Original Research

Mifepristone Antagonization With Progesterone to Prevent Medical Abortion

A Randomized Controlled Trial

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OBJECTIVE: To estimate the efficacy and safety of mifepristone antagonization with high-dose oral progesterone.

METHODS: We planned to enroll 40 patients in a double-blind, placebo-controlled, randomized trial. We enrolled patients at 44–63 days of gestation with ultrasound-confirmed gestational cardiac activity who were planning surgical abortion. Participants ingested mifepristone 200 mg and initiated oral progesterone 400 mg or placebo 24 hours later twice daily for 3 days, then once daily until their planned surgical abortion 14–16 days after enrollment. Follow-up visits were scheduled 3±1, 7±1, and 15±1 days after mifepristone intake with ultrasonography and blood testing for human chorionic gonadotropin and progesterone. Participants exited from the study when they had their surgical abortion or earlier for gestational cardiac activity absence, gestational sac expulsion, or medically indicated suction aspiration. We assessed the primary outcome of continued gestational cardiac activity at approximately 2 weeks (15±1 day), side effects after drug ingestion, and safety outcomes including hemorrhage and emergent treatment.

RESULTS: We enrolled participants from February to July 2019 and stopped enrollment after 12 patients for safety concerns. Mean gestational age was 52.5 days. Two (one per group) voluntarily discontinued 3 days after mifepristone ingestion for subjective symptoms (nausea and vomiting, bleeding). Among the remaining 10 patients (five per group), gestational cardiac activity continued for 2 weeks in four in the progesterone group and two in the placebo group. One patient in the placebo group had no gestational cardiac activity 3 days after mifepristone use. Severe hemorrhage requiring ambulance transport to hospital occurred in three patients; one received progesterone (complete expulsion, no aspiration) and two received placebo (aspiration for both, one required transfusion). We halted enrollment after the third hemorrhage. No other significant side effects were reported.

CONCLUSION: We could not estimate the efficacy of progesterone for mifepristone antagonization due to safety concerns when mifepristone is administered without subsequent prostaglandin analogue treatment. Patients in early pregnancy who use only mifepristone may be at high risk of significant hemorrhage.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT03774745.

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Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

Mitchell D. Creinin is a consultant for Danco Laboratories, providing medical consultation for clinicians that contact Danco with questions regarding mifepristone. Laura Dalton is an employee of Planned Parenthood. The other author did not report any potential conflicts of interest.

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In the United States, approximately 862,000 abortions occur per year, of which almost 40% occur using medical abortion.[1] The treatment approved by the U.S. Food and Drug Administration for medical abortion is a combination of mifepristone and miso-

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prostol through 70 days of gestation.[2] Mifepristone acts as a competitive progesterone receptor antagonist and promotes decidual necrosis to weaken implantation, enhances uterine sensitivity to prostaglandins, and softens the cervix.[3] Accordingly, mifepristone has some activity to induce abortion when used alone. However, overall efficacy is generally 80% or less, and these studies typically included patients at less than 49 days of gestation.[4] Medical abortion efficacy is improved significantly with the addition of a prostaglandin analogue.[4] Mifepristone followed in 24–48 hours by misoprostol is 96–97% effective through 70 days of gestation; however, as gestation advances from 49 to 70 days, complete abortion rate decreases and continuing pregnancy rate increases.[2] Approximately 0.3% of patients at 49 days of gestation or less experience a continuing pregnancy compared with 3.1% of patients at 64–70 days.[2] A recent U.K. study of patients who initiated medical abortion at 64–70 days found that 9 of 89 (10%) patients with continuing pregnancies detected at follow-up opted to continue the pregnancy.[5]

Case series have reported that some patients may change their minds about terminating their pregnancies after ingesting mifepristone and before misoprostol treatment.[6–8] Although an exact proportion is unknown, the best estimate is that fewer than 0.005% of patients who use mifepristone choose to continue their pregnancies.[9] Because mifepristone binds strongly to the progesterone receptor and has a long half-life,[4] some scientists believe that this action is potentially irreversible. However, others have questioned this theory and believe that providing high doses of progesterone may antagonize the effects of mifepristone when administered for abortion.[6]

No clinical trials have been performed to adequately study antagonizing mifepristone with progesterone treatment. Case series reported to date have significant limitations, including using investigational treatment (high-dose progesterone) after mifepristone ingestion without consenting patients for this experiment; incomplete reporting of outcomes; use of varying progesterone doses, routes and durations; and lack of control groups to understand true efficacy.[6–8] The largest case series (547 patients evaluated) reported a 48% continuing pregnancy rate using various progesterone regimens, with the highest rates (64–68%) using various intramuscular or oral treatments.[8] To address these issues, we conducted a double-blind placebo-controlled randomized trial to evaluate continuing pregnancy rates, safety, and side effects of high-dose oral progesterone in patients who used mifepristone during early pregnancy.

METHODS

We conducted this randomized, double-blind, placebo-controlled trial at the University of California, Davis Medical Center. We approached patients who had completed counseling and consent for a surgical abortion and were 63 days of gestation or less about study participation. Inclusion criteria were 18 years or older, English-speaking, singleton pregnancy, and willingness to delay the abortion by approximately 2 weeks. Exclusion criteria were medical contraindications to medical abortion per the mifepristone U.S. Food and Drug Administration label,[2] an allergy to mifepristone or progesterone, or a peanut allergy (on-label contraindication to oral progesterone). The University of California, Davis, Institutional Review Board approved this study and all participants gave written study consent before beginning any study procedures.

The screening visit included obtaining study consent, recording demographic information, soliciting baseline pregnancy symptoms (subjectively rated as none, mild, moderate or severe), and inquiring whether they had used mifepristone or progesterone previously. Patients for whom transvaginal ultrasonography demonstrated gestational cardiac activity and a gestational age 44–63 days of gestation based on Goldstein and Wolfson's criteria[10] could enroll that day. Patients who were at less than 44 days of gestation at screening returned for enrollment, at which time transvaginal ultrasonography was repeated to confirm gestational cardiac activity and gestational age.

Enrolled participants had blood drawn for human chorionic gonadotropin (hCG) and progesterone levels, then swallowed mifepristone 200 mg in front of an investigator. Study treatment (progesterone or placebo) was prepared by the University of California, Davis Investigational Drug Service by placing 38 capsules of progesterone 200 mg or similar-appearing placebo capsules in opaque pill containers. The Investigational Drug Service could not over-encapsulate the drugs due to product size. The Investigational Drug Service performed the randomization allocation using a computer-generated random sequence in blocks of four, sequentially numbered the containers, and maintained the randomization log to ensure drug allocation concealment until study completion. Participants were instructed to start study treatment 24 hours after mifepristone ingestion by taking two capsules twice daily for 3 days, then two

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capsules once daily until the study exit visit. We chose this dosing regimen because it was the most effective option previously described in a case series of mifepristone antagonization.[8] Participants received a diary to document any side effects and capsule intake. Participants also received the standard medical abortion bleeding and side effect instructions distributed to medical abortion patients at the University of California, Davis.

Research staff contacted participants 24 hours after mifepristone administration to confirm the start of study treatment. Follow-up visits were scheduled 3 (±1), 7 (±1), and 15 (±1) days after mifepristone intake. Each visit included diary review, assessment of symptoms or drug side effects, ultrasonography to establish presence or absence of gestational cardiac activity, and blood testing for hCG and progesterone. Additionally, a research coordinator independently counted unused study drug to maintain investigator blinding. The patient's planned surgical abortion was scheduled concurrent with her last study visit. Participants exited from the study when they had their surgical abortion, or earlier for gestational cardiac activity absence, gestational sac expulsion, or medically indicated suction aspiration. At the final visit, participants were asked whether they knew what treatment they received or looked up the capsules online for identification.

The primary outcome was continuing pregnancy with presence of gestational cardiac activity after approximately 2 weeks (15±1 days). Secondary outcomes included expulsion rates over 2 weeks, change in hCG and progesterone levels during treatment, study drug side effects, and safety outcomes (eg, hemorrhage, emergency department visit, emergent suction aspiration). Safety evaluations (adverse events review) were performed by the principal investigator after each patient completed the study and at research review meetings every 2 weeks by the primary study team. The principal investigator was responsible for continued safety oversight and decisions to stop the study for safety reasons.

We estimated a 68% continuing pregnancy rate with oral progesterone treatment based on a report using the same dosing after mifepristone administration in early pregnancy, stating that 68% of patients had pregnancies that continued to 20 weeks of gestation or more.[8] We also estimated that only 25% of patients receiving placebo would have continuing pregnancies.[11] Using 80% power and $\alpha=0.05$, 20 participants per group were required.

We performed an intention-to-treat analysis, using Fisher exact test or χ^2 test as indicated, *t* test for continuous variables and Mann-Whitney *U* for comparing median values.

RESULTS

We enrolled 12 patients from February 2019 to July 2019 (Fig. 1). Patient characteristics are presented in Table 1. Two patients exited the study voluntarily related to side effects; both underwent suction aspiration 3 days after mifepristone administration. The first patient, in the placebo group, was 48 days at enrollment and had a prior medical abortion. She had increased anxiety about bleeding that started 2 days after mifepristone use and requested a suction aspiration. The second patient, in the progesterone group, had three prior pregnancies and mild nausea and vomiting at baseline. She had developed increasing nausea and vomiting after enrolling, resulting in dehydration that required intravenous fluids as an outpatient. She took only two of her four treatment doses before requesting a suction aspiration.

Overall, four of six patients in the progesterone group and two of six patients in the placebo group had continuing pregnancies at 2 weeks. Excluding the two patients who did not finish treatment, these rates are four of five and two of five, respectively. A detailed listing of individual patient characteristics and outcomes is included in Appendix 1, available online at http://links.lww.com/AOG/B658.

Four pregnancies did not continue, including one patient at 48 days in the placebo group who had no gestational cardiac activity 3 days after mifepristone use and had an uneventful suction aspiration. Three other patients had severe bleeding requiring ambulance transport to an emergency department. The first patient received progesterone treatment after enrollment at 56 days of gestation. She reported no bleeding at the first follow-up visit 2 days postmifepristone. Shortly after her visit, she started having brisk bleeding and called an ambulance. Transvaginal ultrasound examination in the emergency department found no gestational sac and a heterogenous endometrial lining of approximately 1.5 cm. Heavy bleeding lasted about 3 hours overall, and no intervention was needed. The second patient received placebo and enrolled at 60 days of gestation. She noted new mild bleeding at a follow-up visit 2 days after mifepristone use. The following day, she called an ambulance after onset of heavy vaginal bleeding. In the emergency department, a study physician found significant heterogenous material in the uterine cavity on ultrasound examination with continued brisk bleeding, so a suction

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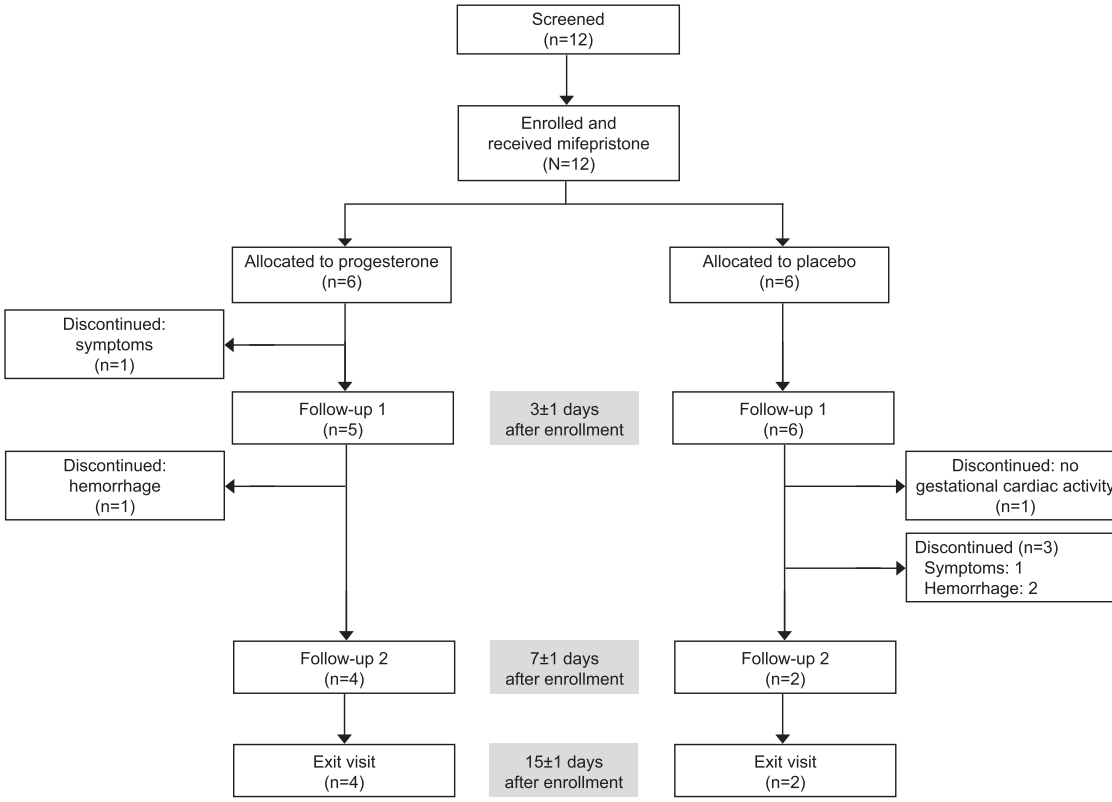


Fig. 1. Participant flowchart of patients who received mifepristone 200 mg followed by progesterone for up to 2 weeks.
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aspiration was performed. Pathology demonstrated normal chorionic villi. The third patient also received placebo and enrolled at 60 days of gestation. She noted new mild spotting at a follow-up visit 2 days after mifepristone use. The following day, she called an ambulance after experiencing hemorrhage. In the emergency department, a study physician evaluated the patient, who had significant brisk bleeding, hypotension, and tachycardia. Transvaginal ultrasound examination showed that the gestational sac was still in the uterine cavity, so an emergent suction aspiration was performed. This patient's hemoglobin level decreased in the emergency department from 9.2 to 7.5 g/dL, and she received a 1-unit transfusion of packed red blood cells. At safety contacts 2 and 4 weeks later, the patient reported no issues. We stopped enrollment for safety reasons after the third patient required emergent evaluation and a transfusion.

Baseline and follow-up serum hCG and progesterone levels are presented in Figures 2 and 3, respectively. Median baseline hCG and progesterone levels for the progesterone group were 76,776 milli-international units/mL (range 21,062–126,647 milli-international units/mL) and 12.4 ng/mL (range 10.5–24.0 ng/mL), respectively. Median baseline hCG and progesterone levels for the placebo group were 153,908 milli-international units/mL (range 25,450–246,638 milli-international units/mL) and 16.3 ng/mL (range 11.2–18.9 ng/mL), respectively. In the progesterone group, progesterone levels increased 240–1,010% within a few days of starting treatment among patients with continuing gestational cardiac activity at 2 weeks; the one patient with hemorrhage demonstrated an increase of only 45% despite being adherent to study drug instructions.

Table 2 describes side effects related to pregnancy or treatment. One patient in the progesterone group noted the onset of severe nausea and vomiting shortly after mifepristone intake that preceded progesterone treatment; otherwise, no appreciable differences in development of new severe side effects were identified between treatment groups. All patients experienced some spotting (n=8) or bleeding (n=9) during treatment, except for the patient with the highest baseline progesterone level (24.1 ng/mL).

Only two participants believed they received progesterone, of whom one did (continuing

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Table 1. Characteristics at Enrollment for Patients Receiving Mifepristone and Randomized to Progesterone or Placebo Treatment

Characteristic	Total (N=12)	Progesterone (n=6)	Placebo (n=6)
Age (y)	27.3 (20.9–39.6)	29.8 (24.6–39.6)	24.1 (20.9–33.8)
Gestational age (d)	52.5 (47–61)	49.5 (47–56)	55 (48–61)
BMI (kg/m^2)	24.6 (19.0–52.3)	24.8 (19.0–36.4)	24.6 (22.7–52.3)
Obese (30.0 or higher)	4 (33)	2 (33)	2 (33)
Race			
White	3 (25)	0	3 (50)
Black or African American	5 (42)	4 (67)	1 (17)
Asian	4 (33)	2 (33)	2 (33)
Ethnicity			
Hispanic or Latina	2 (17)	1 (17)	1 (17)
Marital status			
Never married	7 (58)	3 (50)	4 (67)
Married	2 (17)	1 (17)	1 (17)
Divorced or separated	3 (25)	2 (33)	1 (17)
Education level			
High school graduate	2 (17)	0	2 (33)
Some college	9 (75)	5 (83)	4 (67)
College graduate	1 (8)	1 (17)	0
Gravidity	4 (1–12)	4.5 (1–10)	3.5 (1–12)
More than 3 prior pregnancies	7 (58)	4 (67)	3 (33)
Parity	1 (0–6)	1.5 (0–6)	0.5 (0–3)
Nulliparous	4 (33)	1 (17)	3 (33)
Prior abortion	9 (75)	4 (67)	5 (83)
More than 3 prior abortions	4 (33)	2 (33)	2 (33)
Past mifepristone use	4 (733)	1 (17)	3 (33)
Prior progesterone use	0	0	0

BMI, body mass index.
Data are median (range) or n (%).

pregnancy at 2 weeks) and one did not (hemorrhage requiring emergent aspiration). The remaining 10 patients were evenly split between placebo and unsure. None of the patients looked on the internet to identify the study capsules they received.

DISCUSSION

Although the study sample size was powered to demonstrate a difference in continuing pregnancy rates between progesterone and placebo treatment after mifepristone ingestion, we could not evaluate this outcome owing to stopping enrollment for safety reasons. However, we can make a few global and important conclusions from this very small, randomized trial. First, patients who receive high-dose oral progesterone treatment do not experience side effects that are noticeably different than placebo. Although patients using progesterone did report worsening of some pregnancy symptoms such as vomiting and tiredness, these issues were rarely severe.

Second and most important are the lessons about treatment safety. Providing treatment in any medical situation requires a full understanding of the potential benefits and risks. Previous case series reports do not describe outcomes for the one third or more patients without continuing pregnancies after progesterone treatment.[8] Three of 12 patients enrolled experienced very heavy bleeding resulting in ambulance transport to an emergency department, a rate higher than reported with medical abortion, in which 0.6% of patients may have emergency department visits.[12] Patients who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment. We stopped the study because of these complications and, thus, could not quantify the full extent of this risk. Because of the potential dangers for patients who opt not to use misoprostol after mifepristone ingestion, any mifepristone antagonization treatment must be considered experimental.

The study has multiple limitations, primarily the inability to safely reach the enrollment goal to fully assess the primary outcome. Additionally, blinding for progesterone capsules is difficult and imperfect; however, we believe we maintained blinding because the

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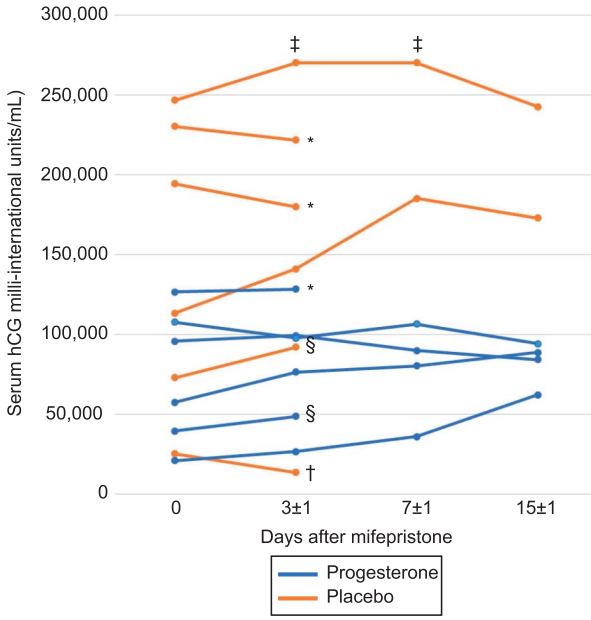


Fig. 2. Serum human chorionic gonadotropin (hCG) levels in patients who received mifepristone 200 mg followed by progesterone for up to 2 weeks. *Participants experiencing hemorrhage. †Participant experienced loss of gestational cardiac activity. ‡Value greater than 270,000 (upper limit of hCG test). §Discontinued related to side effects.

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patients enrolled had never used progesterone and none looked up the treatment to identify the drug. Of note, the variability in progesterone level among patients in the progesterone group may be explained by differential oral absorption of progesterone.[13] Although one may postulate another route of progesterone administration might affect the outcome, the case reports in the literature suggest similar continuing pregnancy rates after oral and intramuscular treatment.[8]

Our study established outcomes at 2 weeks as a surrogate for ongoing pregnancy; as such, it does not capture those who may still experience pregnancy loss more than 2 weeks after mifepristone exposure.[14] Accordingly, the outcomes described may not reflect the ultimate rate of pregnancies that continue past 20 weeks of gestation. Progesterone levels declined from high peaks to levels near baseline with continued treatment for 2 weeks. These findings raise two opposing questions: First, if progesterone can prevent medical abortion after mifepristone, is treatment necessary for more than 2 weeks? The case report from which the oral progesterone regimen for this study was based used the treatment through the "end of the first trimester."[8] Second, do those treated with placebo just expel the pregnancy earlier than those who receive progesterone but no overall long-term difference in continuing pregnancy exists?

The context of this study is the question of whether a patient who has taken mifepristone 200 mg for a medical abortion and decides not to proceed with misoprostol treatment will be less likely to expel the pregnancy if she receives high-dose progesterone as compared with no treatment. Although mifepristone can cause abortion when used by itself in early pregnancy, the exact rate is not clear because studies were small and limited primarily to pregnancies of 49 days or less. Medical abortion today is used through 70 days of gestation. Additionally, a background rate of pregnancy loss is present regardless of mifepristone treatment. In patients with gestational

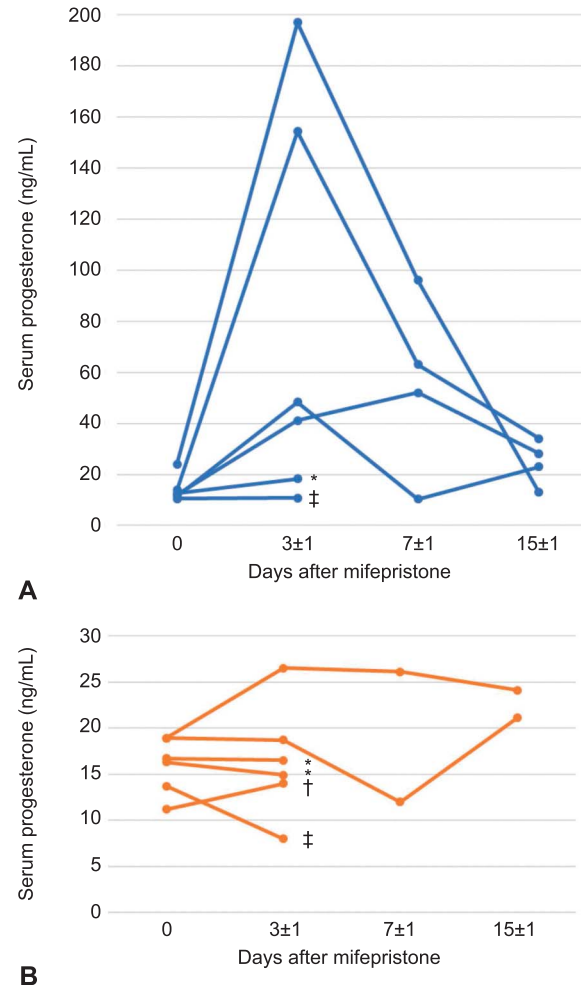


Fig. 3. Progesterone levels in patients who received mifepristone 200 mg followed by progesterone (**A**) or placebo (**B**) for up to 2 weeks. *Participants experiencing hemorrhage. †Participant experienced loss of gestational cardiac activity. ‡Discontinued related to side effects.

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Table 2. Side Effects* Noted During Follow-up of Patients in Early Pregnancy Receiving Mifepristone and Randomized to Progesterone or Placebo Treatment for Up to 2 Weeks

	Reported at Baseline		Increased From Baseline†		Increased to Severe During Follow-up†	
	Progesterone (n=6)	Placebo (n=6)	Progesterone (n=6)	Placebo (n=6)	Progesterone (n=6)	Placebo (n=6)
Nausea	4 (67)	5 (83)	2 (33)	2 (33)	2 (33)	1 (17)
Vomiting	2 (33)	3 (50)	4 (67)	0	2 (33)	0
Mastalgia	4 (67)	5 (83)	1 (17)	0	0	0
Tiredness	5 (83)	4 (67)	3 (50)	0	0	1 (17)
Mood changes	4 (67)	5 (83)	0	0	1 (17)	0
Reflux	2 (33)	2 (33)	1 (17)	0	0	0
Dizziness	2 (33)	1 (17)	0	0	0	0
Bleeding	0	0	4 (67)	4 (67)	1 (17)	3 (50)
Spotting	1 (17)	1 (17)	3 (50)	4 (67)	0	0
Cramping	3 (50)	2 (33)	4 (67)	5 (83)	0	0

Data are n (%).
* Subjectively assessed by participant as none, mild, moderate, or severe.
† At any time during follow-up.

cardiac activity demonstrated by ultrasonography at 6–10 weeks, 13.4% will spontaneously have an early pregnancy loss.[15]

This study, although small, provides important insight into the safety of mifepristone antagonization with progesterone during early pregnancy. We should not dismiss mifepristone antagonization as impossible; fully understanding outcomes will serve as the best means to accurately inform our patients, the medical community, and legislators. Existing literature before this study is comprised of case reports and series, which are not evidence of efficacy and do not address safety.[6–8] This level of evidence is inadequate to support or refute the benefits and risks of any treatment. Unfortunately, legislators often fail to understand differences in levels of evidence and some states now require physicians who provide medical abortion to counsel patients that the actions of mifepristone can be reversed if they change their mind. In 2015, Arkansas implemented mandatory abortion-reversal counseling, followed by Arizona (later repealed in 2016), South Dakota, Utah, Idaho, and, most recently, North Dakota. Several other states have introduced and passed legislation, although some was vetoed by the governors. Abortion is no different than any other medical treatment when considering clinical practice guidelines; laws should not mandate counseling or provision of any treatment when we do not fully understand treatment efficacy (including best route of administration, dose, and duration) and safety.

The dilemma that has been created around mifepristone antagonization exists only because of the void in high-quality research addressing the issue. For now, such a treatment is experimental and should be offered only in institutional review board–approved human clinical trials to ensure proper oversight.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Yes.*

What data in particular will be shared? *Data included with the submission in Appendix 1, available online at* http://links.lww.com/AOG/B658.

What other documents will be available? *No.*

When will data be available (start and end dates)? *With publication.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *In Appendix 1,* http://links.lww.com/AOG/B658.

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