

World Bank Special Programme of Research, Development and Research Training in Human Reproduction: Programme's priorities for development of new fertility regulation technologies. Progress in human reproductive research. 1997. No. 44. P. 1-7.

Programme's priorities for development of new fertility regulation technologies.

World Bank Special Programme

(1) Program's Priorities for Development of New Fertility Regulation Technologies

The currently available methods of fertility regulation do not meet all the varied needs of women and men in differing geographical, cultural and religious settings and at different times of their reproductive lives. Moreover, many people continue to have concerns about the safety and efficacy of current methods. This is illustrated by the fact that more than 10% of users of all methods stop using them within 12 months because of health concerns or method/user failure (see [figure](#)). Thus, there remains an urgent need to improve existing methods and to develop new ones.

Since its inception the Program has conducted and supported research to improve existing methods-in order to make them safer, more effective and more acceptable-and to develop new fertility regulation technologies to fulfil expressed needs that are as yet unmet.

Because the number and cost of potential projects for technology development have grown considerably over the years, and since financial resources and personnel remain limited, the Program took steps to re-prioritize its work in this area. In December 1995, the Program convened a meeting of biomedical and social scientists, drug development experts, health care planners and women's health advocates to review its technology development activities. This group ranked the activities as high, medium or low priority according to four criteria: (1) user needs and preferences; (2) feasibility of development into a product; (3) feasibility of service delivery; and (4) commercial interest and potential

Percentage of users discontinuing a fertility regulation method within 12 months because of method/user failure or health concerns (including side-effects)

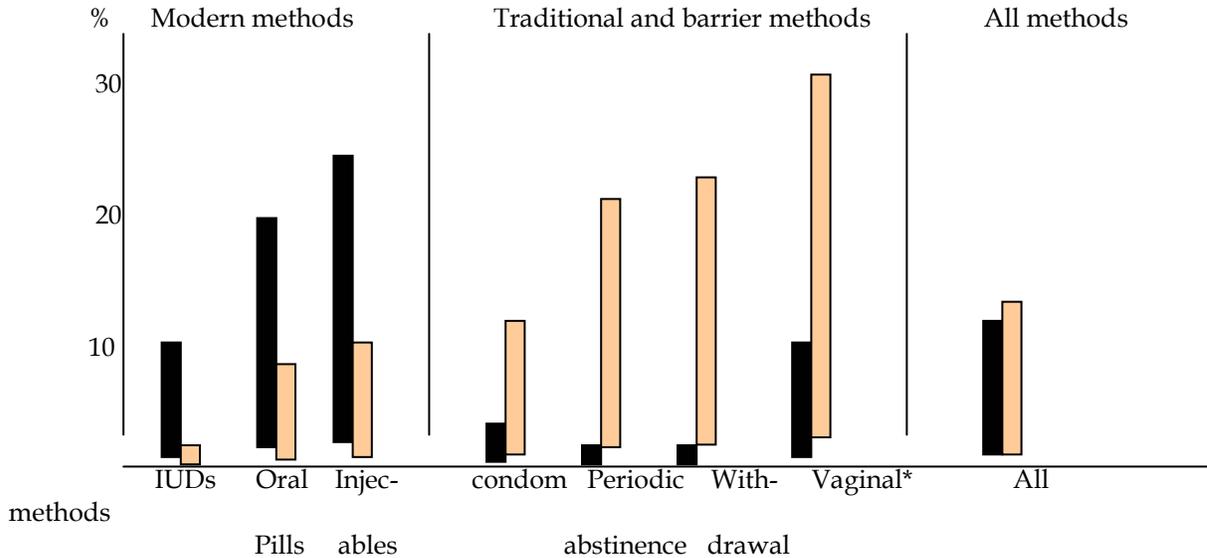


Figure adapted from: Shan IH, Perspectives on methods of fertility regulation: setting a research agenda (forthcoming).

* Diaphragm, cervical cap, spermicides, etc.

As a result of this process, nine potential fertility regulation products were classified as high priority. Those for women included: use of the antiprogesterone mifepristone as a daily or weekly contraceptive pill; a three monthly progesterone-only injectable; a 6- or 12-monthly injectable immunocontraceptive; emergency contraception using only an antiprogesterone or only a progesterone; and an antiprogesterone and prostaglandin combination for the termination of early pregnancy. Two potential technologies for men classed as high priority were a combination of progesterone and androgen for suppressing reversibly the production of sperm, and a simple method of blocking the vas with silicone plugs. Four additional potential technologies for fertility regulation were classed as medium priority and five were assigned low-priority.

In November 1997, the Scientific Review Committee for Technology Development and Assessment reviewed the current research portfolio again. During the intervening two years, work was either completed or terminated (owing to unfavorable results) on several potential products, including on the use of mifepristone as a daily or weekly pill. This issue of Progress looks at the

Program's current work in the development of new products. It describes the high priority technologies that are under development, explains why they are needed, what research has been undertaken, and the likely implications for service delivery of the new technologies. Also included in this issue is an article that summarizes the findings of a survey of readers of Progress. A big thank you to all those who responded to the questionnaire.

High-Priority Leads for Development of New Methods of Fertility Regulation

(2) Antiprogestogen-only Emergency Contraception (mifepristone)

Rationale

Large numbers of unwanted pregnancies and abortions could be avoided by the use of emergency contraception. The current standard method, known as the Yuzpe regimen, [1] fails to prevent about one-quarter of pregnancies, however, and can have unpleasant side-effects. Insertion of an intrauterine device (IUD) is more effective but is not suitable for young nulliparous women and/or when there is a risk of pelvic infection. The Program has been in the forefront of research on antiprogestogens and is also the only international body that has pursued the clinical development of new drug regimens for emergency contraception.

Research

Research on the use of mifepristone in emergency contraception began in 1989 after it was noted that if administered before ovulation the compound blocks ovulation, and that if given shortly after ovulation it retards endometrial development. Two studies supported by the Program showed that 600 mg of mifepristone was more effective than the Yuzpe regimen and caused less nausea and vomiting. Mifepristone would be easier to administer than the Yuzpe regimen in that the former involves only one dose rather than two. However, in view of the sensitivity regarding antiprogestogens, the use of mifepristone was considered to be an advantage only if a very low dose, insufficient to induce abortion, proved to be useful in emergency contraception.

A single-blind randomized trial was carried out in 11 centers to identify the optimal dose of mifepristone for emergency contraception. The study involved 1717 women given 600 mg, 50 mg or 10 mg of mifepristone postcoitally. The results confirmed that mifepristone was effective in emergency contraception

(apparently equally in all three dose groups), pre-venting 85-90% of the pregnancies that would have occurred.

Time Frame

The Program plans to start a multicenter study to compare the efficacy and side-effects of 10 mg of mifepristone with two regimens of levonorgestrel (see Progestogen-only emergency contraception below). This is expected to continue through 1998-1999.

Implications for Service Delivery

Emergency contraception has been called the best-kept secret of family planning. Few women know about it. Thus the greatest challenge with regard to this method lies in informing women about the options available to them for emergency contraception.

With the Yuzpe regimen upto 50% of women taking the treatment experience nausea and 20% experience vomiting. Mifepristone, given as a single dose, promises to be more effective in preventing pregnancy than the Yuzpe regimen and has been shown not to cause any unpleasant side-effects. A single-dose method with greater efficacy and fewer sideeffects would mean less need for clinical interventions by service providers.

(3) Progestogen-only Emergencycon-Traception (Levonorgestrel)

Rationale

As in the case of the previous priority area, there is a need for effective back-up methods to prevent unwanted pregnancy after unprotected intercourse or if a contraceptive method fails. The Program's aim is to identify effective agents for emergency contraception that have fewer side-effects than current methods.

Research

A study in Hong Kong, supported by the Program, suggested that levonorgestrel (when given in two doses of 0.75 mg with a 12-hour interval starting with in 48 hours of unprotected intercourse) was as effective as the Yuzpe regimen but that it had fewer side-effect. Consequently, a double blind, randomized study began in 1995 in 21 centers in 14 countries to compare levonorgestrel (with the same dose regimen as the Hong Kong study but started within 72 hours of unprotected intercourse) with the Yuzpe regimen in emergency contraception. This study is expected to produce data on some 2000 subjects.

Although research has proved that the Yuzpe regimen, mifepristone, and levonorgestrel are effective in emergency contraception, their exact mechanisms of action are not well understood. It is important to clarify the mechanism of action so that woman can decide if the method is acceptable to them. A study is under way to examine how each of the methods acts on the body to prevent pregnancy.

Time Frame

The Yuzpe regimen involves two doses with a 12-hour interval in-between. This means that if a client seeks treatment in the afternoon she has to take the second dose in the middle of the night. A single-dose treatment would make compliance easier. A study is planned to begin in early 1998 to find out if levonorgestrel can be given in a single dose of 1.5 mg for emergency contraception. This double-blind study will compare the efficacy and side-effects of a single dose of levonorgestrel with the efficacy and side-effects of a single dose (10 mg) of mifepristone.

A study is currently under way in 20 centers in China to assess the effectiveness, acceptability and side-effects of IUD insertion for emergency contraception. Another study that will begin soon and will last until at least 1999 is an investigation of the efficacy and side-effects of gestrinone (a registered product used in over 40 countries for the treatment of endometriosis and which has some antiprogestogenic activity). In this study, gestrinone will be compared with mifepristone.

Implications for Service Delivery

Emergency contraception with levonorgestrel has the advantage that it involves a drug with which there is more than 30 years' clinical experience: levonorgestrel

is the most commonly used progestogen in oral contraceptive pills. Levonorgestrel is also relatively inexpensive, which will be an advantage for both users and health services, particularly in developing countries. Moreover, this method promises to be more effective than the Yuzpe regimen, and it will also have fewer side-effects.

(4) Non-Surgical Abortion Regimen (Mifepristone Plus Misoprostol)

Rationale

A non-surgical means of terminating early pregnancy would have several advantages over surgically induced abortion. It would, for instance, require fewer medical and other resources and would therefore be of significant benefit to countries with limited trained manpower. A non-surgical method also seems to be more attractive to many women than surgery.

Emergency contraception with levonorgestrel has the advantage that it involves a drug with which there is more than 30 years 'clinical experience: levonorgestrel is the most commonly used progestogen in oral contraceptive pills.

Good, but good enough?

The current modern methods of fertility regulation are highly effective and safe. However, as the figure shows, many users continue to have concerns about these methods. Hence, there is an urgent need to improve existing methods and develop new ones. The Program conducts and supports biomedical and social science research on technologies and methods relating to fertility regulation in both women and men.

One injection of 5-10 mg of levonorgestrel butanoate will provide contraceptive protection for three months, imposing a lower burden of synthetic steroid on the body than DMPA does.

The Program was the first to show that the combination of mifepristone plus a prostaglandin is more effective than mifepristone alone of the termination of early pregnancy. This regimen is now registered in four countries (China, France, Sweden and the United Kingdom) for pregnancy termination.

Research conducted by the Program has also established that a single dose of 200 mg of mifepristone, in combination with a prostaglandin analogue (gemeprost), seems to be the minimum effective single dose. This dose is as effective as 600 mg of mifepristone with the same prostaglandin analogue in the termination of early pregnancy of up to 63 days of amenorrhoea. If the dose is lowered further, to 50 mg, efficacy declines to about 85%-a level that most service providers will regard as clinically unacceptable.

One problem with this regimen is that gemeprost is expensive and not widely available and cannot be stored at room temperature. On the other hand, the prostaglandin misoprostol is relatively inexpensive and widely available (including in developing countries). It has a good and well documented safety record and it can be stored at room temperature. Moreover, it is orally active. Hence, keeping in mind the needs of developing countries in particular, the Program has been conducting research to develop a combination regimen using mifepristone and misoprostol.

Research

A randomized, double-blind multicenter trial was started in 1993 to compare the effectiveness of 200 mg and 600 mg of mifepristone followed by 0.4 mg of misoprostol. However, this dose of oral misoprostol was not sufficiently effective in more advanced pregnancies (50-63 days of amenorrhoea). Since a further increase in mifepristone dosage will not improve efficacy, the prostaglandin dose appears to be critical. The Program is continuing to study misoprostol to try and find a combined regimen that is effective up to 63 days of amenorrhoea. Some research suggested that misoprostol may be more effective if given vaginally so the Program has carried out a study on the pharmacokinetics of the compound after vaginal administration. This study also examined how the compound affects uterine contractility after both oral and vaginal administration. As yet unpublished results suggest that the compound is more effective when administered vaginally as it produces more regular and longer-lasting contractions.

Acceptability of medically induced abortion is likely to be improved if a way could be found to reduce the amount (and duration) of blood loss that follows it. Consequently, in collaboration with researchers in Hong Kong and Shanghai, China, the Program has initiated a study to find out whether starting use of the oral contraceptive pill immediately after abortion would help achieve this control. The pilot study will have 200 subjects.

Time Frame

Since 1994 the combination of mifepristone and misoprostol has been used more and more in the four countries where mifepristone is registered. Research being conducted by the Program is expected to establish within the next two years the optimum dose and the best route for administration of misoprostol that is effective up to 63 days of amenorrhoea.

Implications for Service Delivery

Medical abortion with mifepristone plus misoprostol would be simpler to carry out than surgical abortion and would require surgical facilities and personnel trained in surgical abortion only as back-up. Although the method would not need to be administered by a person with training in surgery, it would nevertheless need to take place in a health center for appropriate follow-up and adequate management of occasional complications such as heavy bleeding associated with this method.

(5) A Three-monthly Injectable (Levonorgestrel Butanoate)

Rationale

Around 15 million women worldwide use injectable contraceptives, and of these some 12 million use depot-medroxyprogesterone acetate (DMPA). DMPA is a very effective contraceptive but there is a high rate of amenorrhoea among women who use it and the return to fertility after stopping use can be slow. In consequence, the Program has encouraged research into alternative injectable preparations that might offer improvements.

Research

More than 230 compounds were tested as potential injectable contraceptives in collaboration with the Contraceptive Development Branch of the US National Institute of Child Health and Human Development (NICHD). One compound--levonorgestrel butanoate--was chosen for further development. So far, research has shown that one injection of 5-10 mg of this compound would give

contraceptive protection for three months. It would also impose a lower burden of synthetic steroid: on the body than DMPA does and would therefore have the potential benefits of less ovarian suppression, less amenorrhoea and a quicker return to fertility upon discontinuing use.

Research has determined the optimal size for levonorgestrel butanoate particles. Other studies showed that this is a chemically stable compound but that if it is stored for a long time the particles tend to aggregate and stick to the glass of the ampoule, making it difficult to resuspend. More recent research suggests that modifications to the manufacturing process and use of prefilled syringes rather than glass ampoules may solve the problem. Studies also suggest that it may be possible to formulate the compound such that it gives contraceptive protection for as long as six months.

Time frame

Further stability testing and investigation of various manufacturing processes and storage methods is under way and will continue throughout 1998. Once an acceptable formulation has been reached, clinical testing will resume again, probably in 1999. Research will be undertaken to confirm the dose needed, and a multicenter study will compare levonorgestrel butanoate with DMPA.

Implications for Service Delivery

The popularity of injectable contraceptives is on the rise in a number of countries in Africa, Asia, and Latin America. A new injectable with the same duration of effect as DMPA, but with lower risk of side-effects, is likely to boost this rise in popularity further. Since levonorgestrel butanoate can be synthesized easily, the cost of producing large quantities is expected to be low. Moreover, since WHO, together with NICHD, has generated a considerable amount of scientific data about the product which would be of value to a future commercial partner, it should be possible to negotiate a favorable public sector price for it.

(6) A 6/12-monthly Injectable (hCG Immunocontraceptive)

Rationale

Many women, in particular those who have achieved their desired family size, want an inexpensive, hassle-free, long-acting method of fertility regulation. The current long-acting methods—the IUD, injectables, and sterilization—are not suitable for all women for a variety of reasons. For example, IUDs cause bleeding problems in some women, most hormonal methods are not recommended for older women or those with cardiovascular risk factors, and sterilization is difficult to reverse. Immunocontraceptives promise to be long-acting, without side-effects associated with hormonal methods, easy to administer, and non-permanent. Hence, the Program is developing an anti-human chorionic gonadotrophin (hCG) immunocontraceptive as a long-acting (six or 12 months) injectable contraceptive.

Research

Exploratory research in this area has been supported by the Program for more than two decades. The December 1995 meeting that determined priorities affirmed the importance of the prototype anti-hCG immunocontraceptive. It also agreed that work should concentrate first on a short-acting multi-injection formulation (which uses the existing emulsion delivery system). Once this is completed, work could then start on the longer acting single-injection formulation (which involves the use of biocompatible and biodegradable microspheres). Consequently, most recent work has concentrated on the emulsion formulation. Previously all emulsion formulations for the anti-hCG immunocontraceptive were prepared by hand just prior to injection, but now machine-prepared, emulsions are available and have been shown to be more stable and more consistent than those made by hand. Research is investigating various combinations of the components of the hCG immunocontraceptive and formulations prepared manually and by machine to find out which gives the best response. Preliminary data have also been obtained from research on experimental batches of microsphere formulation for the single-injection hCG immunocontraceptive.

Immunocontraceptives promise to be long-acting, hasslefree, without side-effects associated with hormonal methods, easy to administer, and non-permanent.

Clinical trials on the anti-hCG immunocontraceptive are expected to start in 1998. A further 5-7 years will be needed for clinical testing before the multi-injection method becomes generally available.

Time Frame

Preclinical studies, followed by Phase I and Phase II clinical trials on the reformulated anti-hCG immunocontraceptive, are expected to start in 1998 and it is estimated that a further 5-7 years will be needed for clinical testing and improvement of the product before the multi-injection method becomes generally available. It will take slightly longer before the single injection method is available.

Implications for Users and for Service Delivery

When available, the anti-hCG immunocontraceptive will fall into the category of long-acting injectable methods. If it lives up to its promise, there would be few, if any, medical contraindications for its use. Thus, most women would be able to use it. It would be easy to make the method widely available through reproductive health services since it would be delivered in much the same way as other injectables are provided: services in many developing countries have considerable experience of providing injectables widely. Health providers will not require any specialized clinical training in the administration of the method.

It is likely that the duration of action of the method will vary slightly among individuals, necessitating periodic testing for the level of antibodies. Scientists plan to overcome this problem by developing a simple saliva test that women will be able to use at home. If a woman finds that her antibody level is falling, and if she wishes to continue with the method, she would be able to get a "booster shot" to restore the anti fertility effect for a further predetermined period. Alternatively, a fixed period of protection may be proposed based on results in clinical trials.

One aspect of this method will, however, require special attention on the part of service providers. Since the contraceptive protection offered by the hCG immunocontraceptive will be longer-lasting than the current injectables, users will need counseling to ensure that they understand fully the implications of using a long acting method that is not reversible before the end of its expected duration of action.

(7) A Three-Monthly Injectable for Men (Levonorgestrel Butanoate Plus Testosterone Buciate)

Rationale

At present there are no systemic contraceptive methods available for men although male steroid hormone methods have been the subject of research for several decades. Feasibility studies in animals and men show that gonadotrophin secretion and spermatogenesis can be suppressed either completely or to a sufficiently low level to render the male infertile by the administration of androgens alone, combinations of androgens and gonadotrophin-releasing hormone antagonists, and progestogen and androgen combinations. In addition, discontinuing the treatment leads to full recovery of gonadotrophin secretion and spermatogenesis and the return of fertility.

Two recent multicenter trials investigating the efficacy of an androgen ester (testosterone enantate, or TE) found a high level of acceptability for the method among both the recipients and their partners, despite the fact that weekly injections were needed. Many of the men who took part in the trials indicated that a longer-acting preparation, such as testosterone buciclate (TB), would be a more attractive option.

Research

Clinical trials supported by the Program show that a single dose of 600 mg of TB is able to maintain serum testosterone levels within the normal range for 100 days in hypogonadal men. Some preliminary data have also been obtained, in a small number of normal men, on the ability of TB to suppress gonadotrophin levels and reduce spermatogenesis.

Recent progress has been hampered by the lack of TB formulations of appropriate quality for clinical trials. Formulation studies are under way to develop a more stable preparation.

Time Frame

It is expected that a clinically acceptable formulation of TB will be available during 1998. The newly formulated compound will then be evaluated in stability, toxicity and dose-finding studies. At the same time, multicenter studies in China, India and Indonesia will assess the potential of several hormonal regimens for male contraception. Studies of acceptability and of mood and behavior changes

of men taking part in trials of this kind are underway. A Phase I trial to investigate the rate and degree of suppression of spermatogenesis caused by a combination of levonorgestrel butanoate and TB will be carried out in 1999 and will be followed by an efficacy study that is expected to begin in 2000.

Implications for Service Delivery

A safe and reversible systemic method of contraception for men would be a valuable addition to the range of methods that can be offered to users. Research shows that both men and their partners are favorably inclined to this kind method.

1. The Yuzpe regimen uses four tablets each containing 50 m g ethinyl estradiol and 0.25 mg of levonorgestrel (or 0.50 mg of dlnorgestrel). Two tablets are given twice with an interval of 12 hours. The treatment should begin within 72 hours of unprotected intercourse.

*UNDP/UNFPA/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP)

Launched by the World Health Organization in 1972, the UNDP/UNFPA/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction is a global Program of technical cooperation. It promotes, coordinates, supports, conducts, and evaluates research on human reproduction, with particular reference to the needs of developing countries.

**** Progress in Human Reproduction Research**

Issued quarterly by the UNDP/UNFPA/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland. For a free subscription, please write to the above address.

*** **Editor: Jitendra Khanna**

This newsletter is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or for use in conjunction with commercial purposes.