

History and Efficacy of Emergency Contraception: Beyond Coca-Cola

By Charlotte Ellertson

As affirmed at the 1994 International Conference on Population and Development in Cairo, women have the right to control the number and timing of their pregnancies. To realize this right, women throughout the world need access to a broad range of contraceptives, as well as to safe abortion services. While most contraceptives are intended for use before or during intercourse, some methods can be used within a short time after unprotected intercourse. Rumored folk methods such as postcoital douching with Coca-Cola are of dubious efficacy, but fortunately are not a woman's only alternative. Within the last 30 years, a number of approaches, which seem safe and efficacious, have been developed.

These options, predominantly variations on oral contraceptive regimens, are often called "morning-after pills." A more appropriate name for them, however, is "emergency contraception," which would dispel the idea that the user must wait until the morning after unprotected intercourse to start treatment—or that she will be too late if she cannot obtain treatment until the afternoon or night after. The name "emergency contraception" also stresses that the regimens are not intended for ongoing use.

The roots of modern emergency contraception date back to the 1920s, when researchers initially demonstrated that estrogenic ovarian extracts interfere with pregnancy in mammals.¹ Veterinarians were the first to apply this finding, administering estrogens to dogs and to horses that had mated when their owner had not wanted them to. Despite scattered reports of clinical use of postcoital estrogens in humans as early as the 1940s,² the first documented cases were not published until the mid-1960s, when physicians in

the Netherlands applied the veterinary practice of postcoital estrogen administration to a 13-year-old girl who had been raped at midcycle.³

At around the same time, U.S. researchers were investigating the efficacy of high-dose estrogens, and toward the end of the decade, these preparations became the standard. Women typically received either conjugated estrogens, the steroidal estrogen ethinyl estradiol or the nonsteroidal estrogen diethylstilbestrol (DES). Today, in places where high-dose estrogens are still used, they are administered in the so-called 5x5 regimen: 5 mg of ethinyl estradiol per day for five days.⁴

In the early 1970s, the high-dose estrogen regimens gave way to a combined estrogen-progestin standard. Canadian physician Albert Yuzpe and his colleagues began studies in 1972 on this combined regimen, guided by their observation that a single dose of 100 mcg of estrogen coupled with 1.0 mg of the progestin *dl*-norgestrel induces endometrial changes that are incompatible with implantation.⁵ The "Yuzpe method," as it came to be known, replaced high-dose estrogen formulations, chiefly because it offered a lower incidence of side effects, but also because the commonly used DES was linked to vaginal cancer in the daughters of women who had taken it to prevent miscarriages. The regimen now begins within 72 hours after unprotected intercourse and typically consists of 200 mcg of ethinyl estradiol and 1.0 mg of levonorgestrel.

Research on regimens that omitted estrogen also began in the early 1970s, predominantly in Latin America. A 1973 report described the results of a large-scale trial investigating five doses of levonorgestrel: 150 mcg, 250 mcg, 300 mcg, 350 mcg and 400 mcg per tablet. The regimen was tested as an ongoing postcoital method, rather than an emergency formulation. Participants in the trial were instructed to

take a tablet as soon as possible within three hours after intercourse and could use the method as often as necessary; some continued to use this method for two years.⁶ The results showed that the lower doses were not efficacious and caused some menstrual disruption, chiefly a shortening of the cycle. This experiment marked the first major venture into ongoing postcoital contraception and laid the groundwork for the levonorgestrel methods that have become available in many developing countries and in Eastern Europe.

The late 1970s were to offer the chief nonhormonal method available today, the copper-releasing IUD. This device causes endometrial changes that inhibit implantation; in addition, the copper ions released appear to be directly embryotoxic.⁷

More recently, two other methods have been investigated: danazol and mifepristone. Danazol, a synthetic progestin and antigonadotropin, was first used as an emergency contraceptive in the early 1980s.⁸ Mifepristone, more commonly known as RU-486, is a potent antiprogesterone registered in four countries as an abortifacient. Relatively little research is available on these newer methods, although mifepristone in particular appears extremely promising as an emergency contraceptive.

Yuzpe Method

The Yuzpe method is the best-studied method of oral postcoital contraception.⁹ (In addition, trials of vaginal administration of the Yuzpe method are under way in Mexico.¹⁰) Although the exact treatment varies widely in developing countries,¹¹ the regimen typically used in North America and Europe consists of 200 mcg of ethinyl estradiol and 1.0 mg of levonorgestrel. Half the dose is taken within 72 hours after unprotected intercourse, and the other half is taken 12 hours later.

One reason for the popularity of the

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Yuzpe method is that the hormones it uses are the active ingredients found in several brands of ordinary combined oral contraceptives. The brand marketed as Ovral in the United States and Canada, for example, contains 50 mcg of ethinyl estradiol and 0.25 mg of levonorgestrel per tablet; therefore, four Ovral tablets (the dosage Yuzpe and his colleagues used after their original pilot study) constitute the complete regimen.*

Several other brands of combined oral contraceptives contain the same hormones needed for the Yuzpe method, but in lower doses.¹² Women using these brands therefore have to take a greater number of pills; for example, women in the United States can use the brands Nordette, Levlén and Lo/Ovral for the Yuzpe method if they simply double the number of tablets of these lower dose oral contraceptives. (In other words, they would take four pills for each half of the regimen.) A number of triphasic oral contraceptive formulations also contain the hormones needed for the Yuzpe method. For example, eight of the yellow tablets (corresponding to cycle days 12–21) of Triphasil or Tri-Levlén constitute the complete regimen.

In the United States, no contraceptives are specifically marketed and packaged for emergency use. As a result, many clinicians simply cut up packages of oral contraceptives that contain the appropriate hormones. In several European countries, tablets equivalent to Ovral are available in four-pill strips labeled explicitly for emergency use. The brands are PC4 in Britain, Neo-Primovlar in Finland and Tetragynon in Switzerland.

Efficacy studies of the Yuzpe method have yielded greatly varying results, in part because the definition of efficacy is slightly different for a postcoital method than for a conventional method. In one approach, researchers observe women using emergency contraception in a given cycle, note the number of pregnancies that occur and divide that number by the number of women who took the drug. When studied in this fashion, the failure rate of the Yuzpe method ranges from about 0.2% to 2%.¹³ This rate is useful insofar as it tells clinicians that of all women they treat with this therapy, 2% or fewer will likely experience pregnancy. However, these results do not account for the fact that some of the women would not have become pregnant even if they had not used the method under study.

Yet women do not generally use the Yuzpe method cycle after cycle. Instead, the method is used sporadically, typical-

ly at times when the probability of pregnancy is highest, such as following mid-cycle intercourse. Therefore, better studies of the method limit their scrutiny to women with regular cycles. For such women, an expected number of pregnancies can be estimated using published fertility tables if investigators record the cycle day of unprotected intercourse (or details about a woman's cycle, such as its usual length and the first day of the last menstrual period). From the 10 available studies that approached this optimal design,¹⁴ it is possible to calculate a proportionate reduction in pregnancy associated with the use of the Yuzpe method. By comparing observed and expected pregnancies, investigators have demonstrated that the Yuzpe method reduces the chances of pregnancy by about 75%.¹⁵

Because the regimen consists of the same active ingredients as certain combined oral contraceptives, and because it has never been specifically regulated by the U.S. Food and Drug Administration, the contraindications for its use sometimes have simply been adopted wholesale from those stated for combined pills: current or past thromboembolic disorders, cerebrovascular disease or coronary artery disease, known or suspected carcinoma of the breast or endometrium, jaundice, and hepatic adenomas or carcinomas. Women older than 35 who smoke heavily have also been considered ineligible for the regimen. General medical consensus, however, is that the regimen has no contraindications.¹⁶

Despite the lack of evidence, some clinicians fear that the Yuzpe regimen may heighten the risk of fetal malformation if administered to a woman in early pregnancy. (A meta-analysis of the 12 available prospective studies failed to detect any statistically significant association between oral contraceptive use in early pregnancy and fetal malformation.¹⁷) To be most conservative, a clinician should talk with a woman before she begins the regimen to rule out the possibility of a pre-existing pregnancy (i.e., one that resulted from an act of unprotected intercourse occurring more than 72 hours earlier).

Side effects of the Yuzpe method are the same as those commonly experienced with short-term use of combined oral contraceptives: nausea (including vomiting in about 20% of cases), headaches, breast tenderness, abdominal pain and dizziness. Nausea, by far the most common of these, typically is reported by 50% of users. Taking the tablets with food or with milk may lessen nausea, although whether such a practice inhibits absorption of the drug or

renders it less effective remains to be investigated. Some clinicians also routinely give an antiemetic or antinausea medication such as dimenhydrinate or cyclizine hydrochloride.¹⁸

Levonorgestrel

The levonorgestrel emergency contraceptive regimen consists of two doses of 0.75 mg of levonorgestrel taken 12 hours apart, starting within 48 hours after unprotected intercourse. Although progestins were among the first drugs used in postcoital contraception, few studies of the emergency levonorgestrel regimen have controlled for cycle day of unprotected intercourse.

The best and most recent of the levonorgestrel emergency contraceptive trials, conducted in Hong Kong,¹⁹ indicates a failure rate of 2% and a proportionate reduction in pregnancy of 60%. The investigators randomly assigned women reporting for treatment within 48 hours after unprotected intercourse to receive either the Yuzpe or the levonorgestrel regimen. During the trial, 410 women used the latter. Investigators did not detect a statistically significant difference between the methods. This trial is being replicated in a multinational study sponsored by the World Health Organization.²⁰

As noted previously, the levonorgestrel regimen has been studied as an ongoing or primary method of postcoital contraception. The Hungarian company Gedeon Richter once marketed a strip of 10 pills containing 0.75 mg each for this use. Now the company markets a four-pill strip, to emphasize that the pills are intended for sporadic or emergency contraception.

The brand (Postinor) is advertised for women who have intercourse fewer than four times per month. Like the Latin American progestin-only formulations that paved its way, Postinor is meant to be taken within eight hours after unprotected intercourse when used as a primary postcoital method. Unlike commercial formulations of the Yuzpe method, Postinor is available in many developing countries and is even sold over the counter in some places.

In addition, nine Chinese brands of "visiting pills" have been developed; eight of them involve a progestin, and some have consisted of levonorgestrel. A randomized, double-blind, multicenter trial was unable to demonstrate a difference between one of these Chinese levonorgestrel formulations and Postinor.²¹

*In other countries, the same dose and active ingredients are available in brands such as Anfert, Anulette, Anulit, Daphyron, Eugynon, Ovran, Planovar, Primovlar and Stediril.

Certain brands of progestin-only oral contraceptives can also be adapted for emergency use. The Ovrette brand, for example, contains 0.075 mg of dl-norgestrel, the equivalent of 0.0375 mg of levonorgestrel, per tablet. Therefore, a total of 40 tablets makes up the complete regimen. Although such a regimen is impractical for most women, this option may be important for women with estrogen contraindications.²²

Mifepristone

Mifepristone, a potent antiprogesterone, has been tested since the early 1980s for its abortifacient qualities.²³ More recently, in two studies evaluating mifepristone as an emergency contraceptive,²⁴ the regimen consisted of 600 mg of the drug taken in a single dose within 72 hours after unprotected intercourse. No pregnancies were observed among mifepristone users in either trial, despite a combined enrollment of nearly 600 women. The side effect profile of mifepristone was also generally superior to that of the Yuzpe regimen, although menstrual disturbances appeared more commonly than with the Yuzpe method.

Lower doses of mifepristone may also be effective, and the time limit in which the therapy may be used could extend beyond 72 hours. The 600 mg dose is the same dose currently used as part of the medical abortion regimen provided in France.²⁵ The World Health Organization is investigating the efficacy of mifepristone in much smaller doses (50 mg and 10 mg).²⁶ If proven safe and effective, a smaller dose (e.g., 10 mg or 1 mg) could be more palatable politically in countries where abortion is restricted, insofar as it might allay fears that women will hoard pills to use for medical induced abortion.

Other Methods

High-Dose Estrogens

Postcoital treatment with high-dose estrogens (the standard regimen wherever emergency contraception was offered during the 1960s and early 1970s) is at least as effective as the Yuzpe method, but produces more side effects. These regimens must be initiated within 72 hours after unprotected intercourse and are administered in two daily doses for five days. Each dose (2.5 mg of ethinyl estradiol, 10 mg of esterified or conjugated estrogens, or 5 mg of estrone) is equivalent to 25 mg of DES. One example of a high-dose estrogen still prescribed as an emergency contraceptive is Lynoral, marketed and used in family planning programs in the Netherlands.²⁷

Danazol

The synthetic progestin and androgen danazol (marketed in the United States as Danocrine) can be used as an emergency contraceptive. The danazol regimen consists of two doses of 400 mg each, taken 12 hours apart. Regimens, involving three doses of 400 mg each, taken at 12-hour intervals, and two doses of 600 mg each, taken 12 hours apart, have also been investigated.²⁸ Danazol's advantages are that its side effects are less prevalent and less severe than those associated with the Yuzpe method, and that it can be taken by women with contraindications to combined pills or estrogen. However, relatively little information is available about the regimen. Of the two most thorough trials of the regimen, one concluded that the method is effective,²⁹ while the other concluded that danazol does not work.³⁰

Copper IUD

A meta-analysis of 20 studies of the postcoital insertion of a copper IUD³¹ reveals that the failure rate of this approach is probably no higher than 0.1%. The IUD offers the additional advantage of providing up to 10 years of contraceptive protection. The service delivery challenges raised by the method, however, may be severe, particularly in some developing countries. In addition, the method is contraindicated for women at risk of sexually transmitted diseases,³² who frequently are the same women who need emergency contraception.

Research Guidelines

Of the hundreds of articles published on emergency contraception, only a few dozen reflect good research designs and appropriate methodologies for answering the basic questions about efficacy, safety and user issues. Consequently, more data, particularly from developing countries, are needed; additional clinical research is being planned and implemented. Research in Scotland, for instance, will assess the effects on pregnancy rates of giving women packets of emergency contraceptive pills to have on hand when needed.³³ Similar research is planned in the United States and elsewhere.³⁴ Also needed are qualitative studies to document women's experiences, surveys to assess women's and providers' knowledge, and experiments to discover the optimal ways to educate women, as well as additional basic research.

Efficacy Studies

To evaluate efficacy, a researcher must compare an observed number of pregnancies with an expected number. The

number of pregnancies that would be expected in a group of fecund women is a function primarily of the cycle day on which unprotected intercourse occurred, yet many emergency contraception trials fail to control for this factor.

To reduce the likelihood of error and increase the reliability of estimates, researchers should limit study populations to women with regular cycles and should define midcycle (when ovulation occurs) as 14 days before the expected onset of the next menses for women with 28-day cycles. Using published estimates of the probability of conception on each day of the cycle,³⁵ researchers can calculate the expected number of pregnancies among women in their trials. Results of such calculations, however, should be regarded as lower bounds, because the published estimates are based in part on women who have undergone artificial insemination using frozen sperm and in part on couples who may have been selected for below-average fecundity.³⁶

Another problem with many trials of emergency contraception is that they may include some women who had become pregnant because of an act of unprotected intercourse occurring more than 72 hours before the start of the emergency contraception regimen. Where feasible, investigators should establish that no such women are participating in the trial. Sensitive human chorionic gonadotropin assays may play a role here, particularly for trials of methods that can be initiated later than the traditional 72 hours after unprotected intercourse. With five-day cutoffs, for example, ultrasensitive pregnancy tests could be used to rule out preexisting pregnancies.

Investigators should also limit analysis of failure to women who did not have further acts of unprotected intercourse during the treatment cycle. A number of trials have made participants' willingness to abstain or to use condoms for the rest of the cycle a condition of inclusion. (Of course, trials of the IUD need not impose this rule, since this method is a highly effective ongoing contraceptive.)

Because it is unclear whether a relationship exists between the exact time elapsed since unprotected intercourse and the efficacy of the regimen, investigators should record and analyze the number of hours between unprotected intercourse and initiation of therapy.

Some research suggests also that the time limit for the Yuzpe regimen may be extended to five days.³⁷ Additional data on this point would be most valuable.

If proposals to try novel service delivery systems, such as vending machines or emergency contraception kits dispensed prophylactically, bear fruit, the effects of these new ways to administer the medicine would be worthy of study.

Investigators may also wish to limit analysis in their studies to women of proven fertility. Although such a practice may slow the trials unacceptably (because many women seeking emergency contraception are young and have never been pregnant), it might afford more precise estimates of a regimen's efficacy. Of course, women who are not of proven fertility may also require emergency contraception. Researchers should not deny such women access to the therapy, but should analyze them separately from women reporting prior pregnancies.

Similarly, although efficacy tests should exclude women who have had more than one act of unprotected intercourse during a menstrual cycle, such women should receive treatment when they request it. Studies that required women to state that they had not had any other acts of unprotected intercourse in the cycle prior to the 72 hours before initiating treatment found that women frequently misreported their experience in order to obtain treatment.³⁸ Later protocols by these same investigators allowed any women requesting the treatment to obtain it, but limited analysis to women who had had only one act of unprotected intercourse in the cycle and whose one act had occurred less than 72 hours prior to the start of treatment.

Because the conditions of the ideal trial may be burdensome to women, investigators must take special care to reassure them that they can receive treatment even if, for example, they are not willing to abstain from intercourse for the balance of the cycle. It may be best, in fact, for investigators to treat any woman needing the therapy, and then to analyze data only from those meeting the criteria. If participants are given too many instructions or asked to modify their lifestyles too drastically for the sake of a trial, they may choose not to disclose additional acts of intercourse or other protocol violations.

User-Related Studies

Research on how women can best use emergency contraceptives to suit their needs is crucial, especially in the case of the hormonal methods, which depend far less on providers. Should emergency contraceptive pills be available over the counter and from vending machines? Should they be routinely prescribed or dis-

pensed at every family planning or medical visit for women to keep in case of emergency? Should women be issued an identification card (equivalent to a standing prescription) entitling them to the purchase of a regimen of emergency contraceptives once they have been screened and counseled about the use of the therapy? Would women prefer a specially packaged product to a plain cycle or part of a cycle of oral contraceptives? How much do women know about the methods, and how might they best learn more? The answers to these questions, and many others, will help determine which distribution systems and use patterns would best help women avoid unwanted pregnancy.

Further Research

While the guidelines noted above apply to the study of all emergency contraception regimens, some needs are specific to individual methods. Most important, it would be extremely convenient for health care providers and consumers alike if the Yuzpe method could be broadened to include all of the progestins used in combined oral contraceptives. No published trials have evaluated the combined oral contraceptives that use the progestins desogestrel, norethindrone or ethynodiol diacetate, for example. While there is no reason to believe that these pills would not work as emergency contraceptives, their use for this purpose has yet to be tested and established. If it were indeed the case that women could use any brand of combined oral contraceptive in an emergency dose, barriers to access would be substantially lessened for many women.

The mechanisms of action for the various emergency contraception regimens are poorly understood. Still, preliminary research in the United States indicates that the exact mechanism of action, and particularly the timing of the action in the process of conception, may be important information for women making ethical determinations about whether they would use various regimens.³⁹ Additional basic research could clarify these mechanisms.

Conclusion

More than 30 years of experience with emergency contraceptives has established that the methods can substantially reduce the chances of pregnancy, that their side effects are acceptable to women and that service provision requirements are not generally onerous to clinicians. While there is a need for additional research, the available literature sustains a compelling case for expanding emergency contra-

ception at once, if efficacy and safety considerations are the sole criteria.

Emergency contraceptives are simple to use, relatively inexpensive and, in many cases, already accessible to the women who need them. The chief remaining obstacle to their use may well be ignorance. Reproductive health advocates and providers need to educate each other and to educate women about these important options.

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