**: 1132–1133.
46. **Ping LY et al.** The demographic impact of conversion from steel to copper IUDs in China. *International family planning perspectives*, 1994, **20**: 124–130.
47. **Skegg DCG.** Oral contraceptives and venous thromboembolic disease. *WHO drug information*, 1997, **11**: 53–56.
48. **Walker AM.** Newer oral contraceptives and the risk of venous thromboembolism. *Contraception*, 1998, **57**: 169–181.
49. **Venning GR.** Identification of adverse reactions to new drugs. I: What have been the important adverse reactions since thalidomide? *British medical journal*, 1983, **286**: 199–202.
50. **Collaborative Group on Hormonal Factors in Breast Cancer.** Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*, 1996, **347**: 1713–1727.
51. **Van Look PFA, von Hertzen H.** Clinical uses of antiprogestins. *Human reproduction update*, 1995, **1**: 19–34.
52. **Baird D.** A fifth freedom? *British medical journal*, 1965, **2**: 1141–1148.
53. **Weisz J, Ross GT, Stolley PD.** *Report of the Public Board of Inquiry on Depo-Provera.* Rockville, Food and Drug Administration, 1984.
54. **Mari JJ, Lozano JM, Duley L.** Erasing the global divide in health research. *British medical journal*, 1997, **314**: 390.
55. **Petitti DB et al.** Stroke in users of low-dose oral contraceptives. *New England journal of medicine*, 1996, **335**: 8–15.
56. **Michal F, ed.** *Safety requirements for contraceptive steroids.* Cambridge, Cambridge University Press, 1989.
57. **Skegg DCG.** Vasectomy and risk of cancers of prostate and testis. *European journal of cancer*, 1993, **29A**: 935–936.
58. **Wilson EW, ed.** WHO consultation on the development of new technologies for female sterilization. *International journal of gynecology and obstetrics*, 1995, **51** (Suppl No. 1): S1–S77.