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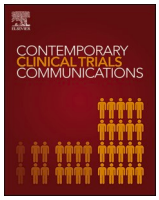

Prevention of postpartum methamphetamine use with micronized progesterone trial (PROMPT): A pilot randomized controlled trial protocol☆

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ABSTRACT

Background: While most pregnant individuals with methamphetamine use disorder (MUD) achieve abstinence, the postpartum period remains a vulnerable time for return to methamphetamine use (MU). Promising data from human and animal models, including three randomized controlled trials, suggest that micronized progesterone may prevent postpartum return to cocaine and nicotine use by reducing cravings. The primary objective of this study is to assess feasibility of enrollment and randomization of postpartum individuals with MUD to micronized progesterone to prevent return to MU. The secondary objectives are to evaluate safety, establish a preliminary estimate of efficacy, and characterize the association between allopregnanolone levels and methamphetamine cravings.

Methods: This is a pilot double-blind placebo randomized controlled trial. We plan to enroll 40 postpartum individuals with MUD over 24-months. Individuals, stratified by opioid use disorder (OUD), are randomized 1:1–400 mg oral micronized progesterone daily or placebo and attend weekly study sessions for 12 weeks. Feasibility is measured by achieving 80 % of enrollment goal. Safety is evaluated by side effect frequency, mental health status changes, lactation and medical complications. Efficacy is assessed by comparing proportion of participants with return to MU and time to return to MU based on self-report or urine testing between treatment and control groups. Salivary allopregnanolone levels and methamphetamine cravings are compared between the groups.

Conclusion: Study results will provide a first critical step towards potential intervention for prevention of return to MU among postpartum individuals. Completion of this trial will set the stage for a large-scale efficacy trial.

1. Background

Methamphetamine use (MU) among pregnant and postpartum people has continued unabated for over a decade in the United States with prevalence rates ranging from 0.17 to 1 % [1–3]. Peripartum individuals with methamphetamine use disorder (MUD) have a one in five chance of severe maternal morbidity and mortality through the year postpartum [4]. Nationwide, pregnancy-associated psychostimulant overdose deaths, defined as deaths in pregnancy and one year postpartum, have more than doubled from 2017 to 2020 [5]. The peripartum period is a particularly vulnerable time for those with methamphetamine and other substance use disorders (SUD) with a high risk of return to use and overdose postpartum [6]. Factors associated with high rates of return to use include co-occurring SUD and mental health condition

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

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destabilization, child custody removal and limited social support [7–11].

A hypothesized contributor to high risk of return to use postpartum is the role of peripartum hormonal changes and their effect on cravings during the peripartum period [12]. Human and animal studies indicate that high levels of progesterone (luteal phase of menses, pregnancy) are associated with decreased frequency of drug-seeking behaviors, fewer stimulant award and cravings effects compared to times of low progesterone levels (follicular phase of menses, postpartum period) [13–16]. Leveraging the idea that exogenous progesterone administration can decrease return to use and cravings among postpartum individuals, three randomized clinical trials showed promising results in the use of micronized progesterone for prevention of return to tobacco [17,18] and cocaine use [19]. The underlying proposed mechanism is that micronized progesterone metabolizes into allopregnanolone, a neurosteroid that regulates neuronal signaling including gamma-aminobutyric-acid (GABA) transmission enhancement to attenuate drug reward [20,21]. These findings suggest exogenous progesterone as a possible intervention among postpartum persons with MUD to prevent return to use. No prior studies have assessed the progesterone as an intervention to prevent MU or decrease methamphetamine cravings.

1.1. Study aims

The primary objective of this study is to assess feasibility of enrollment and randomization of postpartum individuals with MUD to micronized progesterone to prevent return to MU. The secondary objectives are to evaluate safety and preliminary estimate of efficacy. Additionally, we will characterize the association between allopregnanolone levels and methamphetamine cravings. The rationale for this objective is: 1) many participants may be recruited from SUD treatment facilities where return to use is typically low and 2) craving, a criterion of active MUD, potentially increasing risk of return to use, particularly among postpartum individuals [21,22].

2. Methods

2.1. Study design

This double-blind placebo randomized controlled trial (RCT) builds on the protocol reported by Yonkers et al [19]. Participants will be randomized 1:1 to either micronized progesterone (200 mg twice daily) or placebo (Fig. 1), stratified by OUD. We plan to enroll 40 postpartum individuals with MUD over a 24-month timeframe who have discontinued MU for at least four weeks. Data collection will occur at baseline and weekly for 12 weeks. Reporting of the study will follow CONSORT guidelines and the SPIRIT checklist can be accessed as a supplemental file (Appendix A). This study and protocol (version 3.1, updated 4/26/2023) is approved by the University of Utah Institutional Review Board and is registered with ClinicalTrials.gov (NCT 05128071).

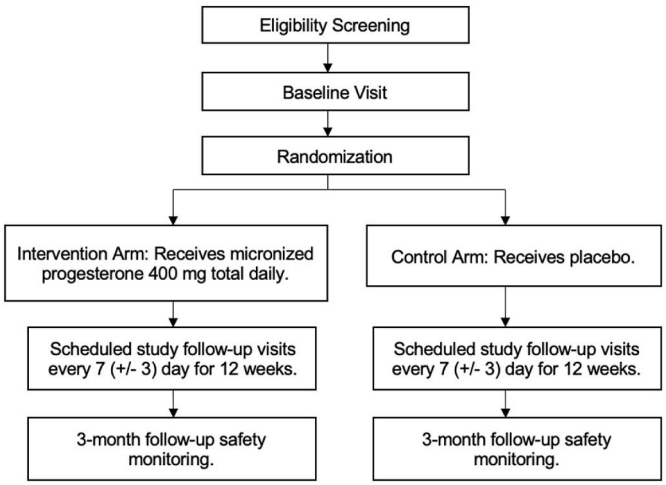


Fig. 1. Study flowchart. Data collection at baseline and follow-up visits.

2.2. Study participants

Participants will be postpartum individuals within 12 weeks end of pregnancy (miscarriage, stillbirth, abortion, or live birth) and have no MU for four or more weeks as the theorized mechanism of action of exogenous progesterone is stabilize the amygdala, thereby reducing cravings and preventing return to MU. We selected this timeframe because allopregnanolone and progesterone levels return to pre-pregnancy levels within 12 weeks post pregnancy [23]. We focus on individuals with MUD within six months prior to conception instead of those with sporadic use, as they are at highest risk for return to use. We included those with cravings without MU within six months prior to conception as this is a criterion of active MUD. Individuals with opioid use disorder (OUD) are also included as 78 % of individuals in the primary recruiting site have co-occurring MUD and OUD [24,25].

2.2.1. Inclusion criteria

Potential participants must meet all inclusion criteria for PROMPT eligibility including.

- DSM-V criteria of any severity for MUD in the 6 months prior to conception, during pregnancy or within twelve weeks postpartum [22].
  - o Cravings, urges and dreams of use are included as symptoms of the SUD. These can occur in the absence of active MU
- No active MU within four weeks prior to enrollment based on either self-report or urine toxicology, a reliable measure of establishing abstinence in research settings [26–28].
- If diagnosis of active OUD (defined as DSM-V criteria of any severity in past six month with self-report or urine toxicology consistent with non-prescribed opioids) must be on stable dose of medication (methadone, buprenorphine, naltrexone) for two weeks prior to enrollment to allow for postpartum dose adjustments.
  - oNo misuse of opioids at time of enrollment or within four weeks prior to enrollment by self-report or urine toxicology.
  - oPrescribed opioids for pain management for medical procedures including birth are acceptable if $\geq$ two weeks from enrollment.
- Intrauterine device, barrier method or permanent female sterilization (e.g. tubal ligation) for contraception during the study period
- End of pregnancy within past 12 weeks
- Residing within 100 miles of study site
- No plans to move more than 100 miles from study site within study period
- Have phone and/or able to provide collateral contact information for two individuals
- Ability to provide informed consent
- Stable on allowable psychiatric medications including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and mood stabilizers for four weeks prior to enrollment

2.2.2. Exclusion criteria

Potential participants may not meet any exclusion criteria including.

- Major medical illness in which progesterone may be contraindicated (significant liver disease, history of thrombophlebitis, stroke, heart disease, suspected or known malignancy, deep venous thrombosis, pulmonary embolism, bleeding disorders) per principal investigator (PI) and/or medical clinician (MC) assessment [29].
- Any laboratory abnormalities within two weeks of screening and enrollment (Table 1)

Table 1
Laboratory value and vital sign exclusion criteria.

Laboratory Values	Vital Signs
• Active hepatic dysfunction defined as AST or ALT that is twice the upper limit of normal. •Anemia defined as hemoglobin less than 8 g/dL. •Renal impairment defined as creatinine greater than 2.0 mg/dL. •Hypothyroidism defines as thyroid stimulating hormone greater than 5 mIU/L	•Temperature <97 or >100.3 °F. •Pulse <50 and >130 beats per minute. •Systolic blood pressure of 160 or ≤80 and diastolic blood pressure of 110 or ≤50. •Oxygen saturation <92 % on room air. •Respiratory rate <9 or >20 breaths per minute.

AST = Aspartate Aminotransferase; ALT = Alanine Transaminase; g = grams; dL = deciliter; milligrams = mg; milli-international units = mIU; L = Liter.

- Abnormal vital signs at baseline visit (Table 1)
- Allergy to micronized progesterone or placebo ingredients (peanut oil, gelatin, cellulose)
- Self-reported progestin-containing oral or depot containing contraceptive intolerance.
- Does not speak English or Spanish
- Taking CYP450 3A4 inhibitors of including: clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal [29].
- Severe depressive symptoms defined as Edinburgh Postnatal Depression Scale (EPDS) score of ≥19 or severe anxiety symptoms defined as Generalized Anxiety Disorder−7 (GAD−7) score of ≥15 at time of enrollment [30–33].
- Active suicidality defined as expressing current thoughts of self-harm verbally to MC or study team member, Columbia Suicide Severity Rating Scale (C-SSRS) score >0, or EPDS Question #10 score of greater than 0
- Current psychosis
- History of psychiatric hospitalization for psychosis within the past six months
    - oHospitalization for management of substance use disorder and its sequelae is not exclusionary
- Suicide attempt with or without hospitalization within the past six months
    - oHistory of suicidal ideation or self-harm (e.g. cutting) with no plan for suicide are not exclusionary
- Current or known pending incarceration.
- Active alcohol use disorder within past six months
- Use of the following concomitant sedating medications or supplements in the two week prior to enrollment: stimulants, barbiturates, benzodiazepines, non-benzodiazepine hypnotics, orexin antagonists, first generation anti-histamine, herbal sedatives, methaqualone and analogues, skeletal muscle relaxants, opioids (other than methadone or buprenorphine), anti-psychotic medications, certain anti-depressants or other medication with significant sedative properties (Appendix C) as evaluated by the PI and/or study clinician.
- Progestin containing medications including the following contraceptives: oral hormonal, vaginal ring, patch, injectable or implant.

2.3. Recruitment and retention strategy

The primary recruitment location for this trial is an integrated multidisciplinary perinatal addiction clinic at an academic institution in Utah. The clinic is staffed with a multi-disciplinary team trained in perinatal SUD including maternal fetal medicine clinicians, mental health professionals, social workers, case managers, research coordinators (RCs), and clinical coordinators. This setting ensures access to a large potential study population and appropriate resources. Study information is also provided to partnering agencies including local outpatient treatment programs, addiction medicine specialists, local obstetrical clinicians, and residential treatment programs for pregnant and parenting individuals for further participant recruitment.

Retention is maintained using study visit reminders sent through participant's preferred format (phone, text, email), participant access to an RC study phone number, and virtual visits. Participants are also compensated $100 for baseline assessment and $50 for each study visit with biological samples. Participants can receive an additional $100 if all 12 study visits are completed, for a potential reimbursement total of $620.

2.4. Screening

To assess eligibility, RCs screen all potential pregnant and postpartum participants medical records for inclusion and exclusion criteria. If individuals express study participation interest and meet eligibility criteria, RC provide detailed study information and participants sign an informed consent. While potential participants may be screened and consented during pregnancy, no study intervention occurs until postpartum. Individuals who enroll and are immediately postpartum do not initiate the study medication until four days postpartum.

All enrollment medical eligibility criteria are reviewed by study MCs including medical history, medications, and laboratory test values. Study enrollment will not occur unless identified or suspected major medical conditions have resolved.

2.5. Randomization

After individuals are screened and consented, randomization occurs 1:1 with stratified random assignment of four block sizes in each stratum by 1) presence of OUD or 2) no OUD. Randomization occurs through a REDCap module. To ensure blinding of study team to treatment allocation, the institution investigational pharmacy triggers the randomization in REDCap, and prepares the study interventions. As this is a double-blinded trial, neither the RC, the MC nor the participant will know allocation group. Only the pharmacists preparing study medication and the study statistician are unblinded. Medications are created and packaged to look identical between treatment arms to guarantee blinding for study staff who dispense and collect unused medication at study visits.

2.5.1. Study medication preparation

The oral micronized progesterone dose of 400 mg (200 mg twice daily) and similar appearing placebo capsules are prepared by the academic institution investigation pharmacy. The placebo capsules are hand packed microcrystalline cellulose gelatin capsules. The institution investigational pharmacy monitors randomized medications by marking the study medication bottle with sequentially numbered containers. The RC provides the institution investigational pharmacy participant numbers and receives the study medication. The RC then provides the participant with study medications.

2.6. Intervention

After screening and consent, individuals are then randomized to 400 mg oral micronized progesterone daily (200 mg twice daily) or placebo. The progesterone dose and timeframe are consistent with the Yonkers et al., 2014 study [17]. After randomization, participants attend once weekly study sessions for 12 weeks. Progesterone administration does not start until at least four days postpartum due to theoretical risk of prolactin inhibition and subsequent decreased breastmilk production [34]. If participants report delayed onset of lactation, medication initiation will be postponed until breastmilk production occurs or participant is no longer breastfeeding. For participants who do not plan to breastfeed, the medication can be initiated any time after four days postpartum without further lactation monitoring.

2.7. Outcome measures

2.7.1. Feasibility

The primary feasibility outcome is measured by successful monthly study recruitment of eligible postpartum persons with MUD. Sample size is based on a power estimate for feasibility [35,36] and the number of potential participants who can be screened and consented within the study timeframe. Calculated based on the volume of patient visits of postpartum individuals with MUD at the primary recruitment site, a total goal of 40 participants will be randomized in this study to progesterone (n = 20) versus placebo (n = 20) if we screen and recruit over 24 months and 70 % are eligible and interested. There is an expected 20 % (n = 8) dropout rate based on previous studies, but our ability to maintain engagement has minimized this to 5–10 % [19].

2.7.2. Safety

Safety outcomes including side effect frequency, mental health status, lactation and medical complications, death, and new pregnancies during a three-month study follow-up are monitored. A Data Safety Monitoring Board (DSMB) is established by the study team and meets upon each quarter of enrollment to review participant summary measures to ensure participant safety. Potential side effects from micronized progesterone are listed in Table 2 and are monitored using the Generic Assessment of Side Effects (GASE) [37]. While prior studies among postpartum persons who received progesterone for substance use prevention showed no difference in depressive symptoms [17–19], mental health is monitored closely given potential risk of increased depression and anxiety from progesterone. Self-reported assessments for ongoing mental health monitoring include the EPDS, GAD-7, and C-SSRS. Lactation is monitored as progesterone can inhibit breastmilk production, though we expect the risk to be low [34]. To ensure adequate breastmilk production and screen for potential infant related adverse events, the Infant Sedation Assessment (ISA) [38], infant chart review, and Bristol Breastfeeding Assessment Tool (BBAT) are collected among lactating participants and breastfed infants only [39]. Participants are referred to a lactation consultant based on clinical assessment and participant's goals and preferences. Feasibility and safety outcome benchmarks are summarized in Table 3.

2.7.3. Preliminary estimate of efficacy

Preliminary estimate of efficacy is assessed by evaluating return to MU and time to return to use by either self-report or urine toxicology testing. Return to MU and abstinence is based on a urine toxicology test or Substance Use Calendar (SuCal), a validated self-reporting tool [40]. SuCal is based on a Timeline Follow back and is a reliable method for daily information collection on quantity and frequency of MU. The urine toxicology test is a two-step process: First, an immunoassay for the qualitative detection of substances including amphetamines, opiates, buprenorphine, methadone, oxycodone, and benzodiazepines using the Siemens Emit II urine toxicology panel (sensitivity and specificity of all substances is >95 %), however false positive results for amphetamines are frequent [41]. Therefore, a confirmatory test using mass-spectrometry is reflexed to quantify amphetamines, cannabinoids, opioids (including oxycodone, methadone, or buprenorphine), benzodiazepines, and their metabolites. If participant experiences return to use, they are offered additional resources including medication management, social work referral for behavioral health, peer support, and escalation of treatment including referral to substance use treatment partners and residential treatment programs for postpartum or parenting individuals.

Table 2
Potential micronized progesterone side effects.

More Common	Less Common
•Dizziness	•Less breastmilk production
•Breast tenderness	•Dry mouth
•Headache	•Anxiety or depression
•Abdominal pain	•Constipation
•Fatigue	•Hypertension
•Viral infection	•Bile duct blockage
•Abdominal distension	•Skin rash
•Musculoskeletal pain	•Allergic reaction
•Emotional lability	•Acne
•Irritability	•Urinary tract infection
•Upper respiratory infection	•Abnormal liver function
	•Deep vein thrombosis or pulmonary embolism

Table 3
Feasibility and safety outcome benchmarks.

Feasibility	Benchmark
Average monthly accrual (participants/month) (primary)	1.6/month
Number of participants enrolled in 24 months	40
Retention Dropout rate	<20 %
Compliance: Number of pills taken	≥80 %
Adherence: Study session completion	≥80 %
Safety	Benchmark
Side effects attributed to medication	<20 % positive
EPDS or GAD7 score increase ≥30 %	≤5 %
Suicidal ideation	≤5 %
Hospitalizations	≤5 %
Breastfeeding difficulty	≤30 %
New pregnancy	≤5 %
Deep vein thrombosis and/or pulmonary embolism	≤5 %
Death	0 %

EPDS = Edinburgh Postpartum Depression Scale; GAD 7 = Generalized Anxiety Disorder 7.

2.7.4. Allopregnanolone levels and methamphetamine craving

The Stimulant Craving Questionnaire-Brief (STCQ-Brief) is used to measure methamphetamine craving and has good external and internal validity [42]. Salivary samples are collected in a tube and processed using a highly sensitive enzyme immunoassay. Allopregnanolone salivary sample collection is further specified in Appendix D. All outcomes are assessed using statistical methods in Appendix E.

2.8. Monitoring

2.8.1. Baseline visit

The baseline visit includes a full medical history, medication, and lab review by study MC (Table 4). MUD of any severity is confirmed using the DSM-V checklist. The SuCal assesses MU 28 days prior to baseline visit and urine toxicology establish no MU for at least 4 weeks.

To ensure there are no significant laboratory abnormalities meeting exclusion criteria, laboratory values are reviewed by the MC. Complete blood count, complete metabolic panel, thyroid stimulating hormone and urine pregnancy test are reviewed. Baseline salivary allopregnanolone levels are obtained. For lactating participants, a BBAT is completed once at baseline assessing components of efficient lactation [39]. Baseline mental health assessments are assessed using the EPDS, GAD-7, and C-SSRS. The MC discusses risks and benefits of progesterone for those with moderate depression or anxiety.

After consent and enrollment, participants are instructed to take their initial randomized medication dose the evening of receiving the study medication and twice daily thereafter, in the morning and evening as close to 12 h apart with food for the next 12 weeks. Participants may use a dosing calendar to monitor compliance.

2.8.2. Follow-up visits

Study visits occur every 7 days (± 3 days) for 12 weeks after enrollment. If participants are unable to be seen within this targeted timeframe, then they are seen as soon as possible. Full study visits occur at weeks 2, 4, 6, 8, 10, and 12 in clinic or a research room. Phone or virtual visits occur weeks 1, 3, 5, 7,9, and 11 unless the participant prefers an in-person visit. Participant retention is facilitated with home

Table 4
Timeline of questionnaires and assessments.

Time point Week	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Medical History, Medications & Lab Review	✓												
DSM V Checklist	✓												
SCQ-Brief	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bristol BAF	✓												
SuCal (28 days prior to enrollment)	✓												
SuCal (7 days prior or since last visit)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Administration of study medication	✓		✓		✓		✓		✓		✓		
Pill count of returned med			✓		✓		✓		✓		✓		✓
C-SSRS (2 weeks prior to randomization)	✓												
C-SSRS Since Last Visit		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GASE Side effects		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IBSA		*	*	*	*	*	*	*	*	*	*	*	*
Breastfed Infant chart review		*	*	*	*	*	*	*	*	*	*	*	*
EPDS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GAD-7	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBC, CMP, TSH[A]	✓												
Salivary sample	✓		✓		✓		✓		✓		✓		✓
Urine pregnancy test	✓						✓						✓
Urine toxicology	✓		✓		✓		✓		✓		✓		✓

DSM V = Diagnostic and Statistical Manual V; SCQ-Brief = Stimulant Craving Questionnaire; Bristol BAF =Bristol Breastfeeding Assessment Form; SuCal = Substance Use Calendar; C-SSRS Colorado – Suicide Severity Rating Scale GASE = Generic Assessment of Side Effects; IBSA = Infant Breastfeeding and Sedation Assessment; EPDS = Edinburgh Postpartum Depression Scale, GAD 7 = Generalized Anxiety Disorder 7; CBC = Complete Blood Count; CMP = Complete Metabolic Panel; TSH = Thyroid Stimulating Hormone.
✓ = *will be collected at each visit.*
* = will be collected as needed for breastfed infants only.
[A] = if results not available 2 weeks prior to enrollment.

or off-site visits in public areas or within the participant's residence.

During full study visit, RCs obtain urine and salivary samples, review of dosing calendar and returned pill counts and provide study medication. At these visits, participants are asked about MU in the last seven days or since the last study visit suing SuCal [40]. They also asked about mental health monitoring, substance use, and side effects include the GASE, SCQ-Brief, EPDS, GAD-7, and CSSRS. The ISA and infant medical record review are obtained for breastfed infants only.

2.9. Safety monitoring

2.9.1. Mental health monitoring

Mental health is monitored closely given potential increased risk of depression and anxiety from progesterone. Patients with severe depression defined as having an EPDS score of $\geq$ 19 or anxiety with a GAD-7 of $\geq$ 15 after enrollment, are evaluated by a qualified mental health professional the same day. Moderate depression or anxiety as indicated by an EPDS score of 14–19 or GAD-7 of 10–14 prompts MC or PI notification. If participants have suicidal ideation based on self-report, or EPDS Question #10 score of >0, or C-SSRS score >0, then a Quick Suicide evaluation will be implemented (Fig. 2). RCs can also contact the PI and/or MC for evaluation and triage within 24 h if they have concerns about worsening emotional well-being despite GAD-7, EPDS, C-SSRS, or GASE findings. The PI and/or MC determines appropriate triage to other mental health services, emergency evaluation, initiation, or adjustment of medications. Study medication is deferred until clinical stabilization is established and study criteria are met.

2.9.2. Adverse events

For further monitoring and safety, participant, and breastfed infant adverse events (AEs) are collected from when the participant initiates the study medication until 24 h after the final study medication dose (elimination half-life of progesterone 5–10 h). All AEs and serious adverse events (SAEs) are recorded. SAEs include infant or maternal death, hospital readmission, and ICU admission during the study period. AEs and SAEs are followed through resolution using chart review or phone calls. Events are reported to the local IRB, participating investigators, and the Food and Drug Administration (FDA). In the event of participant self-report of return to MU or other substance use or positive unexpected urine toxicology, RC will contact MC for assessment, medical treatment and potential referral to higher level of care. If a participant is parenting a dependent minor, the MC will assess safety and follow local mandated reporting laws. **As this is a National Institutes of** Health funded **study, a Certificates of Confidentiality is automatically issued given collection of sensitive information, protecting** the privacy of research participants by prohibiting disclosure of identifiable, sensitive research information to anyone not connected to the research except when the participant consents or in a few other specific situations (medical treatment, mandated reporting of potential child abuse) [43].

The occurrence of each AE and SAE may be compared between treatment arms using Fisher's Exact test or Pearson's chi-2 test as appropriate. Further participant management is outlined in Appendix F. Any protocol amendments are communicated to research staff, participants, the IRB, and the FDA. Data is confidential and stored in a secured password protected REDCap ® web application. Research staff will have access to the final data set. Outcomes will be shared through peer-reviewed publications.

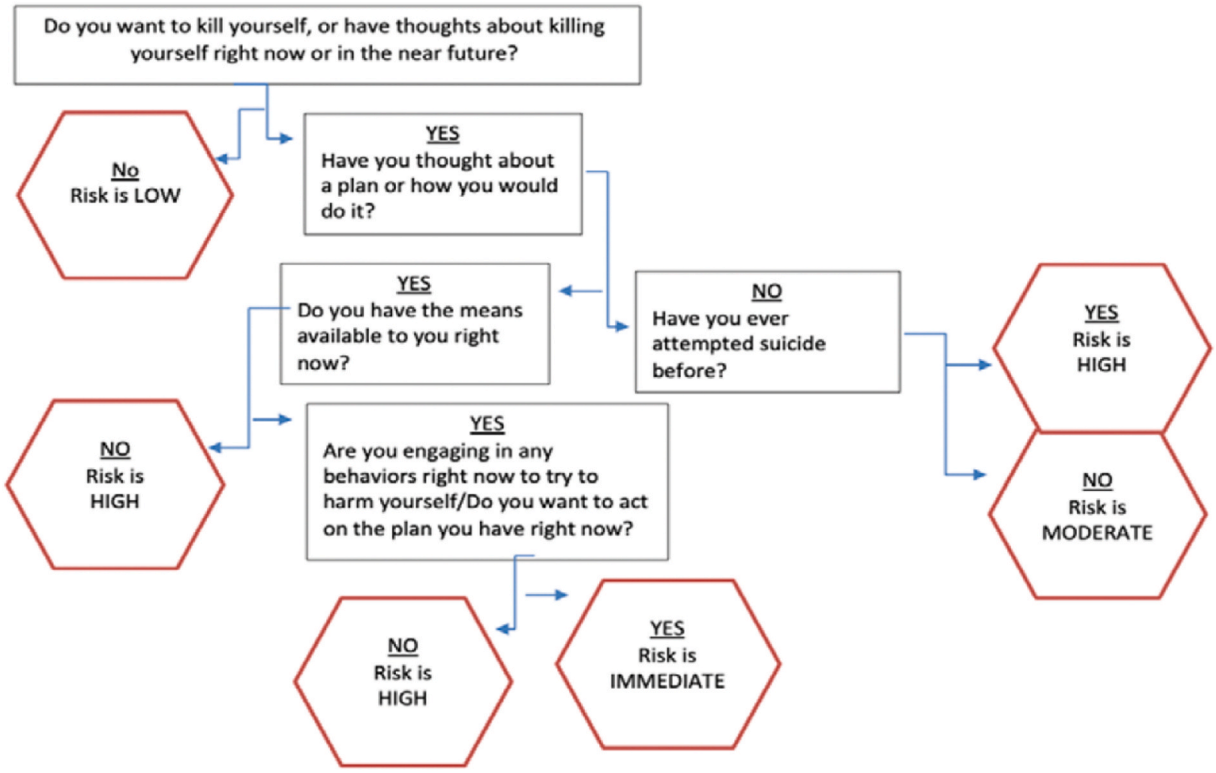
2.10. Statistical analysis

2.10.1. Feasibility and safety

For the primary outcome of feasibility, we will number of enrolled participants as well as number enrolled monthly and 95 % confidence interval. Accrual outcomes will be summarized for the whole cohort. Retention, compliance (number of pills taken), adherence (number of study sessions completed), and safety outcomes (Table 3) will be summarized overall and by randomization arm, and compared at 12 weeks using an exact chi-square, and over time using Kaplan Meier methodology and a log rank statistic.

2.10.2. Preliminary estimate efficacy

For the outcome of preliminary estimate of efficacy, analyses will be conducted using the intent-to-treat principle with all randomized participants. We will assess the success of randomization using independent sample *t*-test and chi square analyses to compare demographic



RISK LEVEL	ACTION
Low	1. Give patient resources (e.g., UNI Crisis Line) 2. Inform PI and medical provider(s)
Moderate	1. Contract for safety with patient & schedule call back within 2 hours 2. Inform PI and medical provider(s) 3. Call back patient at scheduled time and discuss treatment recommendations
High	1. Contract for safety with patient & schedule call back within 1 hour or keep patient on phone 2. Contact UNI/MCOT ASAP 3. Inform PI and medical provider(s) 4. Discuss treatment recommendations with patient
Immediate	1. Keep patient on phone 2. Call 911 3. Follow instructions of 911 4. Inform PI and medical provider(s)

Fig. 2. Quick suicide Screening.
UNI Crisis line = University of Utah Crisis line; PI = principal investigator; UNI/MCOT = University of Utah mental health Institute/Mobile Crisis Outreach teams.

characteristics of the subjects in the placebo and the progesterone group. We will assume any participant lost to follow-up to have returned to use. The preliminary estimate of efficacy endpoint will be dichotomous return to use at or before 12 weeks based on either self-report or positive urine toxicology for methamphetamine. While definitive estimation and hypothesis testing are not the aim of this pilot study, the target sample sizes will allow estimation of odds ratios and 95 % confidence intervals comparing outcome rates in the treatment and control arms. We will assess the odds of return to MU, opioids, and any other substance use by treatment arm. We will assess OUD as an interacting variable in the logistic regression model. As a secondary analysis, we will compare relative risk of use at each week using a generalized linear mixed effects (GLIMMIX) regression model with a log link and a binomial distribution. A GLIMMIX model accounts for correlation within-patient over time. We will use Cox proportional hazards regression to compare treatment groups with time to first use after baseline as the dependent variable. A per-protocol analysis will include only participants who were compliant with the medication regimen.

2.10.3. Allopregnanolone levels and methamphetamine cravings

The association between longitudinally sampled allopregnanolone and continuous methamphetamine craving will be assessed in a linear mixed effects regression model. The distribution of allopregnanolone will be assessed and analyzed on a log scale if right skewed. Craving score will be the continuous outcome, and main effects will be parameterized as allopregnanolone, treatment arm, and their interaction. If the relationship of allopregnanolone and craving does not differ by treatment arm, we will also report the main effect of allopregnanolone on craving, while adjusting for randomization arm. Participants will be the random effect in a mixed-effects modeling approach. In sensitivity

analysis, we will consider adjusting for breastfeeding, depression, anxiety, socioeconomic variables, tobacco, and other substance use as sample size permits. As secondary analyses, we will use this methodology to assess the association between longitudinally sampled allopregnanolone and continuous EPDS and GAD7, an anxiety screening tool (see **Appendix**).

3. Discussion

This innovative study targets postpartum individuals with MUD, a vulnerable population historically excluded from clinical trials [44,45]. Though studies have assessed progesterone treatment for prevention of return to cocaine and tobacco use among postpartum persons [17–19], no prior studies have assessed the outcomes of micronized progesterone on MU among postpartum individuals. Additionally, PROMPT evaluates the association between salivary allopregnanolone levels and methamphetamine cravings while prior studies only assessed progesterone levels and cravings [17–19]. Assessment of this relationship can help provide further understanding of the underlying proposed mechanism of progesterone metabolism to allopregnanolone, regulating GABA transmission enhancement to attenuate drug reward [20,21].

4. Strengths and limitations

This trial has multiple strengths. Bias and confounding are limited as this is a double-blind placebo RCT. The study team recruits potential participants primarily through a multidisciplinary perinatal substance use clinic. There are multiple patient engagement methods to ensure enrollment and retention including an RA study telephone participants can contact, home or off-site visits, visit reminders, and participant compensation to minimize dropout rates. The study uses validated self-reported measurements and reliable laboratory tests to increase internal validity.

There are also some limitations to this study. Though the study team has access to a large potential participant population, this is limited to a convenience sample in one urban tertiary care clinic likely limiting outcome generalizability. However, this is a pilot study, and if results show promise, it will expand the subsequent work to other diverse geographic locations and further strengthen generalizability. Furthermore, medication compliance may have discrepancies. To address this, a pill count of returned study medication is done during visits 2,4,6,8, and 12 to assess possible medication compliance inconsistencies.

Given the devastating consequences of return to MU among postpartum individuals [7,8,12,46], studies are needed that are tailored to this population and rooted in postpartum and addiction physiology. Micronized progesterone offers a potential novel pharmacological intervention to decrease return to MU for postpartum individuals with MUD that, if effective, can save lives.

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CRediT authorship contribution statement

Marcela C. Smid: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Jerry. **Natasha Seliski:** Writing – review & editing, Writing – original draft. **Jasmin E. Charles:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Stephanie Castro:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology. **Grace E. Humiston:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation. **Elysha Cash:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation. **Amanda Allshouse:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Elizabeth Turner:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology. **Marie Gibson:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Adam J. Gordon:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Gerald T. Cochran:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Unrelated to this work, the University of Utah receives funds to support Marcela. C. Smid from Gilead Science Inc for a study on hepatitis C treatment in pregnancy and Jada device from Alydia/Organon Inc. She serves as a consultant for Organon and Rhia Ventures. The University receives funds to support Jasmin E Charles from Gilead Science Inc for a study on hepatitis C treatment in pregnancy. She also serves as a consultant for Gilead Science Inc.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101359.

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