Contraception xxx (xxxx) xxx

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/contraception

Original Research Article

Single dose letrozole and misoprostol for termination of pregnancy through 63 days' gestation: A pilot study

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ARTICLE INFO

Article history:
Received 19 July 2022
Received in revised form 23 November 2022
Accepted 30 November 2022
Available online xxx

Keywords:
Letrozole
Misoprostol
Medication abortion
Abortion

ABSTRACT

Objectives: We conducted a pilot study to evaluate a single dose of letrozole 30 mg prior to misoprostol 800 mcg buccally for medication abortion

Study design: We enrolled 40 participants seeking medication abortion up to 63 days' gestation at a site in Salt Lake City, UT. Participants received a single dose of letrozole 30 mg in-clinic followed 2 days later by misoprostol 800 mcg buccally at home. They took a second dose of misoprostol if they had no bleeding within 24 hours of the first. Participants returned 7 to 10 days later for assessment of abortion outcome and side effects

Results: Thirty-seven participants (93%) returned for follow-up and 2 (5%) went to another facility from which research staff obtained outcome data. Three-fourths (29/39, 74%, 95% CI: 60%–89%) had a complete abortion; 4 (10%, 95% CI: 0.3%–20%) had an incomplete abortion and opted for aspiration, and 6 (15%, 95% CI: 4%–27%) had an ongoing pregnancy. All subjects with follow-up reported taking the first dose of misoprostol. Ten (27%) took the second dose as well; only three did so due to no bleeding. Nineteen participants (51%) reported side effects after letrozole prior to misoprostol and two people (5%) rated these effects as severe. Side effects following misoprostol occurred in 33 participants (89%) and were as expected based on previous literature. No serious adverse events were reported

Conclusion: A single dose of letrozole 30 mg followed by misoprostol had lower than desirable efficacy and does not warrant further study.

Implications: A single dose of letrozole does not appear to be an effective adjunct to misoprostol for medication abortion.

1. Introduction

A combined regimen of mifepristone and misoprostol [1–5] is the gold standard for early medication abortion [6]. However, mifepristone is not always readily available or easy to access. While misoprostol-alone protocols have demonstrated a wide range of efficacy (78%–99% [7–9]), randomized trials have shown these regimens to be less effective than combined regimens of mifepristone + misoprostol [10,11]. Identifying another medication that could improve upon the efficacy of misoprostol alone would benefit both abortion seekers and health systems globally. Letrozole, a nonsteroidal aromatase inhibitor (i.e., member of a class of compounds that inhibit the production of estrogen) has been identified as one such drug: it is commercially available in many countries and has been judged safe and effective for use in treating breast cancer and infertility [12,13]. Animal data support a critical role for estrogen in early pregnancy and demonstrate interruption of pregnancy with administration of letrozole [14,15]. Human data including results from six randomized controlled trials informed a meta-analysis and a systematic review demonstrating a significant increase in complete abortion with letrozole supplementation to misoprostol [16,17]. These data supported the addition of letrozole used with misoprostol to the WHO safe abortion guidelines for medical management of induced abortion [6].

The published studies to date on letrozole-misoprostol for medication abortion all used at least 3 days of letrozole prior to misoprostol administration, most commonly 10 mg per day for 3 days followed by one dose of misoprostol 800 mcg vaginally [16–20].

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https://doi.org/10.1016/j.contraception.2022.109924

Few of the studies were both conducted in the first trimester and clearly limited their enrollment to viable pregnancies [18–20]. We hypothesized that a more convenient regimen, with fewer medication days and buccal administration of misoprostol, would be more user-friendly, might lead to better compliance, and may be preferred by abortion patients [21–23]. Buccal misoprostol is highly effective when used in mifepristone regimens [24], and single doses of up to 30 mg of letrozole were well tolerated in breast cancer treatment studies [25].

We conducted a pilot study to evaluate the potential efficacy and safety of a single dose of letrozole 30 mg prior to buccal misoprostol for medication abortion. We also assessed acceptability.

2. Material and methods

All people desiring a medication abortion at ≤ 63 days' gestation presenting to a single Planned Parenthood Association of Utah (PPAU) site in Salt Lake City, Utah, were offered the chance to participate in this study. Eligibility criteria for subjects included having an intrauterine pregnancy visible by ultrasonography with a single fetus ≤ 63 days gestational age, speaking English or Spanish, and being willing and able to return for the follow-up appointment and participate in the exit interview. Exclusion criteria included gestations > 63 days, confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass, pregnancy of unknown location, intrauterine device or contraceptive implant in place, history of allergy to letrozole or misoprostol, currently breastfeeding, or history of liver disease or abnormal liver function. All participants completed the informed consent process. The University of Utah Institutional Review Board approved the study, and we registered the protocol on clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT05207644).

All participants took letrozole 30 mg (12 x 2.5 mg tablets) orally on the day of study enrollment. They also received misoprostol 800 mcg (4 x 200 mcg tablets) to administer buccally 2 days later, as well as an additional 800 mcg of misoprostol to take buccally if they did not have any bleeding within 24 hours following the first misoprostol dose. Participants were given information and phone numbers to call if they had concerns related to their abortions, including prolonged or heavy bleeding, abdominal pain, or signs of infection. They also received prescriptions for pain and nausea medications that they could fill at their discretion, per the clinic's standard of care for medication abortion.

Participants were asked to return 7 to 10 days after the initial visit for a follow-up assessment consisting of a clinical exam, ultrasonography, and exit interview. The interview included questions about side effects, including intensity and timing, and the overall experience and acceptability of this method using Likert scales. Based on participant report, clinical exam, and ultrasonography, the clinician provided a final determination of complete abortion, incomplete abortion (cessation of growth without complete passage of the gestation outside the uterus), or ongoing pregnancy. Per the clinic's standard of care, staff offered same-day aspiration to anyone with an ongoing pregnancy and expectant management, additional misoprostol, or same-day aspiration to those with incomplete abortion. Prior to discharge, a study clinician provided post-abortion counseling, including contraceptive information, as per standard practice at the site. Participants received all study-related care without charge. After completion of all study components, participants received a $100 gift card to compensate for time and travel associated with the study. If a participant did not return for the follow-up visit, study staff made three attempts at contact using the participant's preferred method, as well as three attempts with alternative methods including phone, text, and email. If these efforts failed, we considered the person lost to follow-up. Clinic staff conducted an extended follow-up phone call approximately 30 days after letrozole administration to review any side effects or issues that may have occurred since the in-person follow-up visit.

Table 1
Background characteristics of study participants who received letrozole 30 mg followed by misoprostol 800 mcg: median (range) or *n* (%).

Characteristic	*N* = 40
Age (in years)	25 (18-38)
Race/Ethnicity (multiple selections allowed)	
White/Caucasian	25 (63)
Black/African American	1 (3)
Hispanic/Latinx	15 (38)
Asian/Pacific Islander	3 (8)
Other	1 (3)
Prefer not to say	2 (5)
Previous pregnancy	21 (53)
Previous medication abortion	7 (18)
Previous surgical abortion	1 (3)
Gestational age (days)[a]	43 (29-61)

[a]By ultrasonography on day participant took letrozole.

For this pilot study we did not conduct a formal sample size calculation; we selected a sample size of 40 participants to accommodate the project's budget restrictions as that number had also been used for other medication abortion pilot studies [26,27]. For this sample size, a 90% complete abortion rate would provide a 95% CI of 77.5% to 96.5% and provide data to assess safety, potentially identifying unexpected adverse or serious adverse events. The external experts on our Data Safety and Monitoring Board (DSMB) made the final determination on safety. This approach was consistent with guidance we received from Gynuity Health Projects' Advisory Committee and guidelines from the U.S. Food and Drug Administration (FDA) for Phase 1 studies [28].

The DSMB comprised 4 members with clinical and epidemiological experience with medication abortion. We charged the DSMB with reviewing the study data after half of the cases enrolled (n= 20) and with stopping the study if there were concerns about adverse events. They would also stop the study if efficacy (complete abortion without intervention) was less than 50%. In addition, we were to notify the DSMB immediately if any serious events occurred during the study so that they could stop enrollment if deemed necessary.

Study staff entered and managed all data using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt University. REDCap is a secure, web-based software platform designed to support data capture for research studies [29]. We analyzed the data using STATA (version 12, College Station, TX) and present the results in frequencies and means.

3. Results

Forty people enrolled in the study between January 10 and March 8, 2022. Table 1 describes participant characteristics. Thirty-seven participants (93%) returned for follow-up at the study site. An additional two participants (5%) visited a non-study medical location (one visited another PPAU clinic, and one went to a local hospital emergency department) where clinicians documented clinical outcomes and shared the results with study staff. All participants who returned as scheduled reported taking the four misoprostol pills; all but one took the misoprostol 2 days after the letrozole as directed and one took their misoprostol one day early. Ten participants (27%) took the second dose of misoprostol: three because of no bleeding within 24 hours, five because they felt that the bleeding they had experienced was insufficient, one because they didn't think the pregnancy had been expelled, and one to just make sure the medications worked.

Table 2
Efficacy and safety outcomes following letrozole-misoprostol study regimen, among those with follow-up data: *n* (%).

	N = 39
Complete abortion without intervention	29 (74)
Ongoing pregnancy, aspiration at follow-up (FU)	6 (15)
Incomplete abortion, patient opted for aspiration at FU	4 (10)
Emergency department visit	1 (3)
Blood transfusion	0 (0.0)
Hospitalization	0 (0.0)

Table 2 presents efficacy and safety outcomes. At follow-up, three-fourths of participants (n = 29/39, 74%, 95% CI: 60%–89%) had a complete abortion with no intervention; six (15.4%; 95% CI: 4%–27%) had an ongoing pregnancy, and 4 (10.3%, 95% CI: 0.3%–20%) had an incomplete abortion and opted for same-day aspiration. Ultrasonography was used as part of outcome assessment for all participants except for the individual who had follow-up at a different PPAU clinic; that individual utilized a urine pregnancy test. One patient had an inconclusive ultrasound examination at follow-up and following the physician's advice, took a second dose of misoprostol and returned the next day; repeat ultrasonography showed absence of the gestational sac. Most (5/6, 83%) of the ongoing pregnancies had corresponding gestational ages at initial visit of <=42 days. The sixth was 61 days gestation. Half of the six participants with an ongoing pregnancy had taken the second dose of misoprostol.

Three people made unscheduled calls to the clinic during the study; none led to a clinical visit. One participant visited the emergency department due to concerns about heavy bleeding and did not receive any treatment; ED staff determined that the abortion was complete at the time of evaluation and discharged the participant the same day. There were no reported serious adverse events. Clinic study staff reached 33 (89%) of the participants for an extended follow-up call after 30 days. Two participants reported concerns about bleeding; the study physician offered one an appointment, but they did not present for care.

Table 3 presents side effects experienced after each medication. Side effects after letrozole included nausea (n = 12, 32%), diarrhea (n = 7, 19%), and chills (n = 6, 16%); two people (5%) rated these side effects as severe. Side effects following misoprostol were as expected based on previous literature.

Most participants (n = 29/37, 78%) were satisfied or very satisfied with the overall abortion process. All but one (97%) found the side effects experienced to be acceptable or felt neutral about them. Most participants (28/32, 88%) would select this regimen again if they needed abortion care, and 30 of 33 (91%) would recommend it to a friend.

Table 3
Side effects after taking letrozole and misoprostol, as reported by patient: *n* (%).

	After letrozole n = 37	After misoprostol n = 37
Any side effects	19 (51)	33 (89)
Nausea	12 (32)	18 (49)
If yes		
Mild	9 (24)	8 (22)
Moderate	2 (5)	7 (19)
Severe	1 (3)	3 (8)
Vomiting	3 (8)	10 (27)
If yes		
Mild	1 (3)	4 (11)
Moderate	1 (3)	5 (14)
Severe	1 (3)	1 (3)
Dizziness	1 (3)	8 (22)
If yes		
Mild	0 (0)	5 (14)
Moderate	1 (3)	3 (8)
Severe	0 (0)	0 (0)
Fever	2 (5)	6 (16)
If yes		
Mild	2 (5)	4 (11)
Moderate	0 (0)	1 (3)
Severe	0 (0)	1 (3)
Chills	6 (16)	14 (38)
If yes		
Mild	5 (14)	7 (19)
Moderate	1 (3)	5 (14)
Severe	0 (0)	2 (5)
Diarrhea	7 (19)	11[a] (31)
If yes		
Mild	5 (14)	6 (17)
Moderate	2 (5)	4 (11)
Severe	0 (0)	1 (3)
Other[b]	7 (19)	20 (54)
If yes		
Mild	5 (14)	7 (19)
Moderate	1 (3)	6 (17)
Severe	1 (3)	7 (19)

[a] The denominator is 36; one participant preferred not to answer the question about diarrhea.
[b] "Other" side effects reported, but not asked directly about: After letrozole: bleeding, cramping, back pain, fatigue, and increased bowel movements. After misoprostol: abdominal pain, bleeding, cramping, cold sweats, and sciatica pain.

4. Discussion

A regimen of letrozole 30 mg followed by misoprostol 800 mcg for medication abortion demonstrated moderate success with no unexpected side effects or safety concerns. While the sample is too small to make a conclusive efficacy statement, this regimen does not appear to improve upon misoprostol-alone regimens [7–9] or upon the few multi-dose letrozole-misoprostol studies that had similar parameters [18–20]. This study only utilized one to two doses of misoprostol; the most successful misoprostol-alone regimens have used two or more doses [7–9]. Future studies should focus on identifying a more successful letrozole dosing schedule and compare the most promising letrozole-misoprostol regimen(s) directly to a multi-dose misoprostol-alone regimen, in order to assess more accurately any added benefit from the letrozole.

This study was the first to explore a single larger dose of letrozole in a letrozole-misoprostol regimen for medication abortion. While patients found the single dose of multiple pills acceptable, the relatively low efficacy rate signals caution in proceeding with this regimen in future efforts. We do not consider it surprising that half of the participants reported side effects while taking letrozole prior to misoprostol use as most symptoms were gastrointestinal in nature, a common occurrence in early pregnancy.

The main weaknesses of the study are the small sample size, potential bias (a high percentage of participants were nulliparous), and the lack of a misoprostol-alone comparison group. While none of these factors likely contributed to the high ongoing pregnancy rate, the use of a second dose of misoprostol among only half of those who had ongoing pregnancy likely did. This suggests an imperfect approach and the need for improved instructions for use of additional misoprostol for the future.

The relatively high number of ongoing pregnancies in this study prompted additional analyses and identified a skew of the ongoing pregnancies towards lower gestational ages. This finding is clearly limited by the small sample size and is different than the largest, rigorous randomized controlled trial of letrozole and misoprostol, which showed a significantly higher complete abortion rate for participants ≤49 days gestation at entry compared to those at 50 to 63 days [19]. Future studies may also wish to test letrozole-misoprostol efficacy using enrollment blocks based on gestational

age bands. This is consistent with the WHO statement necessitating further evidence for later gestational ages [6].

The newest WHO guidance highlights the potential for improved equity using this drug, while acknowledging the weak evidence base. Indeed, there are many reasons to believe that equity could be improved in the United States with the availability of another highly effective abortifacient. Letrozole's low price point ($1.80 per patient in our study versus $45 for one dose of mifepristone; written communication with site staff) and wide availability related to breast cancer treatment and infertility make it an attractive option. Additionally, mifepristone is under a U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy (REMS) which imposes strict rules pertaining to its use while letrozole has no such restriction. In other settings, the relatively low cost and pharmacy access might also improve equity of care. Letrozole's current accepted uses for breast cancer treatment and infertility would make limiting its access more challenging.

Access to mifepristone represents a considerable barrier to safe abortion in the United States due to cost and restrictions, not to mention countries where it is not available legally. If a safe and effective regimen using letrozole can be identified that favorably compares to misoprostol alone, it could circumvent those barriers and increase access to this important reproductive health service. However, a single dose of letrozole 30 mg followed by misoprostol does not suggest benefit.

Disclosures and funding

Conflicts of interest: The authors declare no conflicts of interest.

Funding: This project is supported by the OPTions Initiative. The funder had no role in the development of the study or in the collection, storage, or analysis of data.

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