Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial

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Mifepristone ingestion without subsequent misoprostol administration in first-trimester gestations can result in hemorrhage and poses safety concerns.

Abstract

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

Methods: We planned to enroll 40 women in a double-blind, placebo-controlled, randomized trial. We enrolled women 44-63 days gestation with ultrasound-confirmed gestational cardiac activity 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 two weeks (15±1 days), 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 complaints (nausea and vomiting, bleeding). Among the remaining 10 women (5 per group), gestational cardiac activity continued for two weeks in 4 in the progesterone group and 2 in the placebo group. One woman in the placebo group had no gestational cardiac activity 3 days after mifepristone use. Severe hemorrhage requiring ambulance transport to hospital occurred in 3 patients; 1 received progesterone (complete expulsion, no aspiration) and 2 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. Women in early pregnancy who use only mifepristone may be at high risk of significant hemorrhage.

Clinical Trial Registration: ClinicalTrials.gov, NCT03774745.

Introduction

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 Food and Drug Administration (FDA) for medical abortion is a combination of mifepristone and misoprostol through 70 days 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 women less than 49 days 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 gestation; however, as gestation advances from 49 to 70 days, complete abortion rate decreases and continuing pregnancy rate increases (2). Approximately 0.3% of women at 49 days or less experience a continuing pregnancy compared to 3.1% of women at 64 to 70 days (2). A recent United Kingdom study of women who initiated medical abortion at 64 to 70 days found that 9/89 (10%) women with continuing pregnancies detected at follow-up opted to continue the pregnancy (5).

Case series have reported that some women may change their minds about terminating their pregnancies after ingesting mifepristone and prior to misoprostol treatment (6-8). Although an exact proportion is unknown, the best estimate is that <0.005% of women 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) following mifepristone ingestion without consenting women 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 women 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 women 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 women who had completed counseling and consent for a surgical abortion and were 63 days 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 two weeks. Exclusion criteria were medical contraindications to medical abortion per the mifepristone FDA label (2), an allergy to mifepristone or progesterone, or a peanut allergy (on-label contraindication to oral progesterone).

The UC Davis Institutional Review Board approved this study and all participants gave written study consent prior to 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 if they had used mifepristone or progesterone previously. Patients for whom transvaginal ultrasonography demonstrated gestational cardiac activity and a gestational age 44-63 days gestation based on Goldstein and Wolfson's criteria (10) could enroll that day. Women less than 44 days 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 UC Davis Investigational Drug Service (IDS) by placing 38 capsules of progesterone 200 mg or similar-appearing placebo capsules in opaque pill containers. The IDS could not over-encapsulate the drugs due to product size. The IDS 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 three days then two 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/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 subject'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 if 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 two weeks (15±1 days). Secondary outcomes included expulsion rates over two weeks, change in hCG and progesterone during treatment, study drug side effects, and safety outcomes (e.g., hemorrhage, emergency department visit, emergent suction aspiration). Safety evaluations (adverse events review) were performed by the principal investigator after each subject completed the study and at research review meetings every two 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 women had a pregnancy that continued to 20 weeks or more (8). We also estimated that only 25% of women receiving placebo would have a continuing pregnancy (10). Using 80% power and α=0.05, 20 participants per group were required.

We performed an intention-to-treat analysis, using Fisher's Exact Test or Chi-square test as indicated, t-test for continuous variables and Mann Whitney U for comparing median values.

Results

We enrolled 12 women from February to July 2019 (Figure 1). Patient characteristics are presented in Table 1. Two women exited the study voluntarily related to side effects; both had a suction aspiration 3 days after mifepristone administration. The first, 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, 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 only took two of her four treatment doses before requesting a suction aspiration.

Overall, 4/6 women in the progesterone group and 2/6 women in the placebo group had a continuing pregnancy at two weeks. Excluding the two women who did not finish treatment, these rates are 4/5 and 2/5 respectively. A detailed listing of individual subject characteristics and outcomes is included in Appendix 1, available online at http://links.lww.com/xxx.

Four pregnancies did not continue, including one subject 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 women had severe bleeding requiring ambulance transport to an

emergency department. The first subject received progesterone treatment after enrollment at 56 days gestation. She reported no bleeding at the first follow-up visit 2 days post mifepristone. Shortly after her visit, she started having brisk bleeding and called an ambulance. Transvaginal ultrasound 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 subject received placebo and enrolled at 60 days gestation. She noted new mild bleeding at a follow-up visit two days after mifepristone use. The following day, she called an ambulance due to onset of heavy vaginal bleeding. In the emergency department, a study physician found significant heterogenous material in the uterine cavity on ultrasound exam with continued brisk bleeding, so a suction aspiration was performed. Pathology demonstrated normal chorionic villi. The third subject also received placebo and enrolled at 60 days gestation. She noted new mild spotting at a follow-up visit two days after mifepristone use. The following days, she called an ambulance after experiencing hemorrhage. In the emergency department, a study physician evaluated the subject who had significant brisk bleeding, hypotension and tachycardia. Transvaginal sonography showed the gestational sac still in the uterine cavity, so an emergent suction aspiration was performed. This subject's hemoglobin decreased in the emergency department from 9.2 to 7.5 gm/dL and she received a one-unit transfusion of packed red blood cells. At safety contacts two and four weeks later, the subject reported no issues. We stopped enrollment for safety reasons after the third subject 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 mIU/mL (range 21,062-126,647 mIU/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 mIU/mL; range 25,450-246,638 mIU/mL) and 16.3 ng/mL (range 11.2-18.9 ng/mL), respectively. In the progesterone group, progesterone levels increased 240-1010% within a few days of starting treatment among women with continuing gestational cardiac activity at two weeks whereas the one subject with hemorrhage demonstrated an increase of only 45% despite being adherent with study drug instructions.

Table 2 describes side effects related to pregnancy or treatment. One subject 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 women experienced some spotting (n=8) or bleeding (n=9) during treatment except for the subject with the highest baseline progesterone (24.1 ng/mL).

Only two participants believed they received progesterone, of whom one did (continuing pregnancy at two weeks) and one did not (hemorrhage requiring emergent aspiration). The remaining ten women were evenly split between placebo and unsure. None of the women 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 due to stopping enrollment for safety reasons. However, we can make a few global and important conclusions from this very small, randomized trial. First, women who receive high-dose oral progesterone treatment do not experience side effects that are

noticeably different than placebo. Although women using progesterone did report worsening of some pregnancy symptoms, like vomiting and tiredness, these issues were rarely severe.

Second, and most importantly, 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 women without continuing pregnancies after progesterone treatment (8). Three of 12 women enrolled experienced very heavy bleeding resulting in ambulance transport to an emergency department visit, a rate higher than reported with medical abortion in which 0.6% of women may have emergency department visits (12). Women 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 women 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 women enrolled had never used progesterone and none looked up the treatment to identify the drug. Of note, the variability in progesterone level among women 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 two 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 gestation. Progesterone levels declined to levels near baseline from these high peaks with continued treatment for two weeks. These findings raise two opposing questions: first, if progesterone can prevent medical abortion following mifepristone, is treatment necessary for more than two 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 that receive progesterone but no overall long-term difference in continuing pregnancy exists?

The context of this study is the question of whether a woman 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 to 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 gestation. Additionally, a background rate of pregnancy loss is present regardless of mifepristone treatment. In women with gestational 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 level of evidence and some states now require physicians who provide medical abortion to counsel women 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 were vetoed by the Governor. 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 don't fully understand treatment efficacy (including best route of administration, dose and duration) and safety.

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

References

1. Jones RK, Witwer E, Jerman J. Abortion incidence and service availability in the United States, 2017, New York: Guttmacher Institute, 2019. Available at https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017 (Accessed October 8, 2019).
2. Mifeprex® label. Danco Laboratories, LLC. March, 2016. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf (Accessed October 8, 2019).
3. Spitz IM, Bardin CW. Mifepristone (RU 486)--a modulator of progestin and glucocorticoid action. N Engl J Med 1993;329:404-12.
4. Mahajan DK, London SN. Mifepristone (RU486): a review. Fertil Steril 1997;68:967-76.
5. Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception. 2019;100:178-81.
6. Delgado G, Davenport ML. Progesterone use to reverse the effects of mifepristone. Ann Pharmacother 2012;46:e36.
7. Garratt D, Turner JV. Progesterone for preventing pregnancy termination after initiation of medical abortion with mifepristone. Eur J Contracept Reprod Health Care 2017;22:472-5.
8. Delgado G, Condly SJ, Davenport M, Tinnakornsrisuphap T, Mack J, Khauv V, Zhou PS. A case series detailing the successful reversal of the effects of mifepristone using progesterone. Issues Law Med 2018;33:3-13.
9. Grossman D, White K, Harris L, et al. Continuing pregnancy after mifepristone and “reversal” of first-trimester medical abortion: a systematic review. Contraception 2015;92:206-11.

10. Goldstein SR, Wolfson R. Endovaginal ultrasonographic measurement of early embryonic size as a means of assessing gestational age. J Ultrasound Med 1994;13:27-31.
11. Maria B, Chaneac M, Stampf F, Ulmann A. Early pregnancy interruption using an antiprogesterone steroid: mifepristone (RU 486). J Gynecol Obstet Biol Reprod (Paris) 1988;17:1089–94.
12. Upadhyay UD, Desai S, Zlidar V, et al. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125:175-83.
13. Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications--a review. Contraception 1987;36:373-402.
14. Bernard N, Elefant E, Carlier P, Tebacher M, Barjhoux CE, Bos-Thompson MA, et al. Continuation of pregnancy after first-trimester exposure to mifepristone: an observational prospective study. BJOG 2013;120:568-74.
15. Papaioannou GI, Syngelaki A, Maiz N, Ross JA, Nicolaides KH. Ultrasonographic prediction of early miscarriage. Hum Reprod 2011;26:1685-92.

Legend

Figure 1.

Title:

Participant flow in women who received mifepristone 200 mg followed by progesterone for up to two weeks

Footer:

GCA: gestational cardiac activity

Figure 2.

Title:

Serum hCG levels in women who received mifepristone 200 mg followed by progesterone for up to two weeks

Footer:

hCG: human chorionic gonadotropin

* Participants experiencing hemorrhage

† Participant experienced loss of gestational cardiac activity

‡ Value >270,000 (upper limit of hCG test)

¥ Discontinued related to side effects

Figure 3.

Title:

Progesterone levels in women who received mifepristone 200 mg followed by progesterone (Figure A) or placebo (Figure B) for up to two weeks

Header Figure 2A: Progesterone users

Header Figure 2B: Placebo users

Footer:

* Participants experiencing hemorrhage

† Participant experienced loss of gestational cardiac activity

‡ Discontinued related to side effects.

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/xxx*

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/xxx.*

357

358 Table 1. Characteristics at enrollment for women receiving mifepristone and randomized to
359 progesterone or placebo treatment

Characteristic	Total N=12	Progesterone n=6	Placebo n=6
Age (years)	27.3 (20.9-39.6)	29.8 (24.6-39.6)	24.1 (20.9-33.8)
Gestational age (days)	52.5 (47-61)	49.5 (47-56)	55 (48-61)
Body Mass Index (kg/m^2)	24.6 (19.0-52.3)	24.8 (19.0-36.4)	24.6 (22.7-52.3)
Obese (≥30.0)	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/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)
>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%)

360

Prior Abortion	9 (75%)	4 (67%)	5 (83%)
>3 prior abortions	4 (33%)	2 (33%)	2 (33%)
Past Mifepristone Use	4 (733%)	1 (17%)	3 (33%)
Prior Progesterone Use	0	0	0

361 Data are presented as n (%) or median (range)

Table 2. Side effects* noted during follow-up of women in early pregnancy receiving mifepristone and randomized to progesterone or placebo treatment for up to two 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

* subjectively assessed by participant as none, mild, moderate or severe

† at any time during follow-up

Data are presented as n (%)

Appendix. Individual subject characteristics at enrollment and outcomes for women receiving mifepristone 200 mg and randomized to progesterone or placebo treatment

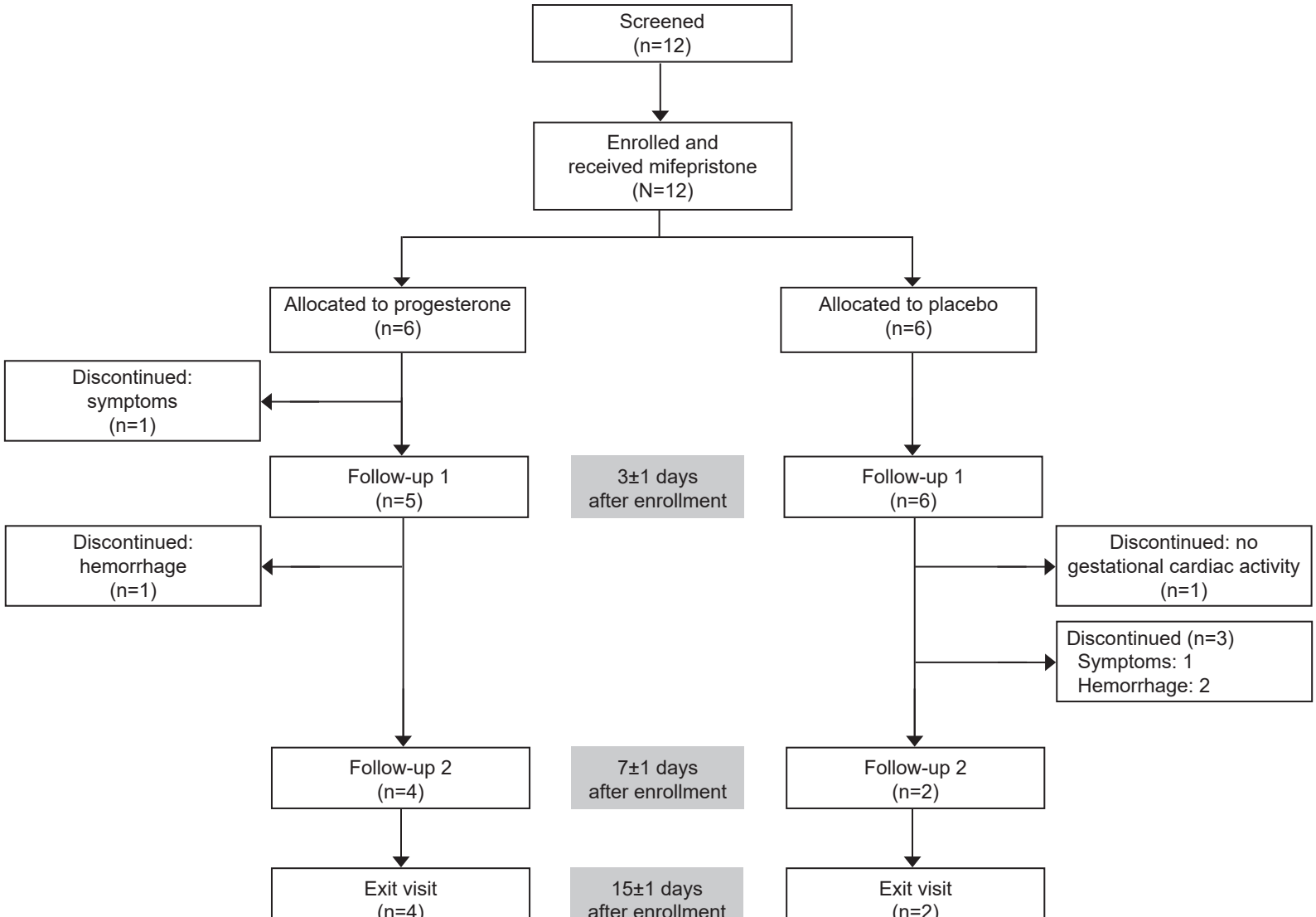
Subject Number	Study group*	Age (years)	Gestational Age (days)	Race	Ethnicity	Education	Marital Status	Smoking	Alcohol	Marijuana Use	Drug Use	Total Pregnancies	Vaginal Delivery	Cesarean Delivery	Miscarriages	Abortions	Weight (kg)	BMI (kg/m^2)
1	Progesterone	24.6	53	Asian	Not Hispanic	Some college	Never married	Never	Never	Never	Never	1	0	0	0	0	84.2	32.9
2	Progesterone	30.9	50	Black	Not Hispanic	Some college	Separated	Never	Current	Current	Never	8	3	0	0	4	68.9	23.8
3	Placebo	20.9	50	Asian	Not Hispanic	Some college	Never married	Never	Never	Never	Never	1	0	0	0	0	61.8	24.1
4	Placebo	22.6	48	White	Hispanic	Some college	Married	Current	Current	Current	Current	2	0	0	0	1	152.0	52.3
5	Progesterone	39.6	49	Black	Not Hispanic	Some college	Never married	Current	Never	Never	Never	5	2	0	0	2	51.8	19.0
6	Placebo	24.8	61	Asian	Not Hispanic	Some college	Never married	Never	Current	Current	Never	3	0	0	1	1	66.7	24.4
7	Placebo	23.5	48	White	Not Hispanic	High School graduate	Never married	Former	Never	Current	Never	7	0	1	0	5	71.8	22.7
8	Progesterone	27.7	56	Black	Not Hispanic	Some college	Never married	Never	Current	Never	Never	10	1	0	1	7	100.8	36.4
9	Progesterone	31.9	47	Asian	Not Hispanic	College graduate	Married	Never	Never	Never	Never	4	0	2	1	0	66.0	25.8
10	Placebo	27.0	60	Black	Not Hispanic	High School graduate	Never married	Never	Current	Current	Never	4	2	0	0	1	63.5	24.8
11	Placebo	33.8	60	White	Not Hispanic	Some college	Separated	Current	Former	Former	Former	12	6	0	0	5	105.5	34.3
12	Progesterone	28.6	48	Black	Hispanic	Some college	Divorced	Never	Current	Current	Never	3	1	0	0	1	53.8	19.7

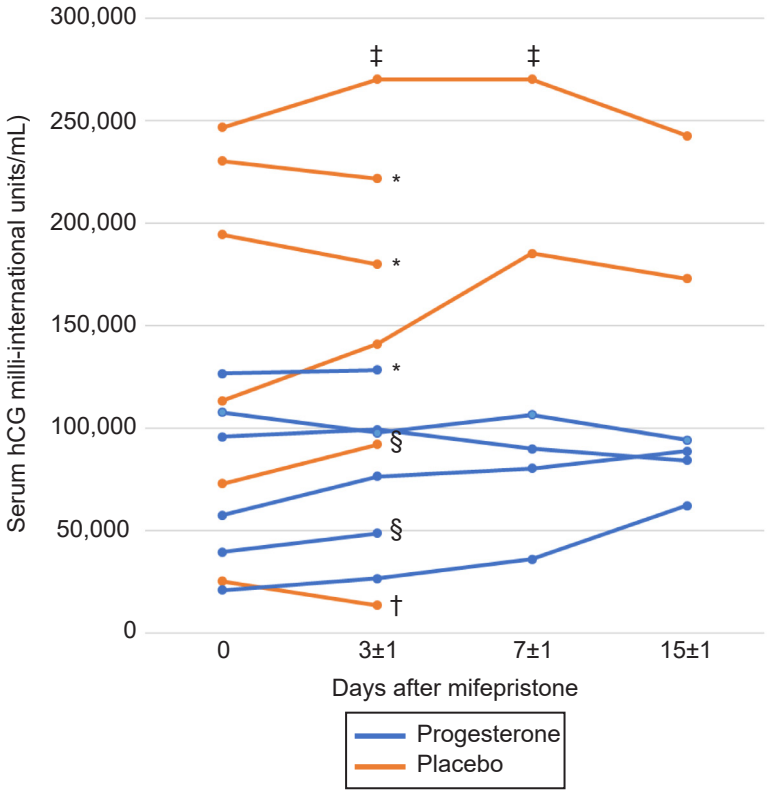
Subject Number	hCG (mIU/mL)	Progesterone (ng/mL)	Exit Study Day†	FINAL OUTCOME	Hospital visit	Reason for Hospital visit
1	95,870	12.1	17	Continuing GCA at exit visit	No	N/A
2	57,681	11.5	16	Continuing GCA at exit visit	No	N/A
3	113,431	18.9	16	Continuing GCA at exit visit	No	N/A
4	25,450	13.7	4	No GCA at follow-up visit	No	N/A
5	107,780	24.1	16	Continuing GCA at exit visit	No	N/A
6	246,638	18.9	16	Continuing GCA at exit visit	No	N/A
7	73,018	11.2	4	D&C requested (bleeding, anxiety)	No	N/A
8	126,647	12.6	3	Expelled pregnancy, no D&C	Yes (ER), Day 3	Hemorrhage, hemoglobin 10.4 gm/dL
9	39,660	10.5	4	D&C requested (nausea, vomiting)	Yes (L&D), Day 3	Dehydration, nausea, vomiting
10	230,220	16.3	5	Expelled pregnancy, incomplete, emergent D&C	Yes (ER), Day 5	Hemorrhage, hemoglobin 9.6 gm/dL
11	194,384	16.7	6	Expelled pregnancy, incomplete, emergent D&C, transfusion	Yes (ER), Day 6	Hemorrhage, hemoglobin change 9.2 to 7.5 gm/dL
12	21,062	13.9	15	Continuing GCA at exit visit	No	N/A

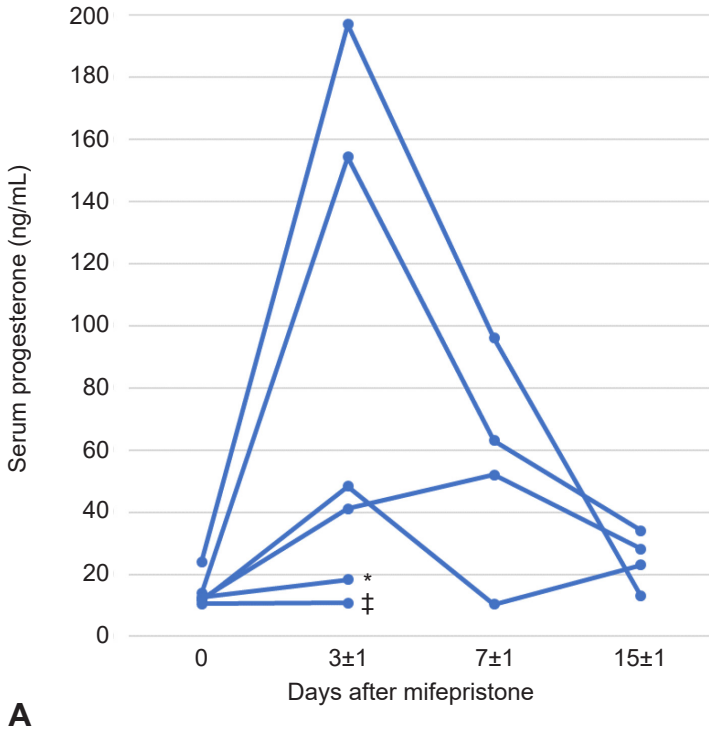
BMI: body mass index; GCA: gestational cardiac activity; ER: emergency room; L&D: labor and delivery; N/A: not applicable

* Initiated on study day 2 (24 hours after mifepristone ingestion)

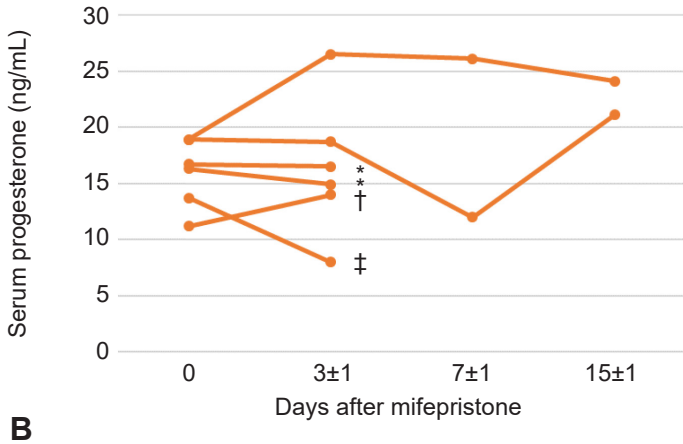
† Day 1: day of mifepristone administration


Screened
(n=12)
Enrolled and
received mifepristone
(N=12)
Allocated to progesterone
(n=6)
Allocated to placebo
(n=6)
Discontinued:
symptoms
(n=1)
Follow-up 1
(n=5)
3±1 days
after enrollment
Follow-up 1
(n=6)
Discontinued:
hemorrhage
(n=1)
Discontinued: no
gestational cardiac activity
(n=1)
Discontinued (n=3)
Symptoms: 1
Hemorrhage: 2
Follow-up 2
(n=4)
7±1 days
after enrollment
Follow-up 2
(n=2)
Exit visit
(n=4)
15±1 days
after enrollment
Exit visit
(n=2)


300,000
250,000
200,000
150,000
100,000
50,000
0
Serum hCG milli-international units/mL)
‡
‡
*
*
*
§
§
†
0
3±1
7±1
15±1
Days after mifepristone
Progesterone
Placebo


200
180
160
140
120
100
80
60
40
20
0
Serum progesterone (ng/mL)
*
‡
0
3±1
7±1
15±1
Days after mifepristone

A


30
25
20
15
10
5
0
Serum progesterone (ng/mL)
*
†
‡
0
3±1
7±1
15±1
Days after mifepristone

B