

PEER REVIEWED

Levonorgestrel for Emergency Contraception

Controversy continues regarding Plan B®

by Susan Kleppin, RPh

Emergency post-coital contraception can be defined as use of a drug or device taken with the intention to prevent pregnancy after unprotected sexual intercourse or contraceptive failure.¹ Since the 1960s, hormonal agents have been used as emergency contraception. High-dose estrogen was used first, followed by combination estrogen and progestin regimens using oral contraceptive products (the Yuzpe method). Insertion of a copper-releasing intrauterine device can also be used for emergency contraceptive purposes. Since 1999, levonorgestrel (Plan B®) has been available in the United States as a third type of emergency contraception.

Public awareness about the availability of emergency contraception is low.² With all of the attention in the lay press and medical literature surrounding the use of Plan B® (levonorgestrel) for emergency contraception, the FDA's refusal to approve the manufacturer's application for over-the-counter sale of the product, and moral objections raised over the prescribing and dispensing of Plan B® and other oral contraceptives, it is important for all health care providers to be well informed and provide accurate information about levonorgestrel, its proper use, and the controversies associated with it.

MECHANISM OF ACTION

The exact mechanism of action of hormonal emergency contraception is unknown. Levonorgestrel is believed to act as an emergency contraceptive by preventing ovulation or fertilization, inhibiting implantation by altering the endometrium, with one study concluding that levonorgestrel most often inhibits ovulation.³ More recent studies demonstrate that levonorg-

estrel works by preventing ovulation or fertilization and likely has little effect on implantation.^{4,6}

There is confusion about the difference between emergency contraception and medication abortion. Medication abortion is the use of medications that can induce abortion. There are currently two such medications available and used in the United States – mifepristone and methotrexate. Mifepristone (formerly known as RU-486) was approved by the FDA in 2000 and works by blocking the hormones necessary for maintaining a

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pregnancy. Unlike mifepristone or methotrexate, levonorgestrel cannot interrupt or disrupt an already established pregnancy.

CLINICAL EFFICACY

There have been two major prospective randomized controlled trials published that compare the clinical efficacy of levonorgestrel to the Yuzpe method.

Ho et al⁷ conducted a prospective randomized controlled trial in which

834 women were enrolled; 410 were randomized to receive levonorgestrel 0.75 mg on admission with a second dose administered 12 hours later, and 424 were randomized to receive 0.05 mg ethinyl estradiol and 0.25 mg levonorgestrel (the Yuzpe group) on admission with a second dose administered 12 hours later. Fifteen of the women in the Yuzpe group (3.5%) became pregnant and 12 of the women in the levonorgestrel group became pregnant (2.9%). Of these pregnancies, six in the Yuzpe group and four in the levonorgestrel group occurred in participants who had had further intercourse during the treatment cycle. After excluding these subjects, the failure rates were 2.7% (95% confidence interval [CI]: 1 - 4.1%) in the Yuzpe group and 2.4% in the levonorgestrel group (95% CI: 0.8 - 4.1%), a difference that was not statistically significant. The incidence of adverse effects including nausea, vomiting and fatigue, was significantly higher in the Yuzpe group. The authors concluded that levonorgestrel is an effective drug for post-coital contraception with a lower incidence of side effects than the Yuzpe regimen.

The second study, conducted by the World Health Organization, was a double-blind, randomized controlled trial that enrolled 1,998 women at 21 centers worldwide.⁸ Patients were randomized to receive either levonorgestrel 0.75 mg initially with a second dose 12 hours later (n=1001) or ethinyl estradiol 0.05 mg and 0.25 mg levonorgestrel initially with a second dose 12 hours later (n=997).

Forty-three women were lost to follow-up. Among the remaining 1955 subjects, the pregnancy rate was 1.1% (11/976) in the levonorgestrel group as compared to 3.2% (31/979) in the Yuzpe group. The data analysis also demonstrated that with either regimen, the earlier that emergency contraception was initiated, the more effective it was (see Table 1).

SIDE EFFECTS/CONTRAINDICATIONS

The most common adverse effects associated with levonorgestrel include nausea, abdominal pain, fatigue, headache and menstrual changes.⁹ These adverse effects are usually mild to moderate in severity and are self-resolving.

Contraindications to the use of levonorgestrel include known or suspected

pregnancy, hypersensitivity to any component of the product and undiagnosed abnormal genital bleeding.⁹ According to the American College of Obstetricians and Gynecologists and the World Health Organization, there are no absolute medical contraindications to the use of emergency contraception with the exception of pregnancy, and this is only because it is ineffective.^{1,6}

CONSULTATION FOR PATIENTS

Women who receive a prescription for levonorgestrel for emergency contraception should be counseled on the following:

Take the pills as soon as possible after unprotected sex. It is best to take levonorgestrel within 72 hours of unprotected sexual intercourse. The sooner you take this medication, the more effective it is. Take the first tablet as soon as possible after unprotected sex or suspected birth control failure and the second tablet 12 hours later.

Levonorgestrel is safe and effective. Taken as directed, levonorgestrel reduces the risk of pregnancy by 89%. Other contraceptive methods are more effective for regular, long-term use however.

Emergency contraception does not protect you against sexually transmitted diseases, including HIV/AIDS. You should still follow-up with your health care provider if you have concerns about having contracted a sexually transmitted disease.

Levonorgestrel will not cause an abortion. This medication is not effective after pregnancy has occurred and cannot interrupt it.

Side effects may include nausea, vomiting, fatigue and headache. Should you vomit within 1 hour after taking either tablet of this medication, contact your health care provider to discuss whether to repeat that dose.

If normal menstrual bleeding does not occur within 21 days after taking levonorgestrel or by 28 days if an oral contraceptive was initiated after levonorgestrel use, a pregnancy test should be taken. If needed, see your health care provider.

CONTROVERSY ABOUT OVER-THE-COUNTER AVAILABILITY

From a public health perspective, the use of levonorgestrel as emergency contraception could play an important role in helping to prevent unwanted pregnancies and in limiting the number of abortions performed. However, this public health goal cannot be achieved if women are not aware of the availability of levonorgestrel as an option for emergency contraception or if its availability is limited.

Barriers to the use of emergency contraception have been identified including: lack of knowledge of patients, patient fear of side effects, patient fear of or actual judgmental attitudes of health care providers, the need to see a health care pro-

vider to obtain a prescription for the medication, and lack of accessibility to clinics due to limited hours of operation.^{6,10}

Opponents to wider availability of levonorgestrel cite several concerns that could result in poor patient outcomes. These include concerns that easier access to levonorgestrel will result in women engaging in more frequent, unprotected sex; an increase in the incidence of sexually transmitted disease; a decrease in the use of effective, routine contraception; and the potential for repeat use.¹¹

Those in support of wider access to levonorgestrel point to use in other countries and to published medical literature that contradicts these opinions.^{2,11-16} In the United Kingdom for example, emergency contraception has been available without a prescription since 2001. Studies show that there is little evidence to suggest that easier access has led to frequent repeat use.²

Levonorgestrel is available without a prescription in several other countries including Canada, Portugal, Great Britain, Finland and France. In the United States, eight states, including Alaska, California, Hawaii, Maine, Massachusetts, New Hampshire, New Mexico and Washington, currently allow women to access levonorgestrel for emergency contraception directly from a pharmacist via a collaborative practice agreement.¹⁷ Legislation for pharmacy access has also been introduced in Illinois, Kentucky, Maryland, New Jersey, New York, Oregon, Texas and Vermont.

FDA ACTIONS AND LEGAL PROCEEDINGS

National Actions

On April 23, 2003, the manufacturer of Plan B®, Women's Capital Corporation, submitted an application to the FDA requesting a change to over-the-counter (OTC) status. Barr Laboratories has since acquired Women's Capital Corporation and has continued to pursue OTC status for this medication.

After consideration of the available medical evidence, the FDA's Reproductive Health Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee voted 23-4 in December 2003 to recommend that the FDA allow the OTC sale of Plan B®. In February 2004, the FDA announced that it needed an ad-

TABLE 1. PREGNANCY RATES BY TIME SINCE UNPROTECTED INTERCOURSE AND TREATMENT GROUP^a

Sexual intercourse-to-Treatment interval	Pregnancies/Total	Pregnancy rate (95% CI)
ALL WOMEN		
Yuzpe	31/979	3.2% (2.2 – 4.5)
Levonorgestrel	11/976*	1.1% (0.6 – 2)
≤ 24 HOURS		
Yuzpe	9/459	2% (0.9 – 3.7)
Levonorgestrel	2/450	0.4% (0.1 – 1.6)
25 – 48 HOURS		
Yuzpe	15/370	4.1% (2.3 – 6.6)
Levonorgestrel	4/338	1.2% (0.3 – 3)
49 – 72 HOURS		
Yuzpe	7/150	4.7% (1.9 – 9.4)
Levonorgestrel	5/187	2.7 (0.9 – 6.1)

^aOne subject did not have information on intercourse-to-treatment interval

ditional 90 days to consider the issue. An amendment to the application was offered by Barr in March 2004, offering to change the indication to allow for the marketing of Plan B as a prescription-only drug for those women less than 16 years of age and as an OTC drug for those 16 and older, in an attempt to expedite approval of the application.

In early May 2004, the FDA took the unusual action of rejecting its own advisory committee's recommendation and issued a "non-approvable" letter to Barr, citing a lack of safety data in younger women and further delaying final action on the application. In the letter, the FDA also requested additional information from the company regarding policy and regulatory issues that need to be resolved, including: 1) how a prescription and OTC version of the same drug could be marketed as a single product; 2) the proposed education for consumers and health care providers; and 3) what kind of program could be put into place to monitor implementation and how the age limitation could be enforced. The FDA then issued an advance notice of proposed rule-making on this topic in August and asked for public comment, with the 60-day comment period slated to end on November 1, 2005.¹⁸ The delay in the final ruling on whether Plan B[®] should be available OTC ultimately led to the resignation of Susan Wood, the former director of the FDA's Office of Women's Health, in late August 2005. The FDA has not made any announcements regarding this topic since the comment period ended.

Several medical organizations including the National Family Planning and Reproductive Health Association, the American College of Obstetricians and Gynecologists and the American Association of Pediatrics, support the OTC sale of Plan B[®] and have voiced their concerns on the issue to the FDA. On January 21, 2005, the Center for Reproductive Rights filed a federal lawsuit against the Commissioner of the FDA for failure to grant OTC status to Plan B[®].¹⁹

The Government Accountability Office (GAO), an independent, nonpartisan agency that investigates for Congress how the federal government spends taxpayer dollars, issued a report stating that the FDA has departed from its own policies when it considered the OTC status re-

quest for Plan B[®].²⁰ The report cited four inconsistencies with FDA policy in this case: 1) FDA directors of the offices that reviewed the Plan B[®] application, who would normally be required for signing any decision about a change to OTC status, refused to sign the non-approvable letter because they disagreed with it; 2) FDA's high-level managers were more involved in the review of Plan B[®] than was customary with other applications; 3) there was evidence suggesting that the decision not to approve the change to OTC status was already made even before review of the application was completed; and 4) the FDA's reasoning for postponing the approval did not follow the usual practices. The report went on to state that the Plan B[®] application for OTC status was the only one that the FDA did not approve since 1994, after advisory committees had recommended approval. The report was refuted by the FDA as being factually incorrect.

Wisconsin Actions

Wisconsin Attorney General Peg Lautenschlager joined others in seeking legal action when she announced on December 1, 2005 that she was seeking Governor Jim Doyle's permission to file a lawsuit against the FDA for the delay in approving the OTC status of Plan B[®]. She cited that the FDA delay in approving Plan B[®] as an OTC drug leaves few options for individuals who have had unprotected sex and that this could lead to unwanted pregnancies and births that adversely affect state residents and resources. Governor Doyle subsequently granted permission for the lawsuit to be filed on behalf of the citizens of the State of Wisconsin. On March 15, 2006, Lautenschlager announced that she had asked a federal court judge in New York that Wisconsin join the lawsuit filed by the Center for Reproductive Rights.

CONCLUSION

Politics and moral objections aside, it is important that women are educated about the availability of levonorgestrel as a form of emergency contraception, its use and side effects. Improved access to the medication, whether in pharmacies with a valid prescription or by over-the-counter purchase, remains the desire of the public

health community at large, and this issue will continue to be debated in health care provider offices, pharmacies, the state and federal governments, and perhaps even in our courts. ●

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