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ORIGINAL ARTICLE

A Proof-of-Concept Study of Ulipristal Acetate for Early Medication Abortion

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Abstract

BACKGROUND The current regimen for early medication abortion in many countries is mifepristone and misoprostol, but mifepristone is relatively expensive and limited in many regions. Ulipristal acetate, with a similar chemical profile, might be an alternative. This proof-of-concept study evaluated ulipristal acetate and misoprostol for medication abortion through 63 days of gestation.

METHODS We conducted a two-stage clinical study to choose an effective and acceptable ulipristal–misoprostol regimen. First, we undertook a dose-finding study. Sixty-six participants were randomly assigned to either 60 mg or 90 mg of oral ulipristal, followed by 800 μg of buccal misoprostol. Because the two groups had similar efficacy and safety profiles, we opted for the 60-mg ulipristal dose for an open-label study with 100 additional participants, resulting in a total of 133 participants using the same regimen. To evaluate acceptability, we applied a structured questionnaire at the end of the follow-up visit.

RESULTS Pregnancy termination occurred with the combination of oral ulipristal 60 mg and buccal misoprostol 800 μg in 129 out of 133, or 97.0%, (95% confidence interval [CI], 94.1 to 99.9%), of participants. Among those for whom this regimen did not result in pregnancy termination, one participant had a completion with sharp curettage, two received manual vacuum aspiration, and one underwent a repeat medication abortion with misoprostol alone. Side effects included chills (77.4%; 95% CI, 70.3 to 84.5%), diarrhea (66.9%; 95% CI, 59.0 to 74.8%), and nausea (48.1%; 95% CI, 39.7 to 56.5%). No serious adverse events were reported. The regimen was deemed "acceptable" or "highly acceptable" by 97.7% (95% CI, 95.2 to 100.0%) of participants.

CONCLUSIONS This study suggests that ulipristal acetate followed by misoprostol is an effective and acceptable medication abortion regimen with no reported serious adverse events. (This project is supported by the OPTions Initiative. The study registered as ISRCTN35625202.)

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Introduction

Medication abortion using a combined regimen of mifepristone and misoprostol is a safe and highly effective outpatient abortion treatment for first-trimester pregnancies up to 77 days of gestation.[1-8] It is widely recognized as the clinical

standard by international health bodies.[9] The first approval of mifepristone was in France in 1988, and the combination of mifepristone and misoprostol was commercialized in the United States in 2000. This regimen now constitutes a substantial proportion of abortions in places where mifepristone is readily available.[10-12] However, mifepristone is a relatively expensive medication, and its accessibility is limited in many countries where it is not available in pharmacies and requires a clinician to provide it. Ulipristal acetate, another selective progesterone receptor modulator already on the market, might also be effective for abortion and might offer an opportunity to expand treatment options.

Like mifepristone, ulipristal acetate binds to the progesterone receptor with high affinity, has good oral availability, and has a wide margin of safety.[13-15] The two drugs have similar chemical structures, are rapidly absorbed when administered orally, have relatively long terminal half-lives (mifepristone, 24 to 48 hours; ulipristal, 32 hours),[13,16-19] and have similar times to peak plasma concentration levels (mifepristone, 1 to 2 hours; ulipristal, 45 minutes to 3 hours).[13,16-19] Ulipristal acetate at a 30-mg dose is registered and marketed in more than 74 countries for emergency contraception (either by prescription or over the counter).[20] In some countries, mifepristone is not yet registered.[21,22]

Animal studies provide early evidence suggesting that ulipristal acetate has a plausible use for abortion.[13,23,24] As an abortifacient, ulipristal reduces progestin levels and has shown efficacy in terminating a pregnancy during the early stages of gestation, comparable to mifepristone.[23] In humans, ulipristal acetate, when used in doses three times higher than the standard emergency contraception dose and combined with misoprostol, has shown to be a feasible and acceptable regimen for cervical preparation in second-trimester abortions prior to dilation and evacuation.[25]

Pharmacovigilance studies, clinical trials, and extensive experience with ulipristal's use in emergency contraception underscores that a 30-mg dose of ulipristal is safe and has an acceptable side effect profile, particularly when prescribed for single use.[13,15,26] In 2017, ulipristal was added to the World Health Organization's model list of essential medicines for emergency contraception.[27]

This case series evaluated a treatment schedule for ulipristal followed by misoprostol for induced abortion through 63 days of pregnancy to assess safety and acceptability to users. First, we evaluated two different doses of ulipristal with misoprostol, and then we evaluated further the lower of these two doses (Fig. 1).

Methods

STUDY DESIGN AND OVERSIGHT

We conducted a two-stage clinical study to evaluate the efficacy and acceptability of an ulipristal–misoprostol abortion regimen among participants with pregnancies through 63 days of gestation. The study was designed by the teams at Gynuity Health Projects and the National Autonomous University of Mexico. Data collection was implemented at the outpatient clinic of a public maternal hospital affiliated with the Mexico City Health Secretariat and Inguarán Maternal & Child Hospital, and supervised by the clinical leadership at that institution. Data analysis was carried out by researchers at Gynuity Health Projects and the National Autonomous University of Mexico. Both the first author and the corresponding author prepared the initial draft of this report. All authors ensured the accuracy and integrity of the data analysis and the fidelity of the study to the study protocol, and all authors reviewed and contributed to the manuscript's final version. The decision to publish the article was made collectively by all the authors, independent of sponsor influence. No confidentiality agreements restricted the sharing of data between the sponsors, the authors, or the involved institutions, ensuring full control over the data, the analyses, and the decision to publish.

The protocol was approved by the Research Ethics Committee of the Mexico City Health Secretariat, and the study was registered at www.isrctn.com as ISRCTN 35625202.

PREPARATORY DOSE-FINDING STUDY

We conducted a randomized, open-label preparatory study to compare two oral ulipristal doses (60 mg and 90 mg) followed 24 hours later by 800 μg of buccal misoprostol. We enrolled 66 participants, with 33 participants in each dosage group. An explanation of the selection of the two ulipristal doses and the sample size calculation for this study is provided in the Supplementary Appendix (see section entitled "Preparatory dose-finding study"). This preparatory study showed no serious adverse events in either group or any apparent differences in side effects between groups (Table S3). Acceptability outcomes were evaluated using a structured exit survey administered by the study team at the end of the follow-up visit, prior to study discharge. Participants rated their satisfaction with the abortion process on a five-point Likert scale, ranging from "very satisfied" to "very unsatisfied." Pain acceptability was assessed using a

similar scale, from "very acceptable" to "very unacceptable." In addition, the pain score was measured on a numerical rating scale from 0 to 10, where 0 represented no pain, and 10 represented the worst possible pain. Acceptability with the overall abortion process, assessed by the instruments noted above, was high for both groups, with 90.9% of participants (95% confidence interval [CI], 81.1 to 100.0%) from the 60-mg dose group being "satisfied" or "very satisfied," and all 33 participants from the 90-mg dose group reporting the same (Table S4). The efficacy rates were also high (97.0% for the 60-mg dose group and 100.0% for the 90-mg dose group; Table S5), with a difference of proportions of 3.0 percentage points (95% CI, − 2.8 to 8.9 percentage points).

An independent Data Safety and Monitoring Board reviewed the study's safety outcomes and recommended proceeding with the next stage of the study. An Advisory Group recommended using the regimen with the lower (60-mg) dose in the open-label efficacy study.

STUDY PROCEDURES

Women who were eligible for a medication abortion as per the study site's criteria and who were 18 years of age or older or were emancipated, were residents of Mexico City, had intrauterine pregnancies less than 64 days of gestational age confirmed by ultrasound, and had a body mass index (BMI; is the weight in kilograms divided by the square of the height in meters) of 32 or less, were approached by trained clinic staff to participate in the study. We included BMI as an eligibility criterion since a high BMI may be associated with a higher risk of failure of ulipristal in emergency contraception.[28] Additional eligibility criteria included access to a telephone for follow-up communication and willingness to respond to a short list of questions to document sociodemographic characteristics and to assess acceptability and satisfaction with the process as part of an exit interview. Exclusion criteria included a history of hepatic or renal disease; confirmed or suspected ectopic pregnancy, gestational trophoblastic disease, or undiagnosed adnexal mass; an intrauterine device (IUD) in place; a history of allergy to ulipristal, misoprostol, or other prostaglandins; an unwillingness to return to the follow-up visit at the clinic; and an inability to provide informed consent. The complete inclusion and exclusion criteria are listed in section 8.2 of the original protocol, which is provided with the full text of this article at evidence.nejm.org.

All eligible women invited to participate provided informed consent and were enrolled in the study. Ulipristal was administered at the clinic. Participants were observed for adverse events up to 1 hour after ulipristal administration and were discharged with an envelope containing four 200-μg pills of misoprostol to take at home. Participants were instructed to take the misoprostol pills 24 hours after the administration of ulipristal, holding two pills in each cheek for 30 minutes and then swallowing any remaining fragments. Per standard clinic protocol, participants were advised to use 400 mg of ibuprofen or any other over-the-counter pain medication for pain management as needed. Participants were scheduled to return for a follow-up assessment 7 to 10 days later, including an ultrasound to assess pregnancy status. We defined efficacy as a complete termination of the intrauterine pregnancy at the scheduled follow-up visit that did not require any additional management (expectant management, additional medication, manual vacuum aspiration [MVA], or dilation and curettage [D&C]). Incomplete abortions were defined as unresolved terminated pregnancies that warranted further intervention (either procedural or with medication), as determined through both ultrasound findings and clinical assessment. In the case of an incomplete abortion, expectant management, additional misoprostol and/or an extended follow-up visit, or an MVA were offered. For ongoing pregnancies at follow-up, participants were offered a medication abortion regimen (either with misoprostol alone or mifepristone and misoprostol) or an MVA. Participants who did not appear at the scheduled follow-up visit were contacted by telephone to reschedule the appointment. Adverse events were captured by participant report, either at the follow-up visit or any other unscheduled visits or encounters post-treatment.

Participants answered questions regarding side effects, overall experience, and acceptability prior to discharge from the study at the final follow-up visit, as described above for the preparatory study.

OUTCOMES AND ANALYSIS

The study's primary outcome was the efficacy and safety of a combined ulipristal–misoprostol regimen. Assuming an expected efficacy rate of 92% for the selected study regimen, we calculated that 114 people would be required to ensure a 95% confidence interval width of 10 percentage points; that is, a confidence interval that ranges from 87 to 97% with a 5-percentage point margin of error.[29] We increased the sample by approximately 15% to account for potential loss to follow-up, resulting in a cohort of 133 participants, 100 more than the original 33 enrolled in the dose-finding study.

Data were analyzed using SPSS software, version 18. The analysis was mostly descriptive. To evaluate differences between groups in the preparatory dose-finding study, we used Pearson's chi-square test (or Fisher's exact test or a likelihood ratio test, as appropriate) for categorical variables. Continuous variables were analyzed using independent t-tests. Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer clinical efficacy.

Results

Between July and September 2023, we enrolled 100 participants to supplement the 33 participants in the dose-finding study who received the 60-mg ulipristal regimen for a total analyzable sample of 133 participants. Figure 1 shows the flow of these participants in the study; baseline characteristics are shown in Table 1. All 133 participants took the misoprostol pills at home as instructed. Follow-up visits occurred a median of 14 days (interquartile range: 13 to 15 days) after ulipristal administration. Pregnancy termination with the study regimen was established for 129 participants at the follow-up visit (97.0%; 95% CI, 94.1 to 99.9%), Table 2. One patient presented to the emergency department 3 days after the initial visit (before the planned follow-up visit) with heavy bleeding and underwent a sharp curettage to manage an incomplete abortion. Two participants had an ongoing pregnancy at the follow-up visit, determined by clinical examination and ultrasound, and received a medication abortion regimen of misoprostol only (two doses of 800 μg were taken buccally 4 hours apart); one resulted in a complete abortion at an extended follow-up visit 5 days later, the other underwent an MVA 8 days later. The fourth patient also had an ongoing pregnancy at the follow-up visit and underwent an MVA at that visit.

In addition to these four participants who underwent additional interventions, three adverse events were reported by participants at follow-up (Table 2). One participant reported that she almost fainted from pain after taking misoprostol and was prescribed analgesics. Another participant had a mild maculopapular rash after misoprostol administration, which was effectively treated with an antihistamine. A third participant reported a urinary tract infection that was addressed with antibiotics. No deaths or serious adverse events were reported.

Figure 2 shows the side effects reported by participants. After ulipristal administration, side effects occurred in less

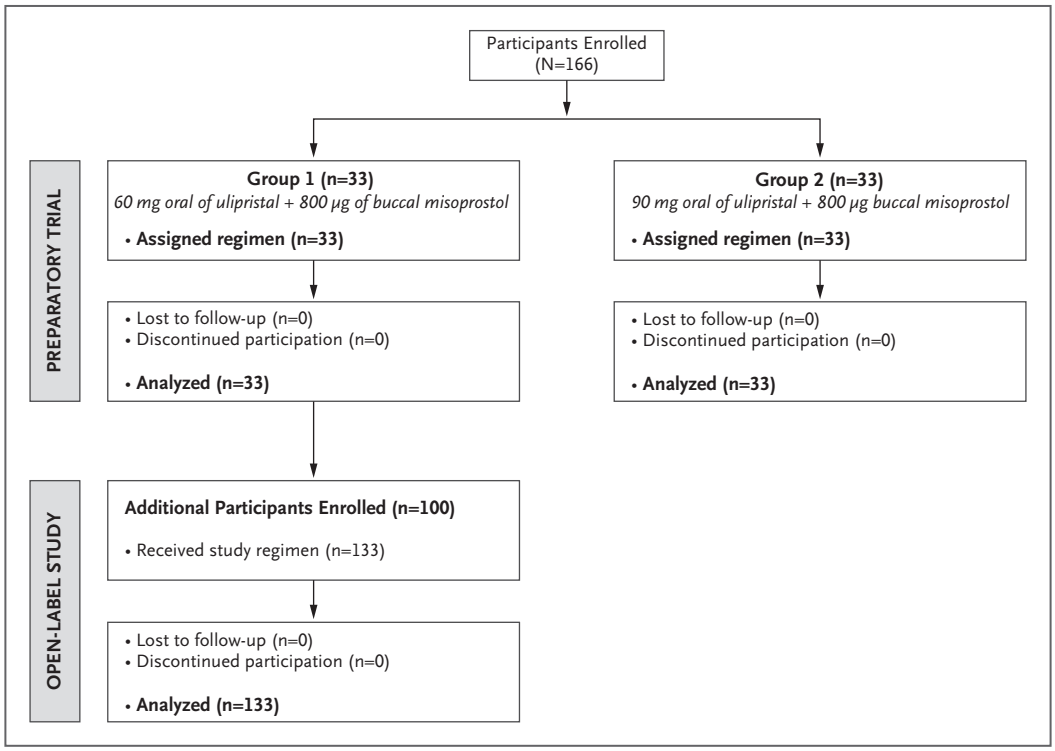

Figure 1. Ulipristal Acetate for Early Medication Abortion: Flow of Study Participants.

Table 1. Participants' Baseline Characteristics.*

Characteristic	Participants (n=133) (%)
Age (years)	
<18	1 (0.8)
18–24	46 (34.5)
25–34	70 (52.6)
35–39	11 (8.3)
≥40	5 (3.8)
Gravidity	
1	45 (33.8)
2	30 (22.6)
3	29 (21.8)
4	22 (16.5)
≥5	7 (5.3)
Parity	
0	53 (39.8)
1	37 (27.8)
2	30 (22.6)
≥3	13 (9.8)
Previous medication abortions	
0	103 (77.4)
1	26 (19.5)
≥2	4 (3.0)
Previous procedural abortions	
0	126 (94.7)
1	6 (4.5)
2	1 (0.8)
Gestational age per ultrasound on day of ulipristal administration	
≤35 days	6 (4.5)
36–42 days	5 (3.8)
43–49 days	51 (38.3)
50–56 days	50 (37.6)
57–63 days	21 (15.8)

*Percentages may exceed 100 because of rounding.

Table 2. Follow-up, Abortion Outcome, and Additional Care.*

Follow-up, Abortion Outcome, and Additional Care	Participants (n=133) (median or %)
Median days between ulipristal and misoprostol	1 (1 to 1)
Median days from ulipristal to follow-up	14 (13 to 15)
Abortion status on day of follow-up	
Not pregnant	129 (97.0)
Incomplete abortion†	1 (0.8)
Ongoing pregnancy	3 (2.3)
Additional care provided at follow-up	
No additional care	126 (94.7)
MVA due to ongoing pregnancy	2 (1.5)
MAB with misoprostol only due to ongoing pregnancy	1 (0.8)
D&C due to heavy bleeding†	1 (0.8)
Antibiotics due to infection (urinary tract)	1 (0.8)
Pain medication due to fainting for pain	1 (0.8)
Antihistamine for mild allergic reaction	1 (0.8)

* Percentages may exceed 100 because of rounding. D&C denotes dilation and curettage; MAB, medication abortion; and MVA, manual vacuum aspiration. All data are presented as n (%) or median (interquartile range).
† Same participant; dilation and curettage performed at the emergency department.

than 4% of participants. After taking misoprostol, the most common side effects were chills (77.4%, 103 out of 133 [95% CI, 70.3 to 84.5%]), diarrhea (66.9%, 89 out of 133 [95% CI, 58.9 to 74.9%]), and nausea (48.1%, 64 out of 133 [95% CI, 39.6 to 56.6%]), followed by fever (38.3%, 51 out of 133 [95% CI, 30.1 to 46.6%]) and vomiting (27.1%, 36 out of 133 [95% CI, 19.5 to 34.6%]).

Overall satisfaction with the abortion process was 97.7%, or 130 out of 133 participants (95% CI, 95.2 to 100.0%) rating the treatment as satisfactory or very satisfactory (Table 3). The pain level was rated as acceptable or very acceptable by 85.0% (113 out of 133 [95% CI, 78.9 to 91.0%]) of participants. Of the remaining 15.0% of participants, 6.0%, or 8 out of 133 participants [95% CI, 2.0 to 10.1%], found it unacceptable or very unacceptable, and 9.0% (12 out of 133 [95% CI, 4.1 to 13.9%]) rated the pain acceptability as neutral. Ninety-one percent of participants (121 out of 133 [95% CI, 86.1 to 95.8%]) would recommend this regimen, and 90.2% (120 out of 133 [95% CI, 85.2 to 95.3%]) said they would choose these medications in a future abortion.

Discussion

In this proof-of-concept study, a regimen of ulipristal 60 mg and misoprostol 800 μg buccally for medication abortion up to 63 days of gestation was effective and acceptable to users, with no serious adverse events reported. Side effects after ulipristal administration were either absent or infrequent; chills and diarrhea were reported after misoprostol. The types of side effects reported and their prevalence after misoprostol administration are consistent with those reported in previous publications.[30]

The success rate of this combined regimen as an abortifacient with minimal additional care needed for ongoing

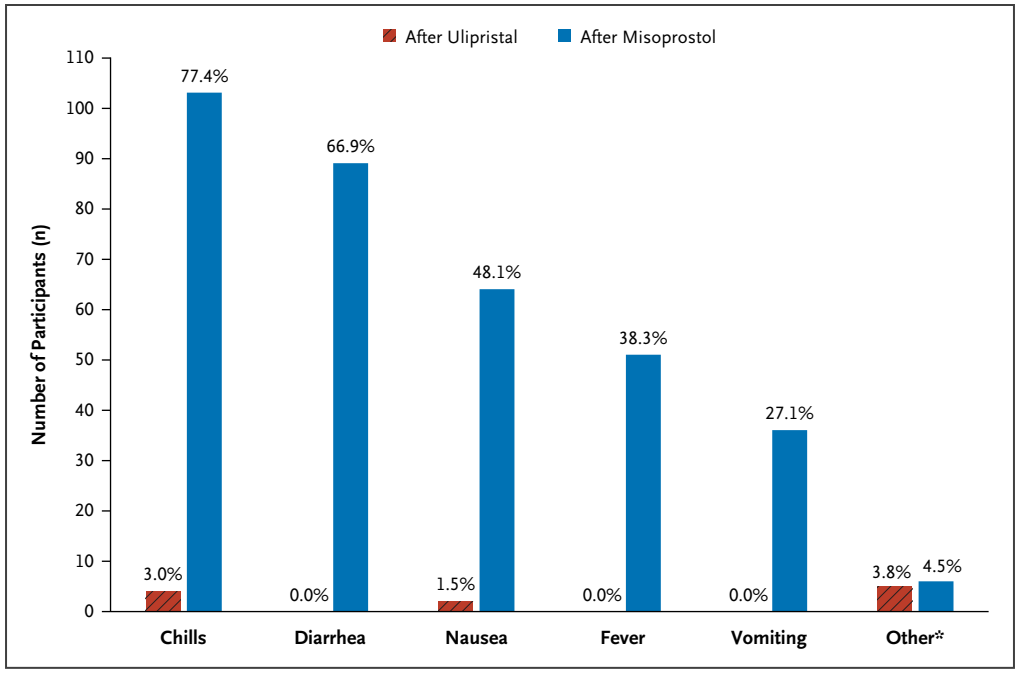

Figure 2. Ulipristal Acetate for Early Medication Abortion: Self-Reported Side Effects.

*Other includes after ulipristal — headache, mild pelvic pain, and mild tinnitus; and after misoprostol — dizziness, headache, mild allergic reaction, and hip pain.

Table 3. Acceptability Outcomes and Pain Score.*

Outcome	Participants (n=133) (% or median)
Overall satisfaction with abortion procedure†	
Satisfied or very satisfied	130 (97.7)
Neutral	3 (2.3)
Unsatisfied or very unsatisfied	0 (0.0)
Pain acceptability related to abortion†	
Acceptable or very acceptable	113 (85.0)
Neutral	12 (9.0)
Unacceptable or very unacceptable	8 (6.0)
Median pain score‡	8.0 (6.0 to 9.0)
Would recommend the study regimen to a friend	
Yes	121 (91.0)
No	11 (8.3)
Not sure	1 (0.8)
Would choose this regimen in future abortion	
Yes	120 (90.2)
No	11 (8.3)
Not sure	2 (1.5)

* All data are presented as n (%) or median (interquartile range). Percentages may exceed 100 because of rounding.
† Satisfaction and acceptability were assessed using a five-point Likert scale.
‡ Level of pain: 0 to 10, where 0 = no pain experienced and 10 = maximum pain possible.

pregnancy, incomplete abortion, or adverse effects is encouraging. Although this study was not designed to answer questions about relative success, safety, acceptability, or cost, our findings provide clinical equipoise compared with other regimens for the purpose of medication abortion; this equipoise sets the stage for controlled clinical trials.[4-6]

Our study has some limitations. Although the dose-finding preparatory study was random assignment, its open-label nature may have introduced performance bias, as participants and health care providers were aware of the assigned treatment. The relatively small sample size may have contributed to imprecision in estimating the safety profile. In addition, the overall study was conducted at an outpatient clinic of a single maternal hospital in Mexico City and included participants from a specific geographic region, potentially limiting the generalizability of the results to diverse health care settings and populations (Table S1 describes the representativeness of participants in this study).

Further research is warranted to explore the feasibility of this new potential indication for ulipristal. Larger studies could provide insights into efficacy and safety. Multicenter studies could potentially support broader applicability and the addition of abortion to the label for ulipristal products. It is important to note that this study did not explore the

30-mg dose of ulipristal that is currently used for emergency contraception. Addressing these aspects in future research will strengthen the reliability and applicability of these findings, moving toward a more comprehensive understanding of ulipristal's potential in medication abortion.

In conclusion, our proof-of-concept study supports the potential of ulipristal in a combined regimen with misoprostol for safe and effective medication abortion. The findings prompt further consideration of ulipristal in the evolving landscape of medication abortion.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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