Review Article

Drug Therapy

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EMERGENCY POSTCOITAL CONTRACEPTION

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EMERGENCY postcoital contraception may be defined as the use of a drug or device to prevent pregnancy after intercourse. Unwanted pregnancy is common; worldwide, about 50 million pregnancies are terminated each year.[1] It has been calculated that each year the widespread use of emergency contraception in the United States could prevent over 1 million abortions and 2 million unintended pregnancies that end in childbirth.[2]

A variety of different methods of emergency contraception are available (Table 1). The first to be described was high-dose estrogen, although currently the most widely used is a combination of estrogen and progestin. Recent interest in the development of alternative regimens has led to trials of progestin alone, the antigonadotropin danazol, and the antiprogestogen mifepristone (RU 486) for postcoital contraception. Highly effective, but much less convenient, is the postcoital insertion of an intrauterine contraceptive device.

PROBABILITY OF CONCEPTION

The probability of conception after a single act of intercourse has been calculated to be about 33 percent per cycle if intercourse occurs on average every other day[12]; if it occurs only once per week, the risk of pregnancy is only 15 percent. Most women who have unprotected intercourse on a single occasion therefore will not conceive. Conception occurs only around the time of ovulation. Surprisingly, the number of days of the menstrual cycle during which a woman is fertile (i.e., on which conception could result if intercourse occurred) has been difficult to quantify. Although sperm remain in the female genital tract and are capable of fertilization for up to five days after ejaculation, the egg appears to be capable of being fertilized for only about 24 hours.

In a recent study of couples actively trying to conceive, in which hormone measurements were used to determine the timing of ovulation, the fertile period lasted about six days, ending on the day of ovulation.[12] There were no conceptions when intercourse occurred after the day of ovulation; acknowledging the small sample size in their study, however, the authors concluded that a probability of conception of up to 12 percent was theoretically possible if intercourse occurred on the day after ovulation. In that study, in which pregnancy was detected on the basis of urinary measurements of human chorionic gonadotropin, 24 percent of the pregnancies ended within six weeks after the last menstrual period and only 68 percent resulted in childbirth.

MODE OF ACTION OF EMERGENCY CONTRACEPTION

Emergency contraception could work by inhibiting or disrupting ovulation, interfering with fertilization or the transport of the embryo to the uterus, or inhibiting its implantation in the endometrium. Any device or drug that acts after implantation is conventionally regarded as an abortifacient rather than a contraceptive. In theory, the most effective method of emergency contraception would be one that inhibited implantation, because it would prevent conception at whatever time in the cycle intercourse occurred, even after ovulation. A method that affected ovulation or fertilization would prevent most but not all pregnancies, because women who used the method after they had already ovulated might still conceive. In practice, the precise mode of action of currently available emergency contraceptives is not known, although there is evidence of effects at several critical stages of the reproductive cycle.

Effects on Ovulation

Most of the research on estrogen alone has concentrated on its effects after ovulation. In theory, large doses of estrogen given before ovulation might be expected to inhibit follicular development and maturation or the release of the ovum itself; there is, however, no evidence of any of these actions. Given before or at the time of ovulation, both estrogen plus progestin and danazol sometimes inhibit or delay ovulation.[13-15] Mifepristone inhibits ovulation,

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TABLE 1. METHODS OF EMERGENCY CONTRACEPTION.

REGIMEN	TIME AFTER INTERCOURSE*	STATUS OF METHOD	REPORTED EFFICACY†	SOURCE OF DATA
Estrogen and progestin (100 μg of ethinyl estradiol and 0.5 mg of levonorgestrel given twice, with 12 hr between doses)	72 hr	Licensed in some countries since early 1980 (e.g., United Kingdom, the Netherlands); available unlicensed in the appropriate combination of oral-contraceptive pills	75–80% of pregnancies prevented	Meta-analysis of 10 trials involving >5000 women[3]
Levonorgestrel (0.75 mg given twice, with 12 hr between doses)	48 hr (possibly up to 72 hr)	Licensed in some countries in Eastern Europe and Asia	Equivalent to estrogen–progestin	One randomized trial involving 350 women[4]
High-dose estrogen (e.g., 5 mg of ethinyl estradiol daily for 5 days)	72 hr	Licensed in the Netherlands; little used elsewhere	Equivalent to estrogen–progestin[5]	Randomized trial involving 250 women; early trials suggested failure rates <1%[6,7]
Mifepristone (a single 600-mg dose)	72 hr	Widely used in China in a variety of lower doses; not licensed anywhere else for emergency contraception	100% effective	Two randomized trials involving a total of 600 women[8,9]
Danazol (400 to 800 mg given twice 12 hr apart or 400 mg given 3 times at invervals of 12 hr)	72 hr	Used only under research conditions	Reports vary from failure rates of <1%[10] to ineffective[9]	Two randomized trials, one involving >1700 women and suggesting failure rates of about 1%,[10] and the other involving 193 women and suggesting little or no effect[9]
Copper intrauterine device	Up to 5 days after the earliest estimated day of ovulation	Available worldwide, but not licensed for emergency contraception	Failure rates <1%	Meta-analysis of 20 published studies involving >8000 women[11]

*The times given are for the first dose.

†Data on efficacy are not comparable since not all are based on exposure during the fertile phase of the cycle (see the text).

even when given at low doses during the follicular phase,[16] and the administration of mifepristone as a postcoital contraceptive before ovulation significantly delays the onset of menses, indicating the inhibition of ovulation.[8]

Effects on Fertilization

There is no direct evidence that any of the hormonal methods of emergency contraception prevent fertilization, although such an effect cannot be ruled out. The intrauterine contraceptive device can compromise fertilization by its toxic effects on sperm[17]; if it is inserted after intercourse but before ovulation, it could theoretically work by preventing fertilization.

Effects on Gamete Transport

Although high-dose estrogen impairs the transport of the ovum in some animal species,[18] there is no evidence of such an effect in humans. Early trials of high-dose estrogen given after intercourse to women at risk for conception were associated with an increased incidence of ectopic pregnancy,[19] but it is likely that, as with the intrauterine contraceptive device, this method is better at preventing intrauterine pregnancies than tubal pregnancies.

Effects on the Function of the Corpus Luteum

Abnormalities of luteal-phase progesterone secretion are associated with a reduction in fertility. Since the corpus luteum is derived from the ovarian follicle, events that affect the developing follicle may influence the function of the corpus luteum. Although estrogen plus progestin (given either before or after ovulation),[13-15] danazol,[14,15] and high-dose estrogen[20] all reduce the magnitude of the midcycle surge in serum luteinizing hormone, reduce progesterone concentrations in the luteal phase, or both, it is not known whether such changes are incompatible with pregnancy. There is better evidence of an effect of mifepristone on the corpus luteum; when given in the mid-luteal or late luteal phase of the cycle, it induces regression of the corpus luteum in about 50 percent of women.[21]

Effects on Implantation

Mifepristone administered immediately after ovulation delays endometrial maturation without affecting ovarian hormone production or menstrual bleeding,[22] and when given in this way it prevents pregnancy.[23] Insertion of an intrauterine device after ovulation causes histologic changes in the endometri-

um that would be expected to impair implantation.[24] In contrast, although the postovulatory administration of estrogen[25] or levonorgestrel[26] inhibits implantation in some animals, evidence of similar effects in women has been difficult to obtain. Minor changes in the histologic and biochemical features of the endometrium occur when high-dose estrogen,[6] the estrogen–progestin combination, or danazol is administered after ovulation,[27] but the effects may not be sufficient to inhibit implantation. In a recent morphometric study, postovulatory administration of estrogen plus progestin had only minor effects on the endometrium, and danazol had no effect.[15]

Interruption of Pregnancy

It is unlikely that danazol, estrogen, or progestin, either alone or in combination, interrupts early pregnancy in women once implantation has occurred. In contrast, mifepristone is effective after implantation in 80 percent of women.[28] Since implantation occurs about seven days after ovulation, emergency contraception within five days after intercourse cannot be considered to interrupt pregnancy.

Conception is much less likely if intercourse occurs after ovulation. At least one trial suggested that both estrogen plus progestin and danazol are less likely to be effective as postcoital contraceptives if they are taken after ovulation.[9] The balance of evidence suggests that the most widely used hormonal emergency contraceptive, estrogen plus progestin, works mainly by inhibiting or delaying ovulation. If the intrauterine contraceptive device is inserted or mifepristone is given after intercourse, the mode of action will depend on the timing of treatment in relation to ovulation.

INDICATIONS FOR EMERGENCY CONTRACEPTION

Emergency contraception is useful after unprotected intercourse or withdrawal that occurs too late and for couples who recognize the failure of a barrier method, such as a burst condom. In a recent study of condom breakage and slippage, 4 to 7 percent of couples using this form of contraception in the United States had a recognized condom failure during a period of up to three months.[29] Emergency contraception is not usually indicated when one or more oral contraceptive pills have been forgotten, because there are established and effective rules for the use of a barrier method as secondary prevention under these circumstances (Fig. 1).

EFFICACY OF EMERGENCY CONTRACEPTION

The efficacy of emergency contraception is difficult to quantify. Most studies include large numbers of young women of unproved fertility, and for obvious reasons there can be no control group. Some couples are not certain that there was spillage of seminal fluid when a condom burst or that ejaculation actually occurred. Many authors simply report failure rates in terms of the number of pregnancies among the women treated, but most of these women would not have conceived even if they had not used emergency contraception. More recently, attempts have been made to estimate the number of women genuinely at risk of pregnancy — that is, those who had unprotected intercourse during the fertile period — and to relate the number of actual pregnancies to the number of expected pregnancies. Even this method has its shortcomings, because neither the precise timing of intercourse nor the exact date of the last menstrual period is always accurately recalled, and for individual women the day of ovulation may vary by as much as two or three days in each cycle. Thus, the timing of exposure to the risk of pregnancy in relation to the day of ovulation is, even in these well-documented studies, an educated guess. In a recent meta-analysis of 10 published studies in which data on the menstrual cycle and the timing of intercourse were reported, the efficacy of estrogen plus progestin was estimated to be 74 percent, on average.[3] Although mathematical calculations have their appeal, when faced with the possibility of an unwanted pregnancy, many women would use a method that was only 50 percent effective or even less if there was no alternative.

COMBINED ESTROGEN AND PROGESTIN

The estrogen–progestin regimen is two doses of a combination of 100 μg of ethinyl estradiol and 0.5 mg of levonorgestrel each, the first dose taken within 72 hours after intercourse and the second 12 hours later. A licensed product is available in several countries in Western Europe and in New Zealand (marketed under a variety of trade names, such as Schering PC4 in the United Kingdom and Tetragynon in Switzerland). First described in 1977 by Yuzpe and Lancee,[30] the combination therapy is often referred to as the Yuzpe regimen. The same hormones are available in some brands of combined oral-contraceptive pills, and these are often used in countries where a marketed preparation is unavailable. It is not known whether the estrogen–progestin regimen is effective if taken later than 72 hours after intercourse,[31] nor whether combined oral contraceptives containing other progestins administered in a similar manner are effective. Neither is it known whether the two-dose regimen is strictly necessary.

Nausea (in up to 50 percent of women) and vomiting (in up to 20 percent) are the main side effects of this regimen.[8] Both, in theory, may occasionally interfere with the woman's taking the second dose, and vomiting may reduce efficacy if it occurs within two hours after the medication is taken, in which

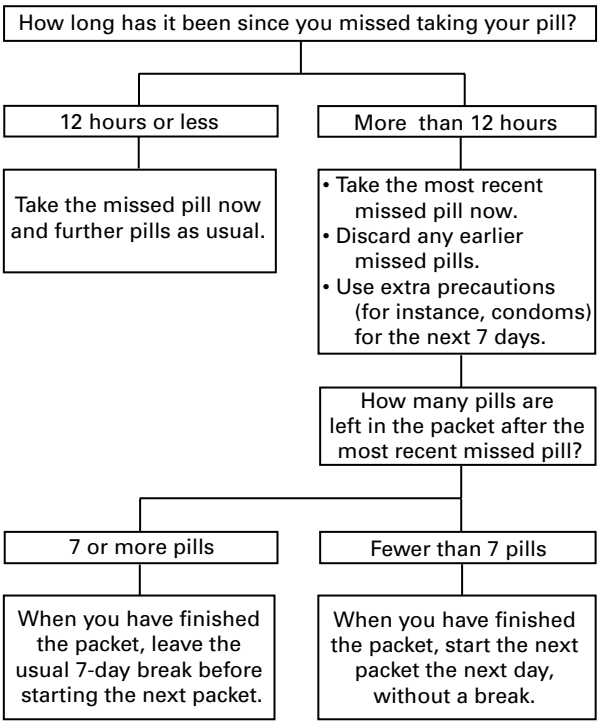

Figure 1. Scheme for the Prevention of Pregnancy in Women Who Miss One or More Oral-Contraceptive Pills.

case absorption may be reduced. Some clinics routinely provide an antiemetic drug, but there are no data to support this practice. Moreover, in practice, nausea and vomiting seldom prevent women either from taking the second dose or from using the regimen on another occasion; vomiting within two hours after swallowing the tablets is uncommon; and failures of emergency contraception do not appear to be associated with vomiting. Subsequent menses normally occur at the expected time[8] but may be heavier than usual, and some women have mastalgia for a few days after treatment.[30]

Although it is widely used in Europe, there are very few data on the safety of the estrogen–progestin regimen. Long-term use of the combined oral-contraceptive pill is associated with an increased risk of both arterial disease (myocardial infarction and cerebrovascular accident)[32] and venous disease (deep venous thrombosis and pulmonary embolism).[33] The risk of venous thromboembolism is thought to be dose-dependent, and it is higher with pills containing 50 μg of ethinyl estradiol than with low-dose pills (containing 30 to 35 μg).[34] Because the estrogen–progestin regimen exposes women to the same type of hormones, there has been a tendency to extrapolate from the risks of combined oral contraceptives. Although the estrogen–progestin regimen exposes a woman to a total of 200 μg of ethinyl estradiol, the exposure is short-term. One small study of the high-dose estrogen regimen[35] demonstrated a detrimental effect on clotting factors, but a similar study failed to show any consistent effect of estrogen plus progestin.[36]

Few adverse events associated with estrogen plus progestin have been reported in the United Kingdom (Committee on Safety of Medicines: personal communication). In the 13 years since Schering PC4 was licensed, it has been used on more than 4 million occasions. By the middle of 1996, there had been 115 reports of 159 "reactions" (some women had more than 1), 61 of which were pregnancies. In the United Kingdom only three cases of venous thrombosis (one fatal) and three cases of cerebrovascular disorder have been reported, and in none was the relation between the administration of estrogen and progestin and the event clear-cut. In contrast, the risk of venous thrombosis during pregnancy is on the order of 60 per 100,000 per year. Both the World Health Organization,[37] which in 1996 added the estrogen–progestin regimen to its "essential drugs list," and the International Planned Parenthood Federation[38] have stated that there are no absolute contraindications to the use of the estrogen–progestin regimen except known pregnancy.

Reliable data on the outcome of pregnancies that occurred after estrogen and progestin were taken are lacking, but the absence of demonstrable teratogenicity of combined oral contraceptives[39,40] and the timing of emergency contraception — long before organogenesis starts — are reassuring. Thus, the estrogen–progestin regimen is contraindicated in pregnancy only because it does not work once pregnancy is established, not because it is known to be harmful.

ESTROGEN ALONE

High doses of estrogen — usually ethinyl estradiol in a variety of regimens — given for five consecutive days are extremely effective as postcoital contraception, with failure rates of only 0.1 to 1 percent.[6,7] Side effects, particularly nausea (in 70 percent of women) and vomiting (in 33 percent), are common, and many clinicians stopped using estrogen alone when the estrogen–progestin regimen was described. The so-called five-by-five regimen (five tablets of 1 mg of ethinyl estradiol each, given daily for five days) is still used in the Netherlands,[41] where some clinicians believe it is more effective than the estrogen–progestin regimen. However, a double-blind, randomized study comparing the two regimens in the Netherlands demonstrated no difference in efficacy or, in fact, in the incidence of nausea and vomiting.[5]

THE INTRAUTERINE CONTRACEPTIVE DEVICE

The copper-bearing intrauterine device is a highly effective postcoital contraceptive, with failure rates of less than 1 percent.[11,42] In the United Kingdom it is used for up to five days after the earliest estimated day of ovulation, which may, of course, be more than five days after intercourse. It is particularly appropriate for women who wish to use the intrauterine device as a long-term method of contraception. However, most women requesting emergency contraception are young and nulliparous, and it can be difficult to insert a device if the uterus is small. Because of the risk of inducing pelvic infection if the device is inserted in the presence of a sexually transmitted disease, it is commonplace to screen women for infection, or to give an antibiotic, before insertion.

PROGESTIN ALONE

Progestin without estrogen has been tested as a postcoital agent in only one randomized trial.[4] Taken within 48 hours after unprotected intercourse, two 0.75-mg doses of levonorgestrel, given 12 hours apart, resulted in failure rates similar to those with the estrogen–progestin regimen (2.6 percent for estrogen–progestin vs. 2.4 percent for levonorgestrel). Side effects, however, were significantly less common with levonorgestrel. A levonorgestrel-only product (Postinor) is available from pharmacists in parts of Eastern Europe, the Far East, and many developing countries.

DANAZOL

The antigonadotropin danazol is an effective emergency contraceptive when given within 72 hours after intercourse. In one study the failure rates were 1.7 percent among women given two doses of 400 mg each 12 hours apart and 0.8 percent among women given three doses at 12-hour intervals.[10] However, a randomized study in the United Kingdom comparing estrogen plus progestin with danazol (two doses of 600 mg each, given 12 hours apart) suggested that danazol may be ineffective when used after intercourse.[9]

ANTIPROGESTINS

The antiprogestin mifepristone has also been tested as an emergency contraceptive. Two randomized trials,[8,9] involving a total of almost 600 women, compared 600 mg of mifepristone with the estrogen–progestin regimen. Mifepristone given within 72 hours after intercourse was 100 percent effective in preventing pregnancy, whereas the estrogen–progestin regimen was estimated to have prevented between 66 percent[22] and 83 percent[8] of pregnancies. The difference between the two regimens is not surprising, because mifepristone is known to inhibit implantation as well as ovulation and so, in theory, should almost always prevent pregnancy. All side effects were much less common among the women given mifepristone; however, in one of the studies 42 percent of women had a delay of more than three days in the onset of the next menstrual period.[8] This delay was particularly likely to occur if mifepristone was given during the follicular phase of the cycle, when it is known to inhibit ovulation.[16] This is an obvious drawback of mifepristone, because the onset of menses reassures the woman who has used emergency contraception that she is not pregnant. A lower dose of a mifepristone compound with a shorter half-life may not disrupt the timing of subsequent menses. Mifepristone is now used in a variety of doses in parts of China as the postcoital contraceptive of first choice.

AVAILABILITY OF EMERGENCY CONTRACEPTION

Emergency contraception is not universally available. It is not licensed, for example, in France or in the United States, although in February 1997 the U.S. Food and Drug Administration (FDA) published a formal notice in the *Federal Register* stating that six brands of commonly used combined oral-contraceptive pills were safe and effective for emergency postcoital use.[43] The main reasons for the lack of wider use of emergency contraception were discussed at a meeting held in Italy in 1995.[44] The par-

ticipants concluded that both women and providers are, by and large, poorly informed about the available methods. Because currently available hormonal regimens must be started within 72 hours after intercourse, a woman has to know about the method before the need for it arises. A number of surveys in some developed countries have demonstrated that whereas knowledge of the existence of emergency contraception is widespread among selected populations of potential users[45,46] (including teenagers[47]), knowledge of the details and practicalities, particularly the time limit, is usually poor. In the United States, a toll-free emergency-contraception hot line operated by the Reproductive Health Technologies Project and Bridging the Gap Foundation (1-800-584-9911) provides callers with information about all available methods and about local providers. In the first year it was available, the service received more than 40,000 calls.

Very few products are marketed for emergency contraception, and pharmaceutical companies appear to be reluctant to enter the market. According to the FDA, no U.S. drug manufacturer has sought formal approval for the emergency use of an oral-contraceptive regimen, despite requests from the agency that they do so.[48] In 1996 several international agencies formed a Consortium for Emergency Contraception that was committed to making emergency contraception a standard part of reproductive health care throughout the world. Working in partnership with the pharmaceutical industry, the consortium aims to improve access through "model introductions" in selected countries of specially packaged and labeled products, including the little-researched progestin-only regimen.

In addition, providers in many countries seem reluctant to provide emergency contraception because it is confused with abortion. It cannot be stressed too strongly that if hormonal emergency contraception works largely by interfering with ovulation, then it cannot be regarded as an abortifacient. When administered within 72 hours after a single act of intercourse, even compounds known to interrupt established pregnancy cannot dislodge an implanted embryo, because implantation would not have occurred yet. For most providers and many potential users, acceptance of emergency contraception would improve if their knowledge improved and if the distinction between a method that a woman can use when she thinks that she might become pregnant (contraception) and something to use when she thinks she might already be pregnant (an abortifacient) were clearly understood.

Even in countries where hormonal emergency contraception is licensed and free, such as the United Kingdom, its use is limited by difficulty of access.[45] In the United Kingdom, emergency contraception must be prescribed by a doctor. Unprotected intercourse, particularly among young people, tends to occur on weekends, when clinics are closed and when calling the emergency doctor seems inappropriate. The proposal that Schering PC4 should be sold over the counter in pharmacies has been widely discussed in the United Kingdom.[49] Despite support for the proposal from the Royal College of Obstetricians and Gynaecologists, the Royal College of General Practitioners, and the Royal Pharmaceutical Society, it has not happened yet. The Ministry of Health in New Zealand had expected emergency contraception to be available over the counter by July 1996.[50] The New Zealand Medical Association and the Royal New Zealand College of General Practitioners opposed the move, however, as did the pharmaceutical industry, which is apparently concerned about misuse, incorrect use, and medicolegal risks. The Ministry of Health promised to allow pharmacists to cut up packets of pills and label them appropriately if the pharmaceutical industry did not respond to the request to change the prescription-only status of the marketed estrogen–progestin regimen. Despite even this governmental pressure, emergency contraception is not yet available over the counter in New Zealand. Of course, in countries where oral-contraceptive pills are available over the counter, hormonal regimens for emergency contraception are already available without prescription.

CONCLUSIONS

Emergency contraception prevents unwanted pregnancy. The most widely used method, a combination of ethinyl estradiol and levonorgestrel, although it is marketed as an emergency contraceptive in only a few countries, is available throughout the world in the form of combined oral-contraceptive pills. Indeed, countless women already have supplies in their bathroom cupboards. When started within 72 hours after intercourse, the estrogen–progestin regimen has been estimated to be at least 75 percent effective and is safe. The antiprogestin mifepristone is even more effective and has fewer side effects.

Use of emergency contraception is limited largely by ignorance. Although it seems likely that the estrogen–progestin regimen works mainly by interfering with ovulation, it is nevertheless regarded by many as an abortifacient because it is taken after, rather than before, intercourse. This confusion is compounded when mifepristone is advocated for emergency contraception since, when taken after pregnancy is established, it can be and is used for the induction of abortion. The prevention of pregnancy before implantation is contraception and not abortion. Intervention within 72 hours after intercourse cannot possibly amount to abortion, because implantation is not achieved until at least seven days after ovulation and the egg is capable of being fertilized for only about 24 hours.

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