A Randomized Trial of Mifepristone Antagonization with High-Dose Progesterone to Prevent Medical Abortion

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1) Protocol Title

Title: A Randomized Trial of Mifepristone Antagonization with High-Dose Progesterone to Prevent Medical Abortion

2) Objectives

Research questions:

1. Does high dose oral progesterone treatment increase the continuing pregnancy rate in women 44-63 days gestation exposed to mifepristone without misoprostol treatment?
2. If oral progesterone may be of benefit, do some characteristics of the pregnancy (e.g., gestational age) or patient (e.g. parity) potentially impact the outcome?
3. If oral progesterone may be of benefit, what sample size would be needed to validate such an outcome for various gestational age ranges in a prospective placebo-controlled randomized trial?
4. How long does it take to recruit women seeking surgical abortion to participate in a double-blind randomized trial evaluating oral progesterone for antagonization of mifepristone treatment for abortion?

Hypothesis: High-dose oral progesterone initiated 18-24 hours after mifepristone 200 mg in early pregnancy will result in more continuing pregnancies after 2 weeks of treatment than placebo.

3) Background

Medical abortion commonly refers to early pregnancy termination (usually before 10 weeks' gestation) performed without primary surgical intervention and resulting from the use of abortion-inducing medications (1). The use of medications to cause abortion has been around for almost 70 years but the modern era of medical abortion treatment evolved with the development of mifepristone (1), a progesterone-receptor blocker with an affinity for the receptor greater than progesterone itself (2).

Early research into modern medical abortion regimens took a leap forward with the discovery that adding a prostaglandin analogue within a few days after mifepristone significantly improved the efficacy of the treatment (3). In the late 1980s, France, China, Switzerland and the UK became the first countries to make medical abortion treatment clinically available, with regimens using mifepristone 600 mg followed 36-48 hours later by a prostaglandin analogue, restricted to use up to 49 days gestation.

Today, our understanding of the agents available and used for medical abortion have advanced the regimen to permit use of a lower dose of mifepristone than originally approved (200 mg) with misoprostol, a prostaglandin analogue that is inexpensive and stable at room temperature, through 70 days' gestation. The advance in gestational age

has nothing to do with mifepristone and is entirely related to the route and dose of the prostaglandin analogue. The latest data available (from 2014) estimates that 31% of all outpatient abortions in the United States are estimated to occur using medications, with the abortion almost exclusively occurring in the privacy of women's homes (4).

Medical abortion with mifepristone and misoprostol is highly effective; however, the risk of continuing pregnancy is still present, especially as gestation advances (5-7). While most women opt for further treatment in these scenarios, such as surgical aspiration, there are some who decide to continue the pregnancy. In an abstract presented at the 2018 National Abortion Federation meeting, data from BPAS in the UK show that among 2,673 women having a medical abortion from 9-10 weeks' gestation, 90 women had ongoing pregnancies after treatment of whom 9 (10%) opted to continue the pregnancy (Jennifer Hsia, MD, MPH; personal communication, poster abstract, NAF 2018). Thus, even following treatment, some women do change their mind.

Legislators began to focus on women who change their mind after mifepristone administration following release of a report of "medical abortion reversal" in which women received high dose progesterone to antagonize the effects of mifepristone. This first report, published in Annals of Pharmacotherapy in December 2012 by Delgado and Davenport (8), described seven patients treated by "[s]ix physicians in the US trained in NaProTECHNOLOGY protocols at the Pope Paul VI Institute." Of the seven patients, one was lost to follow-up, four had continuing pregnancies and delivered healthy newborns, and two had miscarriages. Treatment varied between patients but primarily consisted of Progesterone 200 mg in oil intramuscularly with or without oral micronized progesterone. Four of the six reported women were 8 weeks' gestation or less, one was an unknown gestation and the other woman was reportedly 11 weeks when she received mifepristone. Thus, of the women with follow-up who were possibly within the current medical abortion treatment limits of 10 weeks, 3 of 5 (60%) had continuing pregnancies. Following this report, two literature reviews attempted to synthesize information on continuing pregnancy rates following mifepristone treatment. Grossman et al (9) found

Studies reporting the proportion of women with continuing pregnancies following administration of mifepristone alone for medical abortion

Study	Mifepristone oral dose	*N*	Gestational age limit	Follow-up visit (number of days after mifepristone)	Complete abortion	Continuing pregnancy at follow-up visit (%, 95% C
Birgerson 1988 [9]	10, 25 or 50 mg twice daily for 7 days	153	49 days	8–10 days	67%	27% (20–34%)
Cameron 1986 [8]	150 mg daily for 4 days	20	56 days	14 days	60%	25% (11–47%)
Carol 1989 [17]	600 mg (single dose)	50	39 days	NS	80%	12% (6–24%)
Grimes 1988 [10]	600 mg (single dose)	50	49 days	14 days	88%	10% (4–21%)
Kovacs 1984 [11]	25–100 mg twice daily for 4 days	36[a]	42 days	14 days	61%	8% (3–22%)
Maria 1988a [16]	600 mg (single dose)	149[a]	42 days	7 days	88%	9% (6–15%)
Maria 1988b [18]	600 mg (single dose)	174	49 days	7 days	84%	11% (8–17%)
Maria 1988b [18]	200 mg (single dose)	30	49 days	7 days	63%	23% (12–41%)
Somell 1990 [12]	600 mg (single dose)	70	42 days	7 days	80%	17% (10–28%)
Swahn 1989 [13]	25 mg twice daily for 4 days	14	49 days	14 days	57%	36% (16–61%)
Ylikorkala 1989 [14]	600 mg (single dose)	47[b]	43 days	14 days	70%	11% (5–23%)
Zheng 1989 [15]	600 mg (single dose)	204	42 days	7 days	65%	31% (25–38%)
Zheng 1989 [15]	600 mg (single dose)	95	49 days	7 days	53%	46% (37–56%)

NS, not specified.

[a] One additional participant was later found to have an ectopic and is excluded from the total here.

[b] Three additional participants had a missed abortion at time of treatment and are excluded from the total here.

13 studies meeting appropriate criteria to be included in the review with continuing

pregnancy rates ranging from 8% to 46% when patients were assessed generally 1-2 weeks after mifepristone ingestion. Of note, the studies with the lowest rates of continuing pregnancies typically included women earlier in gestation.

Another review was published in 2017 by Davenport, Delgado and colleagues (10) openly as a rebuttal to the review from Grossman et al (9). This review, published in a journal not indexed in Pubmed, included only three of the same papers meeting inclusion criteria for the analysis by Grossman et al and excluded four of the papers included by Grossman et al stating that these studies did not always use ultrasound to designate if a viable pregnancy was present. These authors report a mean percentage of continuing pregnancies of only 12.6%, with most studies using mifepristone 600 mg or more. Recently, two additional case series have been published. The first is an Australian description of 3 women (at 43 days, approximately 53 days, and 61 days gestation) who initiated treatment with progesterone vaginally for 14 days at 28, 3.5, and 31 hours, respectively, after ingesting mifepristone (11). The first two women had continuing pregnancies and delivered healthy newborns, and the third women experienced a miscarriage on the day she initiated progesterone treatment.

The second is a report from Dr. Delgado's abortionreversalpill.com network (12). Published again in the same journal not indexed in Pubmed, this case series includes 754 women treated in various ways by 325 different providers with "high-dose" progesterone, including progesterone in oil intramuscularly, micronized progesterone orally, micronized progesterone capsules administered vaginally, compounded micronized progesterone vaginal suppositories, progesterone vaginal gel, and progesterone vaginal suppositories. The authors defined successful treatment as viability post 20 weeks' gestation. They excluded 207 women from analysis, including those who received treatment >72 hours post-mifepristone or in whom misoprostol had been used (n=38), were lost to follow-up at <20 weeks' gestation (n=112), or who opted to complete the abortion (changed mind again, n=57). Of 547 women in the analysis, treatment was successful in 261 (48%) women including 257 births and 4 women LTFU after 20 weeks. Subgroups with the highest success rates included 31 women treated with high-dose oral progesterone 400 mg twice daily for 3 days followed by 400 mg daily until end of "first trimester" (68%) and 125 women who received progesterone in oil IM initially or exclusively (64%). Notably, efficacy was higher with more advanced gestational age. The authors estimated that 25% of women would have continued the pregnancy even without treatment; that statistic implies no

Gestational Age	Total	Reversal	Reversal Failure	Reversal %	*P* value	95% Confidence Intervals
5 weeks	76	19	57	25%	0.5	0.15-0.35
6 weeks	113	52	61	46%	<0.001	0.37-0.55
7 weeks	102	50	52	49%	<0.001	0.39-0.59
8 weeks	88	54	34	61%	<0.001	0.51-0.72
9 weeks	30	23	7	77%	<0.001	0.62-0.92

treatment effect for woman earlier than 6 weeks gestation and an overall effect size of any treatment to be 23%.

The dilemma that has been created around medical abortion reversal only exists because of the void in high-quality research addressing the issue; basic concepts need to be addressed to begin to understand if medical abortion reversal is actually possible. These case series reports (8,11,12) lack control groups, and the reports by Delgado and colleagues (8,12) involved experimental treatment without consent or oversight. Unfortunately, even without such trials, conservative lawmakers are using these case reports as medical gospel and passing laws stipulating reversal as fact. In 2015, Arkansas implemented mandatory abortion reversal counseling followed by Arizona (later repealed in 2016), South Dakota, and Utah. The Idaho governor signed such a counseling law on March 20, 2018, which went into effect on July 1, 2018. Numerous other states have initiated bills to create similar laws that have not passed. Conversely, Louisiana Department of Health report in April 2017 found "neither sufficient evidence nor a scientific basis to conclude that the effects of an abortion induced with drugs or chemicals can be reversed" (13). In 2015 and reiterated in August 2017, the American Congress of Obstetrics and Gynecology publicly stood against laws mandating reversal information as lacking scientific standing (14).

In this study, we propose a double-blind randomized trial to evaluate the potential impact of progesterone treatment on early pregnancies exposed to mifepristone. This study is also a first step to understanding if large studies evaluating mifepristone antagonization with high-dose progesterone are indicated and if placebo-controlled randomized trials can be successfully completed when evaluating this question.

4) Inclusion and Exclusion Criteria

Inclusion Criteria

1. Pregnant females 18 years and older at enrollment.
2. Seeking surgical abortion at 44-63 days gestation on Study day 1.
3. Have received counseling and signed informed consent per UCD standard procedures for surgical abortion.
4. Singleton pregnancy
5. Presence of embryonic gestational cardiac activity on transvaginal ultrasonography.
6. English-speaking
7. Willing to sign informed consent and follow study protocol.
8. Willing to experience potential expulsion of the pregnancy with mifepristone treatment.

Exclusion Criteria

1. Medical contraindications to medical abortion.
    a. Poorly controlled hypertension (systolic BP >160 or diastolic BP >95)
    b. Significant anemia – known recent hemoglobin <9.5 gm/dL

   c. Clinically significant cardiovascular disease (angina, valvular disease, arrhythmia, or congestive heart failure)
   d. Breastfeeding
   e. Coagulopathy or therapeutic coagulation
   f. Ultrasound evidence of molar or ectopic pregnancy
   g. Chronic systemic corticosteroid use
   h. Adrenal disease
   i. Sickle cell anemia with frequent/recent crises
   j. Glaucoma
2. IUD in place during conception, even if removed.
3. Peanut allergy.
4. Known intolerance of mifepristone or progesterone.
5. Any other condition, that in the opinion of the clinician, would contraindicate mifepristone, progesterone or medical abortion.

Pregnant women will be included in this research. This study evaluates effect of high-dose progesterone on initiation of medical abortion and only pregnant women can have an abortion. Potential subjects must have gone through appropriate informed consent for surgical abortion per the standard of care within the UCD Department of Obstetrics and Gynecology prior to consent and screening for this research trial.

5) Study Timelines

Subject participation: approximately 15-17 days

Study timeline
- Duration of enrollment: 11 months (Anticipate Feb 2019 through Dec 2019)
- Completion of primary analysis: 2 months after completion of follow-up (Anticipate Feb 2020)

6) Study Endpoints

Primary endpoint: continuing pregnancy with presence of gestational cardiac activity after two weeks of study treatment
Secondary endpoints:
- Expulsion rates over two weeks following mifepristone treatment
- Pathology changes in trophoblast in a subset of dilation and curettage specimens
- Change in hCG and progesterone levels during treatment
- Tolerability of treatment
    - Ability to continue treatment for two weeks
    - Adverse events (side effects) related to progesterone or placebo after mifepristone including but not limited to nausea, vomiting, headache, mood changes, cramping, vaginal spotting, vaginal bleeding

- Safety outcomes: adverse events related to medical safety (e.g., hemorrhage, emergency department visits, emergent dilation and curettage procedures)

Study enrollment, outcomes and safety events will be reviewed continuously by the investigative team and in formal Family Planning Research meetings approximately twice monthly to monitor for events that would indicate safety issues.

7) Procedures Involved

Design: Double-blind placebo-controlled study of the effects of oral micronized progesterone on the viability of early pregnancies treated with mifepristone.

Study Treatment: Subjects will receive mifepristone 200 mg on Study day 1. Intervention treatment of micronized progesterone 200 mg capsules or placebo in a labeled container will be started on Study day 2.

- The UCD Investigational Drug Service (IDS) will supply sequentially numbered containers containing study drug or placebo and labeled specifically for this study.
    - The IDS will prepare a randomization table for the two treatment groups and will maintain the blinding of the randomization from the study team and patients.
    - The IDS will prepare study drug and placebo to ensure blinding.
    - Each study container will contain 38 capsules.
- Dosing schedule is based on the oral dosing regimen using micronized progesterone 200 mg capsules described by Delgado and colleagues (12):
    - Study day 2-4: Two capsules orally twice daily.
    - Study days 5 through 15, 16 or 17: Two capsules orally once daily.
- Progesterone dosing comparison to dosing for approved indication:
    - Dosing for the first 3 days is double the recommended daily dose when progesterone is used orally as treatment for inducing menses in women with secondary amenorrhea (400 mg once daily for 10 days), consistent with a “high” dose initial treatment.

Recruitment:

- Potential participants will be recruited through Planned Parenthood Mar Monte (PPMM), Family Planning Associates (FPA), and the UCD Family Planning clinic.
- Women who call in to either site seeking surgical abortion or who are seen at both sites with an estimated gestational age <63 days will be informed of the study.
- Women who are interested in the study will be given a referral number to the UC Davis Family Planning Research Office.

Methodology:

Clinical Visit Procedures:
An initial clinical visit at UCD will be required to evaluate for medical eligibility for abortion, obtain UCD consent for surgical abortion, perform transvaginal ultrasonography to confirm gestational dating (using criteria of Goldstein and Wolfson [16]) and presence of gestational cardiac activity, and confirm blood type/Rh-factor. This visit is standard care for women seeking abortion services.

Study Procedures:

- Screening visit
    - On the same day as the clinical visit or at another visit if desired, women <63 days gestation who have completed the consent process for surgical abortion will be seen in the UCD Family Planning Research office for study consent and evaluation.
    - After obtaining informed study consent, demographic information and pertinent medical history will be obtained.
- Enrollment visit
    - This visit may occur on the same day as screening if the subject is between 44 and 63 days gestation with a viable pregnancy (embryo present with gestational cardiac activity); otherwise, subject will be scheduled to return for enrollment visit when she is ≥44 days.
    - Subjects having an enrollment visit on a separate day from screening will have a transvaginal ultrasound repeated to confirm an embryo is present with gestational cardiac activity
        - If gestational cardiac activity not present, study physician to determine if enrollment visit should be rescheduled (if viability still possible) or if subject should be referred for clinical care of early pregnancy loss
    - Procedures
        - Confirm study eligibility
        - Two 5 mL tubes of blood will be obtained for baseline serum hCG and progesterone level.
        - Subjects will be questioned about baseline symptoms related to pregnancy (e.g., nausea, headache, mood changes).
        - Subjects will receive mifepristone 200 mg orally once all study entry criteria are confirmed (Study day 1).
        - Subjects will receive study treatment with dispensation of the next sequentially numbered study drug container. Subjects will be instructed as follows:
            - Begin study treatment on day 2, 18-24 hours after mifepristone administration (with the goal of being as close to 24 hours as possible).
            - Take the second dose on day 2 12 hours later or at bedtime (if going to bed less than 12 hours after the first dose).

- On days 3 and 4, take the study treatments about 12 hours apart, one dose in the morning and one in the evening.
- On day 5 through the end of the study, take the study treatment in the morning, at about the same time every day.

- Subjects will be provided with:
  - A daily diary to mark down use of the study drug, adverse effects, and bleeding. The diary will also include information on baseline pregnancy symptoms (present when she started the study). Subjects will be instructed to mark down any adverse effects (e.g., nausea, headache, mood changes) on the back of the diary; for any pregnancy symptom present at baseline, the subject will be instructed only to mark down if this symptom becomes worse than baseline.
  - An information sheet with study office phone numbers and instructions related to expected bleeding and cramping should the pregnancy expel after mifepristone treatment.

- Study day 2: the study site will contact the subject by phone around the time that study treatment is supposed to be started.
- Follow-up Visits: schedule on study days 4 (±1 day) and 8 (±1 day) at UCD Family Planning Research office.
  - Diary will be reviewed.
  - Study drug container will be reviewed and remaining drug counted by study staff.
  - The subject will be asked if she is tolerating the treatment and willing to continue study participation.
  - Two 5 mL tubes of blood will be obtained for serum hCG and progesterone level.
  - Ultrasonography will be performed to evaluate for presence of the gestational sac, interval growth and presence of gestational cardiac activity; the exam should preferentially be performed vaginally unless the gestational age or subject anatomy requires abdominal sonography for clearer visualization.
    - If gestational cardiac activity is absent, the visit will be considered an exit visit.
      - Collect remaining study drug and diary.
      - Refer subject to the original referral source (PPMM, FPA or the UCD Family Planning clinic) for completion of follow-up care; a patient from PPMM or FPA can request to complete care at UCD.
        - Referrals for PPMM-referred subjects returning to PPMM will be made to the Sacramento B Street Clinic.
        - Referrals for FPA-referred subjects returning to FPA will be made to the Sacramento Clinic.

- The subject will be exited from the study after a final outcome is determined by the clinical team.

- If the pregnancy is expelled, the visit will be considered an exit visit.
  - Collect remaining study drug and diary.
  - Refer subject to the original referral location (PPMM Sacramento B Street Clinic, FPA Sacramento Clinic or the UCD Family Planning clinic) for completion of follow-up care; a patient from PPMM or FPA can request to complete care at UCD.
    - Referrals for PPMM-referred subjects returning to PPMM will be made to the Sacramento B Street Clinic.
    - Referrals for FPA-referred subjects returning to FPA will be made to the Sacramento Clinic.
  - The subject will be exited from the study after a final outcome is determined by the clinical team.

- If the subject is continuing in the study, she will be reminded of the correct timing of study treatment intake, to fill our her diary daily, and to bring her diary and study drug with her to the next visit.

- Study exit visit: schedule for study day 15-17
  - Scheduled exit visits (study day 15-17) should occur through the original referral source (PPMM, FPA or the UCD Family Planning clinic) but a patient from PPMM or FPA can request to complete care at UCD.
    - Visits for PPMM-referred subjects returning to PPMM will occur at the Sacramento B Street Clinic.
    - Visits for FPA-referred subjects returning to FPA will occur at the FPA Sacramento Clinic.
  - Diary will be reviewed and collected from the participant.
  - Study drug container will be collected and remaining drug counted by study staff.
  - Two 5 mL tubes of blood will be obtained for serum hCG and progesterone level.
  - Ultrasonography will be performed to evaluate for presence of the gestational sac, interval growth and presence of gestational cardiac activity; the exam should preferentially be performed vaginally unless the gestational age or subject anatomy requires abdominal sonography for clearer visualization.
  - A surgical abortion will be performed through routine care if pregnancy has not passed and patient desires.
- If a subject desires to exit the study early (have a surgical abortion prior to Day 15-17), the exit visit procedures should be performed on the day of the surgical abortion.

- Unscheduled visits: to occur if the subject has any medical concerns or experiences heavy bleeding which may indicate loss of viability or passage of pregnancy
    - Diary will be reviewed.
    - Study drug container will be reviewed and remaining drug counted by study staff.
    - Ultrasonography will be performed to evaluate for presence of the gestational sac, interval growth and presence of gestational cardiac activity; the exam should preferentially be performed vaginally unless the gestational age or subject anatomy requires abdominal sonography for clearer visualization.
        - If gestational cardiac activity is absent
            - Two 5 mL tubes of blood will be obtained for serum hCG and progesterone level.
            - Collect remaining study drug and diary
            - Refer subject to the original referral source (PPMM, FPA or the UCD Family Planning clinic) for completion of care; a patient from PPMM can request to complete care at UCD.
                - Referrals for PPMM-referred subjects returning to PPMM will be made to the Sacramento B Street Clinic.
                - Referrals for FPA-referred subjects returning to FPA will be made to the Sacramento Clinic.
            - The subject will be exited from the study after a final outcome is determined by the clinical team.
        - If the pregnancy is expelled
            - Two 5 mL tubes of blood will be obtained for serum hCG and progesterone level.
            - Collect remaining study drug and diary
            - Refer subject to the original referral source (PPMM, FPA or the UCD Family Planning clinic) for completion of follow-up care; a patient from PPMM can request to complete care at UCD.
                - Referrals for PPMM-referred subjects returning to PPMM will be made to the Sacramento B Street Clinic.
                - Referrals for FPA-referred subjects returning to FPA will be made to the Sacramento Clinic.
            - The subject will be exited from the study after a final outcome is determined by the clinical team.
- Specimen from surgical abortion procedures at UCD will be collected and submitted to the UCD pathology department for research examination for effects of mifepristone or progesterone on the trophoblast or embryonic tissue.
- Copies of clinical visits for completion of abortion or follow-up care after pregnancy expulsion will be obtained from the referral site.

- The UCD Family Planning specialists will be available on call 24 hours/day, 7 days/week for any study participant with a question or medical issue.

A total of 40 mL of blood will be obtained over 2 weeks for laboratory testing.

Subject compensation:
Subject compensation for time and effort will be issued through UCD.

8) Data and/or Specimen Management and Confidentiality

Sample size:

- Delgado and colleagues estimate the oral progesterone regimen in this study has an efficacy of 68% (10) and that about 25% of women will expel the pregnancy after mifepristone 200 mg treatment alone, (10,12) implying an effect size of ~43%.
    - Sample size needed for Effect1=68%, Effect2=25%, Alpha=0.05, Beta=0.20: 20 per group.
    - Sample size needed for Effect1=70%, Effect2=25%, Alpha=0.05, Beta=0.20: 18 per group.
- We plan a convenience sample of 40 women (approximately 20 per group) which is enough to answer the primary question of efficacy proposed by Delgado and colleagues.
    - Should no obvious benefit be observed then a larger trial would not be indicated.
    - If some benefit is present, then a sample size could be estimated for a larger trial with considerations of sample size estimates for different gestational age ranges.
    - Importantly, if we cannot feasibly recruit from this population, then a larger study would also need to consider alternative mechanisms for enrollment.
- Recruitment: expect 36 subjects from PPMM and FPA (competitive enrollment) and 4 subjects from UCD.

Data Analysis Plan:

We will include all women randomized and perform intent-to-treat analysis with no apparent exclusions. In addition, a second analysis will be conducted with a per-protocol population, excluding women who do not report ingesting the study medication per protocol. Evaluations will include primary outcome (continuing pregnancy), expulsion rates, adverse effects, and treatment continuation rates.

At time of enrollment, we will collect baseline demographic data, including age, race, ethnicity, education level, and medical history (including obstetric and gynecologic history).

Fisher's Exact Testing will be used to compare outcomes and baseline characteristics in the two groups.

While not powered to detect a statistically significant difference among the two groups for secondary outcomes, exploratory analyses will be performed to identify possible trends and areas of interest for a subsequent larger trial. Chi square and Fisher's Exact Tests will be utilized to compare dichotomous variables as appropriate.

Data Management Plan:

Participants will be assigned a unique study number for use on source documents and participant study charts. Each participant will be assigned a file to be kept in a locked cabinet of a locked research-only office. Participant files will contain signed consent forms, study allocation number, and paper copies of data collection forms. Identifiers will include name and medical record number. Data from participants' study charts will be entered into a study database without any identifying information. Only password-protected, institutionally secured UCD computers will be used for data entry and analysis. Data will be reviewed by the principal investigator and research coordinator to ensure accuracy and completeness.

Participants will be given standard contact information for all clinical and study-related questions at any time. Our division has a dedicated phone line for Family Planning research subjects that is covered by research personnel during the day (who have close access to an assigned Family Planning physician) and forwarded to the on call Family Planning specialist physician at night. All Family Planning attendings and fellows will be trained as study personnel.

Confidentiality
All research and clinical activities will be conducted in private spaces (clinical exam rooms, preoperative center, or operating room). All research staff will be trained on protocol prior to study initiation and be up-to-date on CITI training.

Specimen Transport Plan
Blood specimens will be submitted to the UCD clinical laboratory for testing. Some study exit visits will occur at the PPMM Sacramento B Street Clinic and FPA Sacremento Clinic. Blood obtained at PPMM and FPA visits will be collected by study personnel who will be present at the visit and transported to the UCD clinical and pathologic laboratory for testing. No pathologic specimens will be obtained at PPMM or FPA.

9) Data and/or Specimen Banking

No specimens will be banked.

The research database will be banked indefinitely for the purpose of future research questions and will contain only de-identified information as above. The database will be maintained on the UCD server in a file with limited access to Family Planning research team. The data can be used for analyses as approved through this IRB submission; other evaluations will require a separate IRB submission to review the de-identified data.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

- Safety data will be collected throughout the study through diaries of potential medication side effects.
- Adverse event (AE): adverse experience such as symptom, physical exam finding, or worsening of a preexisting condition that has a temporal association with research participation. Causal relationship with study treatment is not necessary to designate an AE.
- Serious adverse event (SAE): adverse event that requires hospitalization, causes significant disability, causes a birth defect, is life threatening or results in death.
- AEs will be logged and reviewed by an investigator for study drug relationship
- Any SAE will be reported to the principal investigator. The participant will be managed medically as indicated. All source data will be reviewed. Physician investigators will assess for causality or relatedness of the adverse experience to the study.
- SAEs will be summarized at annual IRB renewal submission. SAEs that are unanticipated and thought to be related to the study (thereby placing research subjects at higher risk of harm than originally thought) will be reported to the IRB by the principal investigator within five days of becoming aware of the event.
- The study will be reviewed approximately twice monthly at the Family Planning division research meeting, which includes all research staff. Any concerns regarding individual or trends in AEs will prompt further review of the study and consideration of study termination.
- Study allocation will remain concealed except in a scenario in which revealing allocation is clinically important for the participant's management

11) Withdrawal of Subjects

Participants may elect to discontinue the study for any reason. Participants will be withdrawn from the study pending investigator review of AE that warrants removal or any SAE (see Section 10).

12) Risks to Subjects

1. Mifepristone side effects:
   The mifepristone label does not provide side effects for mifepristone alone; side effects are provided for the combination of mifepristone and misoprostol. The data,

especially as it relates to bleeding, does not reflect just mifepristone use. Data on mifepristone side effects are taken from reference #19.

Nausea	39%
Cramping	27%
Headache	20%
Dizziness	20%
Warmth/chills	19%
Vomiting	14%
Spotting	9%
Diarrhea	7%

For this study, we expect bleeding and/or spotting to occur in all subjects (even though most will not expel the pregnancy).

2. Progesterone side effects:
From the Prometrium label – use in premenopausal women at 400 mg/day

Dizziness	24%
Abdominal Pain (Cramping)	20%
Headache	16%
Breast Pain	16%
Infection Viral	12%
Musculoskeletal Pain	12%
Fatigue	8%
Abdominal Distention (Bloating)	8%
Diarrhea	8%
Nausea	8%
Back Pain	8%
Irritability	8%
Coughing	8%

3. Teratogenicity: if women decide to continue the pregnancy after receiving one or both study treatments, mifepristone and progesterone are not considered teratogens. Teratogenicity with standard medical abortion treatment is related to misoprostol, which is not being used in this study.

4. Pregnancy expulsion: few women expel the pregnancy with mifepristone 200 mg treatment in medical abortion studies. However, few studies follow women for up to 2 weeks. We do not know the spontaneous expulsion rate with this treatment but expect the rate may be around 30%; Delgado and colleagues estimate the oral progesterone regimen in this study has an efficacy of 68% (10) meaning that at least ~30% will expel the pregnancy, even with progesterone treatment.

   If pregnancy expulsion occurs, the woman will experience bleeding and cramping. The cramping can be very strong for several hours and is typically treated with NSAIDs. Subjects will be made aware that if they need stronger pain medication they can contact the physician on call. Initial bleeding may be similar to, or greater than, a

heavy period and may include blood clots and tissue. Within a few hours bleeding is usually equal to or less than a typical menses. After passing the pregnancy, bleeding or spotting can be expected for an average of 9-16 days and may last for up to 30 days.

Approximately 1-5% of women may experience very heavy bleeding, which is soaking through more than two sanitary pads per hour for two hours in a row.

In 1% of women or less, a suction aspiration (surgical abortion) to stop the bleeding may be indicated. Very rarely (less than 1/1,000 women), the amount of blood loss may be life-threatening and a blood transfusion may be necessary.

In 1-5% of women, incomplete expulsion may occur which would also necessitate a suction aspiration (surgical abortion). In less than 1% of women, a uterine infection could occur from incomplete abortion.

5. Phlebotomy: Temporary discomfort from the needle stick, bleeding at the needle puncture site and bruising may occur. Very rarely (1% or less), fainting may occur.

6. Vaginal ultrasound: Temporary discomfort similar to a pelvic examination may occur.

7. Delay in surgical abortion: A delay of up to 2 weeks in the gestational age range for this study does not incur increased surgical risk.

8. Privacy: There is a risk that protected health information could become known to someone not involved in this study. A unique study number will be assigned and study records will remain in a locked cabinet of a locked research-only office.

13) Potential Benefits to Subjects

There is no direct benefit of study participation for the subject.

14) Multi-Site Research

The UCD study site oversees the study which will also have study procedures performed at PPMM Sacramento B Street Clinic and FPA Sacramento Clinic. Study procedures will only include referral, obtaining specimens (e.g., phlebotomy), and sending copies of medical records to the UCD study site. Thus, no staff at the PPMM Sacramento B Street Clinic or FPA Sacramento Clinic will be considered study personnel. The site physicians and staff coordinators at PPMM Sacramento B Street Clinic and FPA Sacramento Clinic will work administratively with the UCD study physicians and coordinator to ensure the following:

- The site conducts the study appropriately.

- The PPMM and FPA co-investigators and site coordinators have the most current version of the protocol.
- Planned Parenthood Federation of America (PPFA) approval is obtained before the PPMM site begins to refer subjects.
- All modifications are communicated to PPMM and FPA.

Initial communication with the each study site will include an all-staff meeting to inform staff of the study, entry criteria and plan. The purpose of this meeting is to ensure adequate knowledge of staff about the study for referral of study subjects.

Continued communication with the PPMM and FPA site investigators and coordinators will occur routinely through e-mail and monthly through planned conference calls. Issues with recruitment, specimen collection and study progress will be discussed.

15) Sharing of Results with Subjects

Study results will not be shared with subjects or their primary physicians. Outcomes for PPMM Sacramento B Street Clinic patients who expel the pregnancy during the two-week treatment period will be shared with the PPMM Sacramento B Street Clinic study team. Outcomes for FPA Sacramento Clinic patients who expel the pregnancy during the two-week treatment period will be shared with the FPA Sacramento Clinic study team.

16) Provisions to Protect the Privacy Interests of Subjects

All conversations during enrollment and clinical care will be in private clinic spaces as per usual practice. During screening, research staff will review that the study is voluntary and that demographic questions can be skipped. Remaining aspects of the enrollment visit are clinically necessary and will be treated similarly to a standard clinical visit. It will be reinforced that study participation or declination will not change the patient's medical care.

Baseline history questions and pre-operative interview ensure medically safe abortion procedures and give providers information about offering additional social support to women who may benefit. We interview all women to confirm they are making an autonomous decision to terminate a pregnancy and are not being coerced. As Family Planning specialists, our physicians are trained to provide appropriate and thoughtful care to women seeking abortions and there are no deviations in interview practices from standard clinical care for the research described here.

Electronic medical records will only be accessed, addended, or reviewed when clinically necessary. Participants will be notified of this and research staff will review and sign an institutional HIPAA release to grant this access.

17) Compensation for Research-Related Injury

The University of California, Davis Health System will provide care needed to treat injuries directly resulting from taking part in this research. Insurance or third party payers may be billed, if appropriate, for the costs of the care subjects received. Subjects may be responsible for some of the costs. The University of California, Davis does not plan to compensate subjects for injuries.

18) Economic Burden to Subjects

The subject is responsible for costs related to abortion care. The subject will not be responsible for any costs related to study participation. Study participation requires additional visits to the UCD Ambulatory Care Center and may incur transportation cost or additional time away from work.

19) Drugs or Devices

☒ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

20) ClinicalTrials.gov Registration

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☐	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☐	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☐	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.

☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

21) Criteria for 10 Year Approval

N/A.

22) References

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