

**PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLs)**

# Piroxicam Plus Plan B for Emergency Contraception

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**Consider combination therapy using Levonorgestrel with Piroxicam as an option for female patients, seeking a noninvasive, affordable and practical option for emergency oral contraception. (J Am Board Fam Med 2025;38:395–398.)**

**Keywords:** Combination Drug Therapy, Emergency Contraception, Levonorgestrel, Piroxicam

**Strength of Recommendation: B**

Based on moderate quality RCT (Randomized Controlled Trial) with limitations on data collection and implementation.<sup>1</sup>

**Illustrative Case**

A 20-year-old female presents to the Emergency Room with concerns for possible pregnancy. She states she had intercourse the night before. Unfortunately, she is unsure if her male partner wore a condom. It has been less than 24 hours since, and she states she is not ready to be pregnant at this time. She is not currently using any form of birth control. Her Body Mass Index is 22 kg/m<sup>2</sup> and she has no comorbid medical conditions. She has no interest in Long-Acting Reversible Contraception (LARC). In addition

to sexually transmitted infection testing and offering postexposure prophylaxis, should you prescribe her Levonorgestrel alone or would you consider adding a dose of Piroxicam to further decrease her risk of unintended pregnancy?

**Clinical Context**

Unwanted pregnancies present significant challenges for individuals and health care providers, emphasizing the critical need for accessible and effective options for pregnancy prevention and termination. In the clinical context, unwanted pregnancies can occur due to several reasons, including contraceptive failure, unprotected sexual intercourse, sexual assault, or lack of access to reproductive health care services. These pregnancies can have profound physical, emotional, and socioeconomic implications for individuals and their families, underscoring the importance of timely intervention and support.<sup>2,3</sup> Emergency oral contraception (EOC) plays a crucial role in addressing unwanted pregnancies by providing individuals with means for preventing pregnancy following unprotected intercourse or contraceptive failure. EOC methods, such as Ulipristal Acetate, Levonorgestrel, and Piroxicam, offer a noninvasive and convenient option for individuals seeking to avoid unintended pregnancies.<sup>2</sup> Understanding the clinical context surrounding unwanted pregnancies and the available data on all options for EOC is essential for health care providers in guiding patient care and decision making.

Levonorgestrel, a progestin-only contraceptive commonly known as Plan B, is one of the most widely

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used forms of EOC. It primarily works by inhibiting ovulation but only before lutenizing hormone surge. Extensive clinical studies have demonstrated the efficacy of Levonorgestrel in preventing pregnancy when taken within a specific period after unprotected intercourse.<sup>4</sup> Research indicates that Levonorgestrel can significantly reduce the risk of pregnancy when administered up to 72 hours (about 3 days) after unprotected intercourse, with its efficacy decreasing over time.<sup>5-8</sup> Levonorgestrel-based EOC is available over the counter in many countries and is considered safe and well-tolerated by most individuals. Piroxicam, a nonsteroidal anti-inflammatory drug (NSAID), has also been explored as a potential option for EOC. While traditionally used for pain relief and inflammation, studies have investigated its contraceptive properties due to its prostaglandin-inhibiting effects.<sup>9,10</sup> Limited clinical data exist on the use of Piroxicam as EOC, and further research is needed to establish its efficacy in this context. Investigators theorized that Piroxicam may enhance the emergency contraceptive effect when coadministered with Levonorgestrel shortly after unprotected intercourse.<sup>1</sup> This combination type of therapy may offer a synergistic effect by targeting multiple pathways involved in fertilization and implantation. However, further studies are needed to determine the optimal combination regimens and their effectiveness in preventing unwanted pregnancies.

## Methods

This article was identified as a potential PURL through the standard systematic methodology.<sup>13</sup> An additional literature search was conducted by searching UpToDate and PubMed with the terms “piroxicam,” “NSAIDs,” “Levonorgestrel,” and “emergency contraception” to find additional literature to place this research into the context of current clinical practice.

## Study Summary

This randomized double-blinded placebo-controlled trial of 860 women conducted at multiple clinics in the Family Planning Association of Hong Kong from 2018 to 2022, studied the EOC effectiveness of Levonorgestrel 1.5 mg plus Piroxicam 40 mg versus Levonorgestrel 1.5 mg plus placebo (1 tablet each orally within 72 hours of a single episode unprotected intercourse). Women were included if

they were healthy, requested EOC within 72 hours of a single act of unprotected intercourse in the current menstrual cycle, had menstrual cycles length between 24 to 42 days, agreed to abstain from further acts of unprotected intercourse during study period, and were available for follow-up over the subsequent 6 weeks. Women were excluded if they were on hormonal or intrauterine contraception, were breastfeeding or recently pregnant, were post abortion or postpartum and had not resumed menstruation, were at risk for allergy or side effects from the drugs administered (ie, asthma, peptic ulcer disease, drug interaction, etc.), had uncertain of date of last menstrual period, had previously undergone a sterilization procedure, or had concomitant use of hormonal contraception, nonsteroidal inflammatory drugs (NSAIDs), anticoagulants, and other medications which could interact with NSAIDs or Levonorgestrel. This study included women between 28 and 37 years of age, with a body mass index between 21 and 24 kg/m<sup>2</sup>. Women were enrolled after their menstrual history was taken and had a confirmatory negative pregnancy test. They were then assigned in block randomization in sequential order in a 1:1 ratio to placebo or Piroxicam, which resulted in 430 women randomized to each group with 12 women lost to follow-up from each group. All women received a single oral dose of Levonorgestrel 1.5 mg with either Piroxicam or placebo under direct observation. Women were to follow-up within 1 to 2 weeks after their expected next menstrual period. At follow-up, participant’s menstrual history was taken and only if no expected menstrual period, a pregnancy test performed.

The primary outcome of the study was the percent of pregnancies prevented, calculated as the number of expected pregnancies minus the number of observed pregnancies, all divided by the number of expected pregnancies. The number of expected pregnancies was determined by the Trussell’s model using the cycle day unprotected intercourse occurred.<sup>11</sup> The Trussell model calculates the number of expected pregnancies per group, taking into consideration the average number of expected pregnancies and the number of “Efficacy-evaluable” participants.

Secondary outcomes included pregnancy rates in each group, the date and change in bleeding pattern (duration and subjective change in amount) of the subsequent menstruation, occurrence of nonmenstrual bleeding, and occurrence of adverse events.

Eight women were found to be pregnant following EOC. There was 1 pregnancy in the Piroxicam group and 7 in the placebo group. The number of expected pregnancies in the Piroxicam group was 19.0 (4.5%) and in the placebo group was 19.1 (4.6%). The percentage of pregnancies prevented was significantly higher following Piroxicam-Levonorgestrel cotreatment (18.0 [94.7%] of the 19.0 expected) compared with placebo-Levonorgestrel cotreatment (12.1 [63.4%] of 19.1 expected) ( $P < 0.0001$ ); with a risk difference of 31.1% (95% (CI) 26.1 to 36.3). The overall pregnancy rate was 0.2% in the Piroxicam group versus 1.7% in the placebo group, odds ratio of 0.20 (95% CI [0.02 to 0.91],  $P = .036$ ). The number needed to treat is 67 to prevent 1 additional unwanted pregnancy. There were no significant differences in other secondary outcomes.

### What Is New

The addition of the NSAID Piroxicam to Levonorgestrel is not currently part of the standard of care. The data from the above study demonstrated improved effectiveness of the Levonorgestrel with Piroxicam without any increase in side effects or changes in menstrual bleeding. This may be an ideal choice for a woman seeking a simple, cost-effective and noninvasive intervention for EOC.

### Caveats

Only women who did not have a menstrual period within 1 to 2 weeks of the end of their expected menstrual cycle length had pregnancy tests and this could theoretically miss a few pregnancies in both arms of the study. In addition, this study was conducted solely in a single geographic location (Hong Kong), and included women with lower BMIs and regular menses, limiting generalizability.

### Challenges to Implementation

As with Levonorgestrel alone, the combination medication must be taken within 72 hours of unprotected intercourse. Levonorgestrel is less effective in women with a BMI above 30, so it is prudent to assume the same is true for this combination.<sup>12</sup> Another potential challenge is that Levonorgestrel is available over the counter but Piroxicam is by prescription only which means women would need

to present to an urgent care, emergency department, or be able to make a same day appointment with her primary care provider to receive this combination treatment. Finally, due to the theorized mechanism of action of Piroxicam interrupting implantation, some patients may make a values based decision and choose not to add the NSAID.

To see this article online, please go to: <http://jabfm.org/content/38/2/395.full>.

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