CLINICAL PRACTICE

Emergency Contraception

Carolyn Westhoff, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

From the Department of Obstetrics and Gynecology, Columbia University, New York. Address reprint requests to Dr. Westhoff at the Department of Obstetrics and Gynecology, Columbia University, 630 West 168 St., New York, NY 10032, or at clw3@columbia.edu.

N Engl J Med 2003;349:1830-5.

A healthy 19-year-old woman comes in for a routine appointment. She is sexually active in a monogamous relationship. Pregnancy is not currently desired. Her partner uses condoms most of the time. She is uncertain of the date of her last menstrual period but has had sexual intercourse several times since her last menses, including unprotected intercourse four days earlier. A high-sensitivity urine test for pregnancy is negative. Should emergency contraception be prescribed?

THE CLINICAL PROBLEM

About 3 million unintended pregnancies occur each year in the United States.[1] Most of these result from the nonuse of contraception or from a noticeable contraceptive failure, such as a broken condom,[2] and could be prevented with the use of emergency contraception.

A fertile couple has a 25 percent chance of pregnancy with repeated unprotected intercourse during a single menstrual cycle. In a large, prospective study of couples seeking pregnancy, a single act of unprotected intercourse occurring about one to two days before ovulation was associated with an 8 percent risk of pregnancy.[3,4] However, among women 19 to 26 years of age (the age group in which fertility is greatest), the chance of pregnancy may be as high as 50 percent when unprotected intercourse occurs during this interval.[5]

Because sperm can survive in the female genital tract for five to six days, fertilization may occur days after sexual activity. Even the most sensitive pregnancy test will not be positive until after the implantation of a fertilized egg in the uterus, an event that occurs about seven days after fertilization.[6]

STRATEGIES AND EVIDENCE

Immediate use of an emergency contraceptive will reduce a woman's risk of pregnancy to 1 to 2 percent. The effectiveness depends on the regimen used and on the time between unprotected intercourse and treatment. Table 1 lists the main types of emergency contraception.

THE YUZPE REGIMEN

An approach first studied in the 1970s by Yuzpe et al. is the use of two doses of a combination oral contraceptive containing 100 μg of ethinyl estradiol and 1.0 mg of the progestin norgestrel.[7] This treatment has been approved by the Food and Drug Administration (FDA) and is available by prescription (Preven, Roche); two tablets are given twice, 12 hours apart (a total of four tablets).[8] A similar approach with the same efficacy is to use pills from a package of combination birth-control pills that contain the proges-

tin norgestrel; each dose must contain 1.0 mg of norgestrel or 0.5 mg of its active isomer levonorgestrel, along with 100 μg of ethinyl estradiol. Depending on the brand of pill, two to five pills are required per dose. This treatment reduces the risk of pregnancy to about 2 percent, as compared with about 8 percent in the absence of treatment.[9] The main side effects are nausea (in at least 50 percent of women) and vomiting (in about 20 percent), which can be minimized or prevented by prior or concomitant treatment with an antiemetic (e.g., 10 mg of metoclopramide).[10] The next menses after treatment will usually occur within one week before or after the expected date; if menses do not occur within three to four weeks after treatment, then a pregnancy test is indicated.

Table 1. Types of Emergency Contraception.

Class	Dose	Brands Available in the United States
Combined oral contraceptives	100 μg of ethinyl estradiol and 0.5 mg of levonorgestrel twice 12 hr apart	Preven (Gynétics) Ovral (Wyeth)*
Progestin-only oral contraceptives	1.5 mg of levonorgestrel once or 0.75 mg twice 12 hr apart	Plan B (Women's Capital Corporation)
Copper T intrauterine device	—	ParaGard T 380A (Ortho-McNeil)
Antiprogestins	10 mg of mifepristone	None at this dose

* Other hormonal contraceptives that are effective for emergency contraception, along with the doses and instructions for use, are listed at http://www.not-2-late.com.

PROGESTIN-ONLY REGIMEN

A newer, more effective approach to emergency contraception is the use of progestin-only contraceptive tablets. An FDA-approved product (Plan B, Women's Capital Corporation) is available in the United States and consists of 0.75-mg tablets of levonorgestrel, to be taken within 72 hours after unprotected intercourse in two doses separated by 12 hours.[11]

Clinical trials directly comparing a progestin-only regimen with a combined estrogen–progestin regimen indicate that the progestin-only approach is more effective, reducing the risk of pregnancy to 1 percent and the incidence of nausea and vomiting to 22 percent and 8 percent, respectively.[12] Recent data indicate that the levonorgestrel-only treatment can be given once in a single dose, rather than twice in a divided dose, with the same efficacy.[13] In contrast, a single dose of combination hormonal contraceptive pills (including 200 μg of ethinyl estradiol) cannot be recommended, given the lack of data regarding its effectiveness and the likelihood of more severe side effects.

TIMING OF USE

Both the combination and the progestin-only regimens of emergency contraception were originally studied for use up to three days after a single unprotected act of intercourse. Data from a large, randomized clinical trial demonstrated that pregnancy rates were lowest when emergency contraception was initiated within 12 hours after unprotected intercourse, with a monotonic decrement in effectiveness as the interval between unprotected intercourse and treatment increased. The pregnancy rate was less than 1 percent when treatment was given within 12 hours, as compared with over 3 percent when treatment was given 61 to 72 hours after intercourse.[13,14] Other studies, however, have not shown a strong relation between the timing of therapy and efficacy.[15] Two observational studies indicate that treatment 72 to 120 hours after intercourse results in pregnancy rates similar to those in studies of earlier treatment.[16,17] Emergency contraception should thus be offered for any act of unprotected intercourse that has occurred in the preceding five days, even if the patient has had other unprotected acts earlier in the same menstrual cycle. Because the length of the menstrual cycle varies and the day of ovulation is generally unknown even in women who report having regular cycles,[18] treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

OTHER APPROACHES

Other strategies for postcoital contraception are either less well studied or less available than progestin-only or combination regimens. Combination oral contraceptives that contain other progestins may be similar in effectiveness to pills containing levonorgestrel. In a randomized clinical trial that included nearly 1200 women, the pregnancy rate after two doses of a norethindrone-containing oral contraceptive (2.0 mg per dose) did not differ significantly from the rate after two doses of a levonorgestrel-containing pill (the Yuzpe regimen) (2.7 percent and 2.0 percent, respectively).[19]

Insertion of a copper-containing intrauterine device (IUD) up to five days after unprotected inter-

course also reduces the risk of pregnancy. This approach is supported by published case series that included 879 insertions of an IUD after intercourse, with only one pregnancy.[20] A randomized clinical trial compared the use of two different copper-bearing IUDs among 192 women requesting emergency contraception, most of whom were nulliparous. Follow-up data were available for 98 percent of the women at six weeks; there were no pregnancies and no cases of pelvic inflammatory disease.[21] However, the number of pregnancies that would have been expected without treatment was not clear.

An important benefit of IUD insertion is that it provides continued contraception; 80 percent of the trial participants continued using the IUD after completion of the study.[21] In other studies of hormonal emergency contraception, pregnancies occurred in women who had additional acts of unprotected intercourse later in the same cycle,[19] indicating the importance of providing ongoing contraception immediately. An IUD is more expensive than hormonal emergency contraception but is cost effective for women who choose to use it long-term.[22] The copper IUD is approved by the FDA for use for up to 10 years, and clinical data indicate that its effectiveness lasts for at least 12 years.

Mifepristone, a progesterone-receptor antagonist used for medical abortion, is another alternative. Randomized clinical trials show that a single 10-mg dose of mifepristone is as effective as the levonorgestrel-containing regimens,[13] with an even lower incidence of nausea and vomiting. However, the 10-mg dose is not commercially available in the United States. The 200-mg tablet that is used for medical abortion is available in the United States only to physicians who establish an account with the distributor, severely limiting access. In addition, mifepristone is more expensive than other hormonal therapies. New antiprogestins are being studied for this indication and may have similar effectiveness.[23]

SAFETY OF EMERGENCY CONTRACEPTION

A theoretical concern is that the use of combined oral contraceptives for emergency contraception might increase the risk of thrombotic events, such as venous thromboembolism or stroke, that are associated with long-term use of these products.[24,25] Such adverse events did not occur in the clinical trials evaluating these agents; however, the studies lacked power to detect rare events. A Medline search for reports of thrombotic events that occurred in association with hormonal emergency contraception yielded four case reports of cerebrovascular complications[26-29] — all of which followed the use of combination hormonal therapy. No case reports of cerebrovascular events were identified in association with the use of progestin-only emergency contraceptives, nor were there reports of deep-vein thrombosis or pulmonary embolism after either type of hormonal contraception.

Population-based or case–control studies of cerebral thrombosis after emergency contraception have not been performed. A population-based retrospective cohort study[30] assessed the risk of venous thromboembolism among users of combination hormonal emergency contraception, on the basis of data from the General Practice Research Database in the United Kingdom. The analysis included 73,302 women who received 100,615 prescriptions for postcoital contraception between 1989 and 1996; of these women, 19 had a deep-vein thrombosis or a pulmonary embolus during follow-up. There were no venous thromboembolic events during the 45 days after the receipt of any prescription for emergency contraception. In contrast, the risk of venous thromboembolism was increased during pregnancy and with ongoing use of oral contraceptives — observations that support the validity of the analysis.

There are no absolute contraindications to the use of hormonal emergency contraception. Even for women who have contraindications to the long-term use of combination hormonal contraception (such as liver disease or a history of thromboembolism),[31] the balance of risks and benefits may favor the brief hormonal exposure resulting from emergency contraception over the possibility of a high-risk pregnancy. Progestin-only emergency contraception or the insertion of an IUD should be considered first in women with these or other medical contraindications to combination oral contraceptives, especially given the effectiveness of these approaches and the low rate of side effects. Insertion of an IUD for emergency contraception should be performed according to the regular guidelines for IUD use.[32] This approach should be avoided, for instance, in women with active, recent, or recurrent pelvic infections.

OUTCOMES OF PREGNANCY AFTER EMERGENCY CONTRACEPTION

Pregnancies can be established, but not diagnosed, at the time of emergency contraceptive use or can be associated with the failure of the emergency con-

traceptive. Although case reports have described ectopic pregnancy after the use of emergency contraception, there is no good evidence of an increased risk of this outcome.[33,34] In a large World Health Organization trial, only 42 pregnancies were identified after nearly 2000 treatments,[12] and none were ectopic. Five of these pregnancies were continued, with normal outcomes. No studies have been large enough to quantify the teratogenic risk among the very small number of pregnancies that follow the use of emergency contraception. However, observations that there is no increase in birth defects among pregnancies exposed to daily use of combined oral contraceptives are reassuring.[35]

Patients who had a recent menstrual period at the usual time and with the usual flow do not need a pregnancy test before using emergency contraception.[36] If the patient's menstrual history is either vague or unusual, then a pretreatment pregnancy test may allow earlier diagnosis of a pregnancy that is already established, facilitating earlier prenatal care,[37] or an earlier abortion. A physical examination is unnecessary before treatment.[38]

ADVANCE PRESCRIBING

Emergency contraception is currently available by prescription only; therefore, there may be a substantial delay between the time women identify the need for treatment and the time they receive it.[39] Clinicians can help prevent this problem by providing emergency contraception in advance of need. Several clinical trials, three of them randomized, have compared the effects of advance provision of emergency contraception with the effects of education alone.[40-44] All these trials found that advance provision increased the use of emergency contraception, that the use was appropriate, that women did not abandon or decrease the use of their regular contraceptives, and that advance provision led to a reduction in the number of unintended pregnancies. These studies were too small, however, to identify a significant difference in the pregnancy rate. No serious adverse events were observed.

POSSIBLE OVER-THE-COUNTER STATUS

The FDA is currently evaluating an application for a switch to over-the-counter status for the levonorgestrel-only formulation of emergency contraceptive. Hormonal emergency contraception is highly suitable for such a switch. The dose is the same for everyone, there are no contraindications to its use, adverse events are rare, and there is no potential for addiction.[45] Repeated use is safe and reasonably effective but is unlikely to replace long-term contraception, owing to the expense and side effects such as menstrual changes.[46]

AREAS OF UNCERTAINTY

The mechanism of action of emergency contraception is incompletely understood. It does not interfere with an established, postimplantation pregnancy. The use of emergency contraception can delay ovulation and decrease the probability of fertilization after ovulation[47]; at least some of its effect appears to occur after ovulation.[48]

Immediate initiation of long-term contraception is desirable to reduce the risk of pregnancy after treatment. A small, nonrandomized study in which the use of oral contraceptives was initiated on the same day as a levonorgestrel-only emergency contraceptive found that this approach was highly acceptable to patients[49] and was associated with higher rates of continuation of the oral contraceptive than was waiting to start long-term contraception. Whether immediate initiation of oral contraceptives influences the effectiveness of therapy or increases the rate of side effects has not been studied.

GUIDELINES

Both the American Medical Association and the American College of Obstetricians and Gynecologists (ACOG) encourage physicians and other professionals to discuss emergency contraception as part of routine family planning and contraceptive counseling and promote efforts to expand access to such treatment, including making it available in physicians' offices.[50,51] ACOG recommends both combination and progestin-only hormonal methods but advises that the progestin-only approach be considered first. ACOG also specifically supports efforts to make emergency oral contraception available to women over the counter in a designated product.[52]

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the clinical vignette, who had had unprotected intercourse four days earlier, should receive emergency contraception as soon as possible. The preferred regimen is the levonorgestrel-only product at a dose of 1.5 mg, since this is

highly effective and generally well tolerated. If supplies are not available in the physician's office, the physician should be able to identify a local pharmacy that stocks this product. In addition, the physician should provide refills of this prescription or provide a separate prescription that the patient can use in case she has unprotected intercourse again. Having emergency contraception readily available does not lead to the abandonment of other forms of contraception.

The use of regular contraception should also be emphasized, along with condom use to reduce the transmission of sexually transmitted diseases. If hormonal contraception is chosen, it should be initiated immediately, rather than waiting for the patient's next menstrual period. Some pregnancies in clinical trials resulted from additional acts of unprotected intercourse later in the same menstrual cycle. Ample refills should be provided, since running out of pills is a major reason for unintended pregnancy among users of oral contraceptives.[2] A need for emergency contraception should prompt consideration of screening for sexually transmitted diseases, such as chlamydia.[53] A follow-up pregnancy test is indicated if the patient does not have withdrawal bleeding after finishing her first pack of oral contraceptives or, for those who do not immediately begin taking oral contraceptives, if menses do not occur within three to four weeks after treatment.

Until a dedicated product is widely available over the counter, emergency contraception should routinely be provided in advance of need. Eligible women should include those who are not currently sexually active, since they are unlikely to have an ongoing method of contraception and are at risk if they become sexually active.

Dr. Westhoff reports having received research grants from Berlex Laboratories and honorariums for consulting from Barr Laboratories.

REFERENCES

1. Henshaw SK. Unintended pregnancy in the United States. Fam Plann Perspect 1998; 30:24-9, 46.
2. Jones RK, Darroch JE, Henshaw SK. Contraceptive use among U.S. women having abortions in 2000-2001. Perspect Sex Reprod Health 2002;34:294-303.
3. Wilcox A, Weinberg C, Baird D. Timing of sexual intercourse in relation to ovulation: effects on the probability of conception, survival of the pregnancy, and sex of the baby. N Engl J Med 1995;333:1517-21.
4. Baird D, Weinberg C, Zhou H, et al. Preimplantation urinary hormone profiles and the probability of conception in healthy women. Fertil Steril 1999;71:40-9.
5. Dunson DB, Colombo B, Baird DD. Changes with age in the level and duration of fertility in the menstrual cycle. Hum Reprod 2002;17:1399-403.
6. Norwitz E, Schust D, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345:1400-8.
7. Yuzpe AA, Smith RP, Rademaker AW. A multicenter clinical investigation employing ethinyl estradiol combined with dl-norgestrel as postcoital contraceptive agent. Fertil Steril 1982;37:508-13.
8. Preven emergency contraceptive. Somerville, N.J.: Gynetics, Inc., 2000 (package insert).
9. Trussell J, Rodriguez G, Ellertson C. Updated estimates of the effectiveness of the Yuzpe regimen of emergency contraception. Contraception 1999;59:147-51.
10. Raymond EG, Creinin MD, Barnhart KT, Lovvorn AE, Rountree RW, Trussell J. Meclizine for prevention of nausea associated with the use of emergency contraceptive pills: a randomized trial. Obstet Gynecol 2000; 95:271-7.
11. Plan B. Washington, D.C.: Women's Capital Corporation, 2003 (package insert).
12. Task Force on Postovulatory Methods of Fertility Regulation. Randomised controlled trial of levenorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Lancet 1998;353: 428-32.
13. von Hertzen H, Piaggio G, Ding J, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO mulitcentre randomized trial. Lancet 2002;360:1803-10.
14. Piaggio G, von Hertzen H, Grimes D, Van Look PFA. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Lancet 1999;353:721.
15. Trussell J, Ellertson C, Rodriguez G. The Yuzpe regimen of emergency contraception: how long after the morning after? Obstet Gynecol 1996;88:150-4.
16. Ellertson C, Evans M, Ferden S, et al. Extending the time limit for starting the Yuzpe regimen of emergency contraception to 120 hours. Obstet Gynecol 2003;101:1168-71.
17. Rodrigues I, Grou F, Joly J. Effectiveness of emergency contraceptive pills between 72 and 120 hours after unprotected sexual intercourse. Am J Obstet Gynecol 2001;184: 531-7.
18. Wilcox AJ, Dunson D, Baird DD. The timing of the "fertile window" in the menstrual cycle: day specific estimates from a prospective study. BMJ 2000;321:1259-62.
19. Ellertson C, Webb A, Blanchard K, et al. Modifying the Yuzpe regimen of emergency contraception: a multicenter randomized controlled trial. Obstet Gynecol 2003;101: 1160-6.
20. Fasoli M, Parazzini F, Cecchetti G, La Vecchia C. Post-coital contraception: an overview of published studies. Contraception 1989;39:459-68.
21. D'Souza RE, Masters T, Bounds W, Guillebaud J. Randomised controlled trial assessing the acceptability of GyneFix versus Gyne-T380S for emergency contraception. J Fam Plann Reprod Health Care 2003; 29:23-9.
22. Trussell J, Koenig J, Ellertson C, Stewart F. Preventing unintended pregnancy: the cost-effectiveness of three methods of emergency contraception. Am J Public Health 1997;87:932-7.
23. Stratton P, Hartog B, Hajizadeh N, et al. A single mid-follicular dose of CDB-2914, a new antiprogestin, inhibits folliculogenesis and endometrial differentiation in normally cycling women. Hum Reprod 2000; 15:1092-9.
24. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease: World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1995;346:1582-8.
25. Schwartz SM, Petitti DB, Siscovick DS, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke 1998;29:2277-84.
26. Sanchez-Ojanguren J, Escudero D, Zapata A. Occlusion of the right common carotid artery due to oral estrogen overdose. Rev Neurol 1998;27:604-6.
27. Lake SR, Vernon S. Emergency contra-

ception and retinal vein thrombosis. Br J Ophthalmol 1999;83:630-1.
28. Sanchez-Guerra M, Valle N, Blanco L, Combarros O, Pascual J. Brain infarction after postcoital contraception in a migraine patient. J Neurol 2003;249:774.
29. Hamandi K, Scolding J. Emergency contraception and stoke. J Neurol 2003;250: 615-6.
30. Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. Contraception 1999;59:79-83.
31. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2nd ed. Geneva: World Health Organization, 2000.
32. Speroff L, Darney PD. A clinical guide for contraception. 3rd ed. Baltimore: Williams & Wilkins, 2001.
33. Nielsen C, Miller L. Ectopic gestation following emergency contraceptive pill administration. Contraception 2000;62:275-6.
34. Sheffer-Mimouni G, Pauzner D, Maslovitch S, Lessing JB, Gamzu R. Ectopic pregnancies following emergency levonorgestrel contraception. Contraception 2003;67: 267-9.
35. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. Obstet Gynecol 1990;76:552-7.
36. Grimes DA, Raymond EG. Bundling a pregnancy test with the Yupze regimen of emergency contraception. Obstet Gynecol 1999;94:471-3.
37. Arab L, Carriquiry A, Steck-Scott S, Gaudet MM. Ethnic differences in the nutrient intake adequacy of premenopausal US women: results from the Third National Health Examination Survey. J Am Diet Assoc 2003;103:1008-14.
38. Stewart FH, Harper CC, Ellertson CE, Grimes DA, Sawaya GF, Trussell J. Clinical breast and pelvic examination requirements for hormonal contraception: current practice vs evidence. JAMA 2001;285:2232-9.
39. Trussell J, Duran V, Shochet T, Moore K. Access to emergency contraception. Obstet Gynecol 2000;95:267-70.
40. Glasier A, Baird D. The effects of self-administering emergency contraception. N Engl J Med 1998;339:1-4.
41. Raine T, Harper C, Leon K, Darney P. Emergency contraception: advance provision in a young, high-risk clinic population. Obstet Gynecol 2000;96:1-7.
42. Jackson R, Bimla Schwarz E, Freedman L, Darney P. Advance supply of emergency contraception: effect on use and usual contraception — a randomized trial. Obstet Gynecol 2003;102:8-16.
43. Ellertson C, Ambardekar S, Hedley A, Coyaji K, Trussell J, Blanchard K. Emergency contraception: randomized comparison of advance provision and information only. Obstet Gynecol 2001;98:570-5.
44. Ng E, Damus K, Bruck L, MacIsaac L. Advance provision of levonorgestrel-only emergency contraception versus prescription. Obstet Gynecol 2003;101:Suppl:13S. abstract.
45. Grimes DA. Switching emergency contraception to over-the-counter status. N Engl J Med 2002;347:846-9.
46. Efficacy and side effects of immediate postcoital levonorgestrel used repeatedly for contraception. Contraception 2000;61: 303-8.
47. Croxatto H. Emergency contraception pills: how do they work? IPPF Med Bull 2002; 36:1-2.
48. Trussell J, Raymond EG. Statistical evidence about the mechanism of action of the Yuzpe regimen of emergency contraception. Obstet Gynecol 1999;93:872-6.
49. Westhoff C, Kerns J, Morroni C, Cushman LF, Tiezzi L, Murphy PA. Quick start: novel oral contraceptive initiation method. Contraception 2002;66:141-5.
50. American Medical Association. Policy Statement H-75.985: access to emergency contraception. Chicago: American Medical Association.
51. ACOG Practice Bulletin. Gynecology: emergency oral contraception. ACOG Pract Bull 2001;25:1-14.
52. Statement of the American College of Obstetricians and Gynecologists supporting the availability of over-the-counter emergency contraception. Washington, D.C.: American College of Obstetricians and Gynecologists, February 2001.
53. Berg AO, Allan JD, Frame PS, et al. Screening for chlamydia infection: recommendations and rationale. Am J Nurs 2002; 102:87-92.