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study. The Programme will, therefore, launch by mid-1997 a study involving 20 Chinese centres which will be asked to recruit a total of 2000 women. This study will also observe the continuation rate at one year of use.

4. Impact of emergency contraception on abortion rates

The use of effective emergency contraception is likely to reduce the number of unwanted pregnancies and abortions. However, research is needed to collect evidence as to whether the introduction of emergency contraception really does influence abortion rates. This may not be an easy task as many factors play a role and have an effect on the results: desired family size and birth rates may differ from year to year, patterns of contraceptive use may change, immigration and emigration may complicate the situation, etc. The Programme is investigating possibilities of carrying out a study in China to see what impact the introduction of emergency contraception could have on abortion rates. The project will be a collaborative study of the Research Group on Post-ovulatory Methods of Fertility Regulation and the Programme's Strategic Component on Surveillance and Evaluation.

During 1998–1999

It is anticipated that all of the abovementioned studies that are proposed to start in 1997 will continue through part or all of the 1998–1999 biennium.

NON-SURGICAL ABORTION REGIMEN (MIFEPRISTONE PLUS MISOPROSTOL)

Rationale for the product

A non-surgical method of inducing early abortion would have a number of advantages over surgical alternatives. In addition, fewer personnel are required to provide medical abortion services safely and effectively than surgical abortion, an important aspect in those countries with limited trained manpower. Furthermore, a non-surgical method of early pregnancy termination represents an alternative option that appears to be more acceptable to many women than a surgical approach. For a number of reasons, WHO is the only international organization that has been able to pursue consistently the development of new approaches to the termination of pregnancy, including the non-surgical regimens based on mifepristone described here.

Current stage of development and assessment

The Programme has been involved with the clinical testing of mifepristone for early pregnancy termination since 1983 and its research effort in this area has grown steadily since then. The combination regimen of mifepristone and a prostaglandin was first tested by the Programme and is now being used clinically for early pregnancy termination in China, France, Sweden and the United Kingdom.

Clinical research carried out during the last 10 years by the Programme using the combination of mifepristone plus a prostaglandin analogue has provided information on the lowest effective dose of the antiprogestogen. A number of questions still remain to be answered concerning the prostaglandin component of this combination regimen. Also still to be resolved are questions relating to the maximum stage of gestation for which this combination regimen remains safe and effective, and on how to decrease the duration of bleeding, which is often rather long, after this method of abortion. It is expected that answers to these remaining questions will be obtained in the next few years.

The majority of the research carried out in the area of medical termination of pregnancy has been directed at the development of a combination regimen of mifepristone and a prostaglandin as an effective alternative to surgical intervention for the termination of early, first trimester pregnancy. The research supported by the Programme in this area has focused on four issues: (i) the minimum effective dose of mifepristone; (ii) the most appropriate dose and type of prostaglandin; (iii) the maximum duration of pregnancy for which the treatment remains effective and safe; and (iv) the acceptability to users and the service facilities that should be available to women choosing this non-invasive method of abortion.

The minimum effective dose of mifepristone

In the three European countries where mifepristone has been registered, France, Sweden and the United Kingdom, the recommended regimen consists of a single oral dose of 600 mg of mifepristone followed, 36–48 hours later, by a suitable prostaglandin preparation. In France this regimen is used in pregnancies of up to 49 days of amenorrhoea, while in Sweden and the United Kingdom this time limit is extended up to 63 days.

Previous studies have shown that the pharmacokinetics of mifepristone are non-linear and that oral administration of the drug in single doses greater than 100 mg results in serum concentrations that differ only minimally or not at all (see *Annual technical report 1991* for references; Puri and Van Look, *Frontiers of hormone research*, 1991, 19:127–167). It was assumed, therefore, that efficacy rates comparable to those seen after a single dose of 600 mg of mifepristone could be obtained using smaller doses.

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Multicentre trials conducted by the Programme have confirmed this assumption and have demonstrated that the effectiveness of the 600-mg dose of mifepristone can be achieved also by treatment with either repeated small doses of mifepristone (five doses of 25 mg given at 12-hour intervals followed by intramuscular injection of the prostaglandin, sulprostone; World Health Organization, *Fertility and sterility*, 1991, **56**:32–40) or by a single dose of 200 mg of mifepristone followed by a suitable prostaglandin, e.g. vaginal suppository of 1 mg of the prostaglandin gemeprost (World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation, *British medical journal*, 1993, **307**:532–537). These findings have already had an impact on clinical practice. For example, China now produces mifepristone tablets containing 25 mg and the repeated dose regimen (6 25 mg) has become the standard regimen in that country (Sang *et al.*, *Contraception*, 1994, **50**:501–510).

In order to determine if the doses of mifepristone and/or gemeprost could be reduced even further, the Programme carried out a randomized multicentre trial in which women with amenorrhoea of less than 56 days were allocated randomly to treatment with 200 mg or 50 mg of the antiprogestogen plus either a whole suppository (1 mg) or half a suppository (0.5 mg) of gemeprost. The complete abortion rate showed a downward trend from 93% in the group receiving the higher doses of mifepristone (200 mg) and of gemeprost (1 mg) to 86% in the group treated with 50 mg of mifepristone and 0.5 mg of gemeprost. The complete abortion rate in women receiving the 50 mg mifepristone dose plus either 0.5 mg or 1 mg gemeprost was significantly ($p<0.01$) lower than the rate in women who were given 200-mg dose of mifepristone. From these results it was concluded that a single dose of 200 mg of mifepristone, in combination with vaginal gemeprost, appears to be close to the minimum effective dose for this particular combination regimen (WHO Research Group on Post-ovulatory Methods for Fertility Regulation; manuscript in preparation).

The most appropriate dose and type of prostaglandin

In the dose-finding studies described above, the Programme has demonstrated that the mifepristone dose can be reduced from 600 mg to the 200 mg and the vaginal gemeprost dose from 1 mg to 0.5 mg without a reduction in the effectiveness of these early abortion treatment regimens. At the 200 mg mifepristone dose level, it was shown that the efficacy of 0.5 mg gemeprost was the same as that of the 1-mg dose (91.6% versus 92.8%, respectively) in pregnancies of up to 56 days of amenorrhoea. As gemeprost is rather expensive, the use of the lower dose will reduce the cost of this regimen. In addition to being expensive, gemeprost is unstable and requires to be stored in a refrigerator. The Programme has been therefore searching for a prostaglandin derivative that is cheap, stable under ambient conditions and, preferably, orally active, as it would be better suited for use in developing countries.

The oral prostaglandin, misoprostol, registered for the prevention and treatment of gastric ulcer in over 60 countries, seemed to fulfil these criteria. It also appeared to be effective for the termination of early pregnancies (up to 49 days of amenorrhoea) in the combination regimen with mifepristone (Aubény and Baulieu, *Comptes rendus de l'Académie des Sciences Paris*, 1991, **312**:539–545; Norman *et al.*, *The lancet*, 1991, 338:1233–1236). Thus, it seemed likely that misoprostol would become the prostaglandin of choice for use in the combination regimen with mifepristone. However, a trial carried out at the WHO Collaborating Centre in Edinburgh (United Kingdom) strongly suggested that oral misoprostol might be less effective than vaginal gemeprost in more advanced pregnancies (amenorrhoea of eight to nine weeks) (McKinley *et al.*, *Human reproduction*, 1993, **8**:1502–1505). The dose of mifepristone used in the last study was 200 mg and it seemed important, therefore, to examine whether this low dose might have been responsible for the observed decline in the complete abortion rate in more advanced pregnancies.

Consequently, a randomized, double-blind multicentre trial was initiated in late 1993 to compare the efficacy of 200 mg and 600 mg of mifepristone followed by 0.4 mg of misoprostol. It was intended that a total of 2000 women with a menstrual delay of up to 35 days would be recruited to this study. Interim analysis carried out in 1994, when a total of 605 women had completed the study, showed complete abortion rates in the 200 mg and 600 mg mifepristone groups of only 77% (95% C.I.: 60%–90%) and 77% (95% C.I.: 61%–88%), respectively, in women with menstrual delay of 29–35 days. In accordance with the discontinuation criteria of the trial protocol, recruitment of women for this group was stopped and the trial continued with volunteers who had a menstrual delay of 28 days or less. The clinical phase of this study was completed by the end of 1995.

The results were analysed in 1996, by which time a total of 1589 subjects had been recruited in the 17 centres. The complete abortion rate was highest (91.5%) in the group with the shortest menstrual delay (up to 14 days) and lowest (84–86%) in the group with a menstrual delay of 15–28 days. There was no difference in the complete abortion rates between the two doses of mifepristone. There was, however, a trend of decreasing efficacy with the length of menstrual delay in both groups, which was highly significant ($p<0.01$) for the groups combined and within groups. Further, there was a rising trend in the rate of continuing live pregnancies, being as high as 8.4% when the menstrual delay was between 4–5 weeks in both the groups.

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The insufficient efficacy of misoprostol in the more advanced pregnancies in this study was disappointing. It was felt, therefore, that the Programme should continue studying this prostaglandin to identify an effective regimen which could be used up to 63 days of amenorrhoea as many more women could choose medically induced abortion if the regimen would be highly effective beyond 49 days of amenorrhoea. Because the efficacy of the regimen cannot be increased by using higher doses of mifepristone, the prostaglandin component appears to be critical for improved efficacy.

It has been suggested that misoprostol is more effective if it is given vaginally (El-Refaey *et al.*, *New england journal of medicine*, 332:983–987) or in repeated doses (Aubény, personal communication, 1995). As no data were available on the pharmacokinetics of misoprostol after vaginal administration, the Programme carried out a study to compare plasma levels of misoprostol and the degree and duration of uterine stimulation following oral and vaginal administration of the drug in order to identify a suitable dose schedule that might improve the efficacy of the procedure in more advanced pregnancies. Unexpected technical problems have delayed the measurement of plasma levels of misoprostol and the results of this study will only be available in early 1997. The data on uterine contractions indicated that vaginal administration did induce far more powerful contractions than those seen after oral administration of the drug. The study also suggested that, if repeated administration is needed, a suitable interval appeared to be between 3–6 hours.

A small study is also under way to look at possible side-effects of repeated administration of misoprostol after pretreatment with mifepristone. The first dose of 0.4 mg of misoprostol is given vaginally and the same dose is then given twice a day orally for up to two weeks.

The maximum duration of pregnancy for which the treatment remains effective and safe

The previously-mentioned dose-finding studies, in which the Programme has shown that the dose of mifepristone used in combination with gemeprost could be reduced from 600 mg to 200 mg without a reduction in efficacy, had been carried out in pregnancies of up to 56 days of amenorrhoea. However, in both Sweden and the United Kingdom mifepristone is permitted for use by women with amenorrhoea of up to 63 days. It was considered important, therefore, to determine if the mifepristone dose could be lowered to 200 mg in pregnancies of up to 63 days of amenorrhoea without reducing the effectiveness of the treatment.

Therefore, the Programme carried out a multicentre trial in which women with amenorrhoea of between 57 and 63 days were allocated randomly to treatment with either 200 mg or 600 mg of mifepristone, followed 48 hours later by 1 mg of vaginal gemeprost. The results of this double-blind, randomized trial confirmed that the mifepristone dose can be lowered to 200 mg in these slightly more advanced pregnancies without loss of efficacy when the prostaglandin analogue, gemeprost, is used (WHO Research Group on Post-ovulatory Methods for Fertility Regulation; manuscript in preparation).

Thus, the data generated by the Programme during the course of several multicentre trials conducted over the past few years indicate that, for the termination of early pregnancy (amenorrhoea of up to 63 days), a single dose of 200 mg of mifepristone, in combination with vaginal gemeprost, is as effective as a single dose of 600 mg in combination with the same prostaglandin analogue.

Acceptability of medically induced abortion

A concern that is sometimes raised in connection with medically induced abortion is the duration and amount of vaginal bleeding it induces. Prolonged bleeding after termination of pregnancy may affect women's health, particularly in countries where anaemia is prevalent. Women who have a complete abortion following mifepristone plus prostaglandin treatment, generally have vaginal bleeding for about two weeks, as opposed to less than one week following vacuum aspiration. The majority of women describe the amount of blood loss as being more or much more than normal menstruation (World Health Organization Task Force on Post-ovulatory Methods for Fertility Regulation, *British medical journal*, 1993, 307:532–537). In China, where, to date, some two million women have chosen to have a medically induced abortion, the longer bleeding time is a major obstacle, in terms of acceptability of the method, compared to surgical abortion (Sang Guo-wei, personal communication, 1995). It is not unusual for women who select the medical method, even if abortion is complete, to return to the clinic for curettage to stop the bleeding.

It seems likely, therefore, that the acceptability of medically induced abortion would be improved if ways could be devised to control or reduce the amount of blood loss, after the procedure. Researchers in China have investigated the effects of various Chinese herbs and drugs on the length of postabortion bleeding but have not yet identified any treatment that appears to be beneficial in this regard. In collaboration with investigators in Hong Kong and Shanghai (China), the Programme has initiated a study to investigate whether the practice of starting the oral contraceptive pill as soon as abortion has been confirmed to be complete, would be useful for controlling the amount and duration of blood loss after the procedure. This study has a double-blind design and will include a total of 200 subjects.

Ancillary studies

Cervical priming with misoprostol

In spite of advantages offered by medical, non-invasive approaches, surgical termination of pregnancy is likely to remain the option preferred by many women. In addition, surgical termination may continue to be the preferred method in certain situations, such as in late first trimester and early second trimester pregnancies, when a medical abortion method is likely to result in a high proportion of incomplete abortions necessitating subsequent surgical intervention to avoid complications such as excessive bleeding or infection.

It is generally agreed that surgical abortion, carried out by trained personnel and under aseptic conditions, is a very safe procedure. The morbidity and frequency of complications associated with pregnancy termination by suction or mechanical curettage can be reduced even further by preoperative treatment with a priming agent used to soften or dilate the cervix. The Scientific Group Meeting on Medical Methods for the Termination of Pregnancy, convened in April 1994, stated that: "there is a need for a large randomized trial to investigate the cost-effectiveness of cervical preparation". Now that misoprostol, a cheap and stable prostaglandin analogue, is available, it has been suggested that cervical priming with misoprostol be carried out as a routine practice before surgical abortion, as it will make the procedure even more safe, especially in developing countries (El-Refaey *et al.*, *The lancet*, 1994, **343**:1207–1209).

In a previously conducted multicentre study, the Programme has shown that mifepristone is an effective cervical priming agent (World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. *Contraception*, 1994, **50**:461–475). This finding prompted further study of mifepristone in comparison with prostaglandins and a randomized study was carried out in Hong Kong, with the Programme's assistance, to compare the efficacy of 200 mg mifepristone and 0.4 mg oral misoprostol prior to surgical termination of pregnancies of between 8–12 weeks of amenorrhoea. Interestingly, misoprostol and mifepristone seemed to be equally effective for preoperative cervical dilatation. In addition, the duration of the operation and the amount of blood loss were similar in both groups (Ho *et al.*, *Contraception*, 1996, **53**:281–283). The results from another study by the same investigators suggested that oral misoprostol might be better than vaginal gemeprost for cervical dilatation prior to vacuum aspiration in the first trimester pregnancy (Ngai *et al.*, *Contraception*, 1995, **51**:347–350).

Before a study can be launched to investigate whether routine priming of the cervix with misoprostol will improve surgical methods of abortion, it is necessary to identify the lowest effective dose and the shortest time interval that is needed between administration of misoprostol and surgery. To this end the Programme is carrying out a double-blind study to investigate oral and vaginal doses of 0.2 mg and 0.4 mg of misoprostol administered three hours prior to suction evacuation in pregnancies of 8–12 weeks duration.

Termination of second trimester pregnancy

The Programme has not provided financial support for research on the termination of second trimester pregnancies. It has, however, provided technical advice and has procured mifepristone (and placebo) tablets for such studies.

In many countries the use of prostaglandins has become the preferred method for termination of second trimester pregnancies. This procedure is, however, associated with side-effects and the process of abortion in the second trimester is usually long, distressing and painful. The research has, therefore, examined ways for improving the efficacy of the procedure by using mifepristone treatment prior to induction of abortion with prostaglandins as well as by testing different prostaglandin regimens.

In addition to its effect on cervical priming, mifepristone also sensitizes the myometrium to the uterotonic effect of prostaglandins and its use is of clear benefit in the termination of second trimester pregnancy with prostaglandins. Several studies have shown a marked reduction in the induction-to-abortion interval and in the amount of prostaglandin needed to induce abortion with such treatments (for review see, for example, Van Look and von Hertzen, *Human reproduction update*, 1995, **1**:19–34). For instance, when the prostaglandin analogue gemeprost was used after pretreatment with mifepristone (600 mg), the median interval between the start of prostaglandin administration and abortion was less than half that in the placebo-treated controls (6.8 hours compared to 15.8 hours) and the women in the mifepristone group experienced significantly less pain than the women who had received placebo (Rodger and Baird, *British journal of obstetrics and gynaecology*, 1990, **97**:41–45).

In another study (Ho and Ma, *Contraception*, 1993, **47**:123–129), which used the prostaglandin sulprostone, the median interval between the first injection of sulprostone and abortion was only 4.6 hours in the group of women who were given the antiprogestogen, compared to 20.0 hours in the placebo-pretreated group ($p<0.02$). In a subsequent study the same investigators compared the efficacy of laminaria tent and mifepristone in facilitating second trimester pregnancy termination with vaginal gemeprost (Ho *et al.*, *British journal of obstetrics and gynaecology*, 1995, **102**:648–651). In this study, the me-

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dian induction-to-abortion interval in the mifepristone group was 7.5 hours and in the laminaria tent group 11.0 hours ($p<0.01$). In addition, the median amount of gemeprost used in the mifepristone group was significantly lower than that in the laminaria tent group (3 mg versus 2 mg; $p=0.001$) and the amount of pethidine required was also less in the mifepristone group (50 mg versus 75 mg), although the latter difference was not statistically significant. All women in the mifepristone group and 28 (90%) of the women in the laminaria tent group aborted within 24 hours. Abortion was incomplete in 15 (48%) of the women in the mifepristone group compared to 17 (55%) in the laminaria tent group.

It is clear from the studies on mifepristone use in second trimester abortions that, in terms of effectiveness and lack of side-effects, antiprogestogens are superior to any of the currently used alternatives such as natural or hydrophilic dilators or pretreatment with local (vaginal or intracervical) prostaglandin preparations.

While there was no doubt about the superiority of antiprogestogen pretreatment before prostaglandin administration, it was uncertain whether the prostaglandin analogue, misoprostol, was as effective as gemeprost in inducing second trimester abortion. To determine this, a small pilot study was carried out among 50 subjects to compare oral administration of 0.4 mg misoprostol every three hours to vaginal administration of 1 mg gemeprost every six hours, all subjects having been pretreated with 200 mg of mifepristone 48 hours earlier. The results of this study suggested no significant difference between the two groups in side-effects, in the median induction-to-abortion interval (8.7 hours in the misoprostol group and 10.8 hours in the gemeprost group) or in the requirement for analgesics. The abortion was incomplete and evacuation was required in five (20%) women in the misoprostol group and 10 (40%) women in the gemeprost group. There was no significant difference in the estimated amount of blood loss between the two groups (Ho *et al.*, *Contraception*, 1996, **53**:281–283). Thus, oral misoprostol was found to be a good alternative to vaginal gemeprost for the termination of second trimester pregnancy after pretreatment with 200 mg of mifepristone 48 hours earlier.

An ongoing double-blind study will compare the efficacy and side-effects of oral and vaginal misoprostol after pretreatment with a 200-mg dose of mifepristone in the termination of second trimester pregnancy. In one group, a dose of 0.2 mg of misoprostol is given orally every three hours up to a maximum of five doses. In the other group the same dose is administered vaginally every three hours up to a maximum of five doses. From the interim results, vaginal misoprostol appears to be more effective than oral misoprostol. The induction-to-abortion interval is shorter in the vaginal group (8.7 hours) compared to the oral group (14.8 hours; $p=0.0001$), particulalrly among women without previous pregnancies (8.8 hours for vaginal administration compared with 20.0 hours for oral administration). However, the women taking part in this study prefer oral administration of the misoprostol over vaginal administration.

Planned studies

During 1997

First trimester abortion

It is planned to start a multicentre study to test vaginal and perhaps also a repeated regimen of oral misoprostol administration to see whether the efficacy observed in the multicentre trial of mifepristone plus oral misoprostol for termination of early, first trimester pregnancy, can be improved, especially in pregnancies of up to 63 days of amenorrhoea. The design of the study will be finalized when the results of the pilot study on repeated dosing of misoprostol are available.

In collaboration with the Programme's Component on Context, Needs and Perspectives and subject to the availability of funds, it is planned to launch a study, in two East European countries, Albania and Romania, on the impact on service delivery of the introduction of mifepristone and misoprostol for early termination of pregnancy. This project will collect baseline data on current abortion services and then introduce medical technology for pregnancy termination. The study will also assess acceptability of this new technology with clients and providers.

Cervical priming

As suggested by the Scientific Group Meeting on Medical Methods for Termination of Pregnancy in April 1994, the Programme is planning to launch a double-blind multicentre study to observe the effects of routine cervical priming of the cervix prior to vacuum aspiration on morbidity and cost-effectiveness in developing country settings.

Second trimester abortion

A study will be undertaken among 100 women requesting termination of pregnancy between 14–20 weeks of amenorrhoea to determine if higher oral doses of misoprostol would increase the efficacy of treatment. This prospective study will compare the vaginal administration of 0.2 mg misoprostol and an oral dose of 0.4 mg after pretreatment with 200 mg of mifepristone. The Programme will provide technical assistance and procure mifepristone tablets for this study.