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Progesterone Reduces Cocaine Use in Postpartum Women with a Cocaine Use Disorder: A Randomized, Double-Blind Study

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Contributions by the authors were as follows: 1) Drs. Yonkers and Sofuoglu designed the project; Drs. Yonkers, Sofuoglu, Carroll, Forray Ms. Nich and Mr. Merry analyzed and interpreted data; Drs. Yonkers, Forray, and Ms. Hines participated in acquiring the data; 2) Drs. Sofuoglu, Yonkers and Carroll did the initial draft of the text while Ms. Nich and Mr. Merry constructed the initial draft of the results section; all authors critically reviewed the work and sent important additions and changes to the first author; 3) all authors reviewed and provided final approval of the manuscript; 4) Drs. Yonkers and Sofuoglu are accountable for all aspects of the work and ensuring data integrity.

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Abstract

Background—Progesterone modulates multiple brain functions implicated in the pathogenesis of drug addiction. During high endogenous progesterone states, women reduce use of cocaine. We sought to test whether progesterone replacement reduces cocaine use in postpartum women with a cocaine use disorder (CUD).

Methods—A 12-week, double-blind, parallel, randomized, placebo-controlled pilot trial with a 3-month post trial follow-up. 25 women within 12 weeks of delivery were randomized to placebo and 25 to 100 mgs of oral micronized progesterone, administered twice daily. Participants were recruited from obstetrical clinics. Randomization and allocation were performed by the study biostatistician. Attrition was 18% and the analysis included all 50 participants. Outcomes were self-reported days of cocaine use and positive urine toxicology assays for cocaine metabolites.

Findings—Participants randomized to placebo compared to progesterone had increased likelihood of cocaine use per week ($RR=1.19$; 95% confidence interval (CI)=1.05 to 1.36; $p<0.01$). At the three-month post trial visit the difference between groups was not significant (Likelihood Ratio $\chi^2=5.16$; $P=.08$). There were no group differences in rates of submission of a positive urine test. A post hoc analysis showed a higher rate of relapse for participants randomized to placebo ($HR=4.71$; 95% CI= 1.09 to 20.5). We did not observe group differences in the rate of adverse events.

Interpretation—These preliminary findings support the promise of progesterone treatment in postpartum women with a CUD and could constitute a therapeutic breakthrough.

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Keywords

Cocaine Abuse; Cocaine Dependence; Cocaine Use Disorder; Postpartum; Progesterone; Obstetrics and Gynecology; Women

INTRODUCTION

Over one million individuals in the United States¹ and one and one-half million residents in Europe,² endorse past month cocaine use. In Europe, cocaine is the second most commonly used illicit drug. ²Despite such statistics, there are no proven pharmacological treatments for a cocaine use disorder (CUD). Pregnancy and the postpartum period may inform us about treatment for a CUD. ³Women with cocaine addiction typically decrease drug use during pregnancy when progesterone levels are high, but often relapse after delivery when endogenous progesterone levels fall. Other work specifically implicates progesterone as

therapeutic for a CUD. Women with a history of cocaine abuse who are in the progesterone dominant, luteal phase, compared to those in the estrogen dominant, follicular phase of their menstrual cycle, express attenuated subjective responses to the rewarding effects of cocaine.⁴⁻⁶ Similarly, direct administration of progesterone to women who abuse cocaine diminishes cocaine-induced euphoria^{5, 7} and cue-induced craving,⁸ although one small laboratory study did not confirm this finding.⁹

A wealth of preclinical studies also suggest that progesterone has utility as a treatment for a CUD (see Quinones-Jenab et al for a recent review).¹⁰ In ovariectomized compared to vehicle treated rats, progesterone attenuates preference for a cocaine-associated environment.¹¹ In intact female rats, progesterone treatment attenuates cocaine self-administration,¹² and prevents subsequent cocaine-seeking behavior.¹³ Progesterone, when co-administered with estradiol, also attenuates acquisition of cocaine self-administration¹⁴ as well as subsequent cocaine-seeking behavior.¹⁵ Thus, progesterone seems to reverse the effects of estradiol on stimulant drug craving.

There is biological plausibility for the efficacy of progesterone on cocaine use. Progesterone and its active metabolites affect a wide-range of central nervous system functions including modulation of cognitive function, mood, stress response, analgesia, reward processing and response to stimulant drugs;¹⁶ in addition, progesterone and selected metabolites have positive modulatory effects on GABA_A and negative modulatory effects on N-methyl-D-aspartate receptors. Dopamine release in the nucleus accumbens, a critical step for drug reward, is under the control of inhibitory GABA and excitatory glutamatergic neurons.^{17, 18} Both of these effects may contribute to progesterone's proposed effects on a CUD.

The promising preclinical and clinical findings, as well as the biological rationale for progesterone's efficacy, prompted us to conduct a pilot study of progesterone for a CUD. Given that cocaine-using women frequently abstain or reduce use until after delivery,³ we posited that postpartum progesterone treatment might prolong abstinence or stem postnatal increases in cocaine use. We hypothesized that replacement of endogenous with exogenous progesterone, compared to replacement with placebo, would lower the use of cocaine during the postpartum period in women with a recent or current history of cocaine abuse or dependence.

Methods

Trial Design

This was a double-blind, placebo-controlled, parallel-groups trial. Women were given medication or placebo for 12 weeks and were re-evaluated three months after the end of the trial. In this pilot study, we randomized 50 participants to either progesterone or placebo. We used a stratified random assignment with block sizes of four within strata. The two strata were: used cocaine 1) at least ten days or 2) less than ten days, in the 30 days prior to enrollment.

The human subjects' boards of the Yale University School of Medicine and the Hospital of St. Raphael in New Haven, Connecticut approved the study. We obtained a certificate of

confidentiality from the National Institute of Drug Abuse to protect information collected for the purposes of research from forced disclosure.

Eligibility Criteria

Women were eligible to participate if they: 1) were 18 years; 2) met Diagnostic and Statistical Manual IV (DSM IV) criteria for abuse or dependence of cocaine in the six-months prior to conception or during pregnancy; and 3) were postpartum and within four weeks of delivery. Shortly after initiation of the study we extended enrollment to women who were postpartum and within 12 weeks of delivery. For opiate dependent women (n=23), we required use of opiate agonist treatment. Women were ineligible if they: 1) had a history of major medical illnesses that could theoretically complicate treatment with progesterone including clinically significant liver disease, suspected or known malignancy, thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting or bleeding disorders, heart disease, diabetes, history of stroke, untreated abnormal pap smear (cervical intraepithelial neoplasia II or III since cellular atypia may be worsened by progesterone treatment¹⁹); 2) had a known allergy to progesterone or peanut oil (vehicle for micronized progesterone); 3) did not speak English; 4) were planning on moving out of the area prior to six months, the duration of the study; 5) lacked capacity to understand the study or provide informed consent; 6) were incarcerated or pending incarceration; 7) were unwilling to accept randomization; 8) were hospitalized or pending hospitalization; or 9) were unwilling to use a method of birth control.

Test Drug

Oral micronized progesterone and similar appearing capsules were prepared by Rockwell Compounds, Rye, NY. After oral administration, 50-60% of micronized progesterone is absorbed; it is metabolized by the liver to several steroids including pregnanediol, pregnenolone, pregnanediolone, 20 α -dihydroprogesterone, 17-OH progesterone, 5 α dihydroprogesterone and 5 α , 3 β tetrahydroprogesterone (allopregnanolone). Micronized progesterone has an elimination half-life of three to four hours.²⁰ A total daily dose of 150 mg to 200 mg leads to blood levels that are comparable with those of women in the luteal phase.⁵ Normal endogenous progesterone levels in conjunction with a dose of 100 mgs taken twice each day will net progesterone levels similar to those found in pregnancy.

Recruitment Procedures

Recruitment occurred between February of 2011 and February of 2013. We accepted study referrals and conducted on-site clinic screening assessments in three obstetrics clinics associated with the Yale New Haven Hospital. We screened both postpartum and pregnant women although pregnant women could not be enrolled until after delivery. After we obtained written and verbal informed consent, we administered a substance use calendar (SuCal); the calendar included data from the month prior to conception. The cocaine module from the MINI Neuropsychiatric Interview²¹ was used to confirm a diagnosis of cocaine abuse or dependence. We compensated women \$10 for the time spent in screening.

Study Measures

The Substance Use Calendar (SuCal) is based upon the Time Line Follow Back (TLFB)²² and includes information about daily drug use. It is a valid and reliable method for collection of information about the quantity and frequency of all substances used each day. The Cocaine Craving Questionnaire-Brief (CCQ-Brief) is a ten-item questionnaire that was developed from the 45 Cocaine Craving Questionnaire²³ It has good internal consistency ($\alpha=0.90$) and is highly correlated with the previous 30 days of drug use. The substance abuse and dependence modules from the Mini-International Neuropsychiatric Inventory 5.0.0 Clinician-Rated (MINI-CR) were used to generate drug and alcohol use diagnoses.²¹ The MINI-CR correlates moderately to highly with the SCID (0.43 to 0.90), and the Composite International Diagnostic Interview (CIDI) (0.36 to 0.82).²¹ The Edinburgh Postnatal Depression Scale (EPDS) measured depressive symptoms.²⁴ It is designed specifically for use with pregnant and postpartum women and is internally consistent (Cronbach's $\alpha = 0.87$).

The urine toxicology test was a one-step immunoassay for the qualitative detection of cocaine in urine (LifeSign Status DS). A specimen was also mailed to Redwood Laboratories to obtain quantitative levels of cocaine metabolites, cannabinoids, opiates (including oxycodone, but not methadone or buprenorphine), benzodiazepines, methamphetamines, phencyclidine, tranquilizers and cotinine.

Saliva samples were assayed for progesterone using a highly-sensitive enzyme immunoassay (Salimetrics LLC, State College PA). The test used 50 μ l of saliva per determination, has a lower limit of sensitivity of 5.0 pg/mL, a standard curve range from 10 pg/mL to 2430 pg/mL, an average intra-assay coefficient of variation of 6.2%, and an inter-assay coefficient of variation of 7.6%. Method accuracy determined by spike recovery averaged 99.6% and linearity determined by serial dilution averaged 91.8%. The laboratory used for salivary assays reports correlations between serum and saliva samples that are significant for females, median age 20 years, with $r(25) = 0.87$, $p < 0.001$.

Intake and Randomization Visit

The intake assessment was computerized and included questions about earlier cocaine and other ongoing substance use, social support, involvement of the Department of Child and Family Services, the Edinburgh Postnatal Depression Scale (EPDS),²⁴ the Cocaine Craving Questionnaire-Brief (CCQ)²³ and the Mini International Diagnostic Interview.²¹ All participants were administered the Structured Clinical Interview for DSM-IV modules for cocaine abuse and dependence to confirm the diagnosis. We offered all randomized participants Cognitive Behavioral Therapy³ at this and subsequent visits although this treatment was not mandatory. Upon completion of the visit, we reimbursed participants \$50 for their time and scheduled a follow-up visit for one week later.

Allocation

The study statistician generated a randomization list that included identification numbers and treatment condition. The list was given to a technician who had no involvement with the study other than preparation of study medication bottles. She prepared sequentially

numbered containers that masked any information about the test drug. The research assistant (RA) reported a randomization event to the technician and received a bottle containing either progesterone or placebo. This ensured that study staff remained blind to allocation.

Weekly Follow-up Visits

We assessed participants each week (seven $\pm$ three days) for 12 weeks. At visits, the research assistant (RA) obtained the SuCal and a urine sample. The urine was checked for cocaine metabolites, temperature (between 92 and 98 degrees), and elevated β human chorionic gonadotropin level that would indicate a new pregnancy. We collected salivary progesterone levels at weeks two, six, ten, and twelve. We counted pills to determine the number taken. The participant completed a follow-up computer assessment that included the EPDS, the CCQ, and questions about side effects. After these procedures, she met with a study therapist, if desired, and received \$40 for the treatment visit. The therapy was based upon motivational enhancement therapy and cognitive behavioral therapy for cocaine addiction and was adapted for use in pregnant and postpartum women.³ It included six modules that addressed substance use, safe sexual behavior and relapse prevention. At the final treatment visit, we gave participants referrals for ongoing treatment.

Three-month Post-Trial Visit

This visit included the assessments described above and questions about treatment utilization. Participants were reimbursed with \$50 for the visit.

Statistical Analysis

Data analyses were conducted using the intent-to-treat principle and used all randomized participants. The main statistical approach used generalized estimating equation (GEE) regression models with an autoregressive correlation structure. For the analysis estimating differences in rates of change between groups for the average days of cocaine use by week during the 12 week trial we considered time, group and time by group as fixed effects. Time was considered a continuous variable. Curvilinear and quadratic trends were not significant, thus justifying a linear trend. Given the dispersion of the data, we used a negative binomial distribution and log link. The analysis estimating differences between groups in rates of change that included the three-month post-trial follow-up also used GEE with a negative binomial distribution, log link and fixed effects of time, group, and time by group. Time (baseline, end of trial and three-month follow-up) was considered a categorical variable.

In order to estimate possible group differences in the rate of change for submission of a positive urine test, the initial model was limited to the 12-week clinical trial period. Again, differences between groups were estimated using GEE with an autoregressive correlational structure, a binomial distribution and logit link function. These models were repeated and included time as a categorical variable for the model that included the three-month post-trial follow-up visit. Sensitivity analyses were conducted using the same models assuming missing days or missing urines were positive.

The majority of women in our cohort (82%; $n=41$) were not using cocaine in the month prior to intake. Given the high rate of abstinence and low frequency of use, we conducted an

additional post hoc sensitivity analyses to compare relapse to cocaine use in the treatment groups. Accordingly, we used Cox Proportional Hazards regression to compare treatment groups with time to first use after intake as the dependent variable. We checked the proportional hazards assumption and found no evidence that it was violated. This analysis used a one-sided test.

In order to assess group differences in the secondary outcome of cocaine craving, (CCQ) we used the GEE model, an autoregressive correlational structure, gamma distribution and logit link function. The model included the following independent variables: treatment condition, week, urine result (positive or not positive), and all interactions of the three variables.

Adverse events included reported events and EPDS scores. The latter was included to ensure that mood did not worsen in the progesterone treatment group. Differences in the rates of adverse effects were compared using the Fisher's exact test. A comparison of EPDS by group, required log transformation and was modelled using mixed effects regression and an unstructured covariance matrix. The independent variables included time, treatment and the interaction of treatment and time. Analyses were conducted in SAS 9.3

RESULTS

As shown in Figure 1, we screened 1596 women for study eligibility between July 2011 and June 2013. The trial ended when recruitment of 50 women was completed and they finished their three-month post-trial follow-up. Of those screened, 1484 (93%) women were excluded. Of the 112 eligible women, 15 (13%) declined to participate and 22 (20%) were lost to follow-up. Of the remaining 75 eligible women, the first 50 who delivered or were postpartum at screening underwent randomization to progesterone or placebo.

Participant characteristics are presented in Table 1. On average, participants were 32 years old, unmarried, and unemployed. They began use of cocaine at age 20 and were using cocaine an average of 1.1 days in the week prior to study participation. Slight imbalances in race, employment and rates of obsessive compulsive disorder were observed. Overall, 41 patients (82%) completed treatment including 20 in the progesterone group and 21 in the placebo group. Treatment groups were comparable on the number of weeks in the trial (progesterone group: mean=9.4 weeks [SD4.0], placebo group: mean=9.8 weeks [SD3.3]). Participants in the progesterone and placebo conditions took a weekly average of 13.6 (SD 2.92) and 13.2 (SD 4.19) pills, respectively. Seven women in the placebo group and 5 in the active treatment group participated in psychotherapy. The average number of sessions received in the placebo group was 3.6 and 2.6 sessions in the progesterone group. We collected 3-month post-treatment data from 41 participants (82% of intent-to-treat sample), and the two groups were comparable on post-treatment visits (progesterone group: N=19, 76%, placebo group: N=22, 88%).

Primary and post-hoc analyses are presented in Table 2. Participants randomized to placebo compared to progesterone, had an increased likelihood of cocaine use per week (RR=1.19; 95% confidence interval (CI)=1.05 to 1.36; $p<0.01$). (Figure 2) At the three-month post trial visit the difference between groups was not significant (Likelihood Ratio χ^2

=5.16; $P=.08$). There were no group differences in rates of submission of a positive urine test. Assuming that all missing days of cocaine use were positive and missing urines were positive for cocaine did not change results substantially (results available upon request).

In the post hoc model for relapse, (19 in the progesterone group and 22 in the placebo group), participants randomized to placebo relapsed more quickly than did women in the progesterone group. (Hazard Ratio = 4.71; 95% CI=1.09-20.47; $p=.05$). (Figure 3) The Hazard Ratio at three months post trial was (3.5; 95% CI=.92 to 13.31; $p=.06$).

We collected 552 weekly urine samples of which 36 (6.5%) were positive despite denial of use in the prior week. The percentage of positive urine tests in women assigned to progesterone was 9.4 while 12.5 percent of participants in the placebo condition submitted positive urines. The difference in positive urines submitted was not statistically significant in the main model or the model that set missing urines to positive.

There were no significant differences in cocaine craving scores (CCQ-brief) by treatment group over time. As expected, salivary progesterone levels were higher in the progesterone treatment group at each time point. The difference in progesterone levels was 1080.5 pg/ml (95% CI= 596.24 pg/ml to 1564.68 pg/ml; $p < 0.001$).

Scores on the EPDS were measured to detect depression as a possible adverse event. The EPDS decreased over time by an average of -3.73 points from baseline to three month follow-up (95% CI= -4.71 to 0.76). Scores did not differ by group. The most common reported side effects included headache (18%), sedation (16%), dizziness (6%), dry mouth (6%), and nausea (6%). The rates of side effects did not differ by treatment group. No serious adverse events occurred during the trial.

Discussion

Post-partum women with a CUD who were randomized to progesterone, compared to those who were assigned to placebo, reported significantly less cocaine use during the 12-week clinical trial and three-month follow-up period. The differences in groups were not significant at the three-month follow up period. Post hoc analyses for women who were abstinent at baseline suggest a lower risk of relapse for women in the progesterone group. Urine toxicology assays that were positive for cocaine did not differ significantly between groups. Notably, the rate of positive urine tests in this trial was far lower than what is typically seen in a cocaine treatment trial, which may have limited our power to see significant differences.

Secondary analyses of cocaine craving did not show group differences. This may be surprising given the literature on progesterone administration to humans and its effects on craving. However, it may be difficult to detect group differences among a cohort of women who were largely abstinent at study intake. Moreover, we saw women only once a week and outside of a laboratory setting, which makes it difficult to detect differences in cocaine craving. Cocaine use itself increases cravings²⁵ and this is reflected in our data since cocaine use and craving were significantly associated.

Progesterone was well-tolerated by postpartum women. Mood changes were similar among women in the progesterone and placebo groups. Although, the small number of women who were exposed to progesterone in the current study limits our inferences with regard to tolerability findings are consistent with other studies.²⁰ It should be noted that our results with progesterone may not be generalizable to synthetic progestins. Many synthetic progestins are derived from androgens and have associated side effects such as weight gain, acne, facial hair growth and mood swings. Natural progesterone is markedly different and not likely to have these complications.

The means by which progesterone may reduce use of cocaine or prevent relapse is not known. In previous studies, progesterone attenuated cocaine's rewarding effects^{7, 26} and diminished adverse responses to mental stress.⁸ The neurobiological mechanisms of progesterone's effects on reward and stress may include enhancement of GABA transmission as well as interactions with various receptors such as glycine, sigma₁, kainate, serotonin₃, and nicotinic receptors.¹⁶ Additionally, in both women with addiction to cocaine and nicotine cigarettes, progesterone improved performance in the Stroop task, a measure of response inhibition and conflict resolution.^{8, 27} Future studies that investigate possible mediating effects may help elucidate the mechanism of progesterone's effect.

Many women in our cohort had a co-occurring psychiatric disorder, particularly an anxiety disorder. It is possible that progesterone had a therapeutic effect on an anxiety or mood disorder that helped women maintain cocaine abstinence after delivery. Indeed, EPDS scores improved in both groups although the improvement was non-significantly greater in the progesterone group. Whether improvement in psychiatric symptoms partially mediate abstinence for cocaine users should be probed in future studies.

A number of limitations in this study should be noted. First, women were seen only once per week rather than every few days. This compelled us to rely on self-report to a greater extent than urine tests for cocaine metabolites since urine tests would remain positive for only three to four days. However, we had very good retention in a high risk population of women who were contending with child care needs and doctor appointments (>80%). It is likely that we would have had a high rate of missed visits if we compelled women to attend assessments more frequently. A benefit to reduced frequency of visits is that therapeutic effects of close monitoring are attenuated. This may have enabled us to show group differences despite low frequency of cocaine use, and small sample size.

A second limitation is that postpartum women experience a number of issues that influence the likelihood that they will use cocaine, most notably child custody issues. While it is likely that these factors are randomly distributed between groups, future analyses should look at variables such as medical complications and visits and child custody as moderators of treatment outcome.

Third, while we had good follow-up, missed visits may have biased our results since women who missed visits may have had a higher rate of cocaine use. However, we included a sensitivity analyses assuming missing data were positive for use and our findings for days of use remained significant.

Another concern is that the urine results did not perfectly align with self-reported use. However, results were in the same direction. Power from this outcome was limited in that we had a small sample size. Moreover, the overall rate of positive urine tests in this study was roughly half of what is typically seen in cocaine treatment trials. This underscores the need to conduct further research in a larger cohort of postpartum women.

The generalizability of this intervention remains to be established. Participants in this trial were offered payment for their time and behavioral therapy. The uptake and differences between groups may be lessened without these incentives.

Finally, two groups of participants with a CUD were included in this trial: women who were abstinent, and women who were still using cocaine. The outcomes among participants who were abstinent at baseline seem more favorable than women who were not abstinent but the latter group was small (n=9) and we did not conduct direct comparisons. A trial with a larger sample size would allow us to determine if the treatment is effective for any postpartum women or only women who became abstinent in pregnancy. It would make sense that women who became abstinent when exposed to high levels of progesterone in pregnancy would also respond to exogenous replacement. Whether this can be extended to other groups remains to be seen.

In many ways, use of progesterone as a treatment strategy for postpartum women has appeal because it allows women to build on a period of natural abstinence or attenuated cocaine use that often occurs in pregnancy. Progesterone is commonly used by obstetricians for high risk pregnancy so the familiarity with this treatment increases the likelihood that it would be prescribed to postpartum women. If these findings are replicated in a larger cohort, progesterone may be a therapeutic breakthrough for this group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Systematic Review

Previous studies suggest that women are able to quit or reduce their drug use during pregnancy but often relapse to drug use following child birth.³ Reduction in drug use during pregnancy and relapse in the post-partum period coincides with increases and reductions in progesterone and estradiol levels in women, respectively. To investigate the plausible mechanism of these observations, we conducted a PubMed search using terms 'estradiol', 'progesterone', 'cocaine' and 'female'. The results provided strong evidence for possible therapeutic effects of progesterone in preclinical models of cocaine addiction (see Quinones-Jenab et al for a recent review.¹⁰ A few, but not all⁹, human laboratory studies also support the potential efficacy of progesterone as a treatment for cocaine addiction.^{5, 7, 8} No previous clinical trials have examined the effectiveness of progesterone in women with CUD. In contrast, estradiol's effects in preclinical models of cocaine addiction did not support its potential therapeutic actions for CUD. Moreover, progesterone reversed estradiol's facilitatory effects on drug use in preclinical models.¹⁴ Based on these findings, we hypothesized that the progesterone treatment during the post-partum period would reduce cocaine use or reduce relapse in women with CUD.

Interpretation

The results of this proof-of-concept clinical trial suggest that progesterone may have therapeutic effects in post-partum women with CUD, especially in preventing relapse among those who were not using cocaine at the beginning of the trial. These findings are preliminary and need to be replicated in adequately powered clinical trials. Future studies should also address the optimal dose and potential action mechanism of progesterone as a potential treatment for CUD.

Figure 1.
Recruitment and Selection of Study Participants

Figure 2. Rates of Change for Days of Cocaine Use

Model generated using Generalized Estimating Equations, an auto regressive correlation structure, negative binomial distribution and log link. (RR=1.19; 95% confidence interval (CI)=1.05 to 1.36; $p<0.01$)

Figure 3. Survival Analysis for Participants Abstinent at Intake

41 participants were abstinent at intake. 12 relapsed during the 12-week trial period. Relapse included 9 participants assigned to placebo and 3 participants assigned to progesterone. (Wilcoxon Statistic =4.71; 95% CI=1.09 to 20.5; p=.05)

Table 1

Participant Characteristics

Characteristic	Total ^a N = 50	Progesterone ^a N=25	Placebo ^a N=25
Age	32 ± 5.5	31 ± 4.5	33 ± 6.3
Race/Ethnicity	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>
White	28 (56%)	16 (64%)	12 (48%)
Education (years)			
Less Than High School	13 (26%)	4 (16%)	9 (36%)
High School	17 (34%)	9 (36%)	8 (32%)
Post-High School	20 (40%)	12 (48%)	8 (32%)
Marital Status			
Married/Cohabiting	12 (24%)	7 (28%)	5 (20%)
Work for pay	10 (21%)	3 (13%)	7 (29%)
Weeks Postpartum	4 ± 4.8	4 ± 4.6	3 ± 5.1
Lifetime cocaine use (yrs)	7 ± 6.0	6 ± 4.2	9 ± 7.2
Age of first cocaine use (yrs)	20 ± 5.3	19 ± 4.0	21 ± 6.3
Parity	2 ± 1.5	2 ± 1.4	3 ± 1.6
EPDS score at baseline	11 ± 6.9	11 ± 7.2	11 ± 6.7
Baseline cocaine use per week (days)	1.10 ± 3.44	1.68 ± 4.52	0.52 ± 1.76
Motivation for Change score at baseline	51 ± 5.3	52 ± 4.9	50 ± 5.5
Abstinent at Intake	41 (82%)	19 (76%)	22 (88%)
Methadone maintained	22 (44%)	14 (56%)	8 (32%)
Major Depressive Episode	7 (14%)	3 (12%)	4 (16%)
Social Phobia	6 (12%)	1 (4%)	5 (20%)
Obsessive Compulsive Disorder	4 (8%)	0 (0%)	4 (16%)
Generalized Anxiety Disorder	14 (28%)	8 (32%)	6 (24%)
Post Traumatic Stress Disorder	11 (22%)	6 (24%)	5 (20%)

^aNumbers may not sum to 50 secondary to missing data

Table 2

Differences in rates of change for the mean days of cocaine used per week for the 12 week trial were estimated with Generalized Estimating Equations (GEE) using auto regressive correlational structure, negative binomial distribution and log link. Time was considered continuous. Differences in rates of change for the mean days of cocaine at trial end and 3 months post trial were compared with GEE, and employed an auto regressive correlational structure, negative binomial distribution and log link. Time was considered a categorical variable. A comparison in the change in rates for submission of positive urine tests used the same statistical method, with a normal distribution and identity link function. Risk of relapse was modeled using Cox Proportional Hazards models, one sided test.

Primary Analyses				
Outcome	Comparison	Rate Ratio	95% Confidence Interval	P value
Number of days cocaine used per week (12 weeks)	Placebo vs. progesterone per week	1.19	1.04 to 1.36	0.01
Number of days cocaine used per week (baseline, 12 weeks, 3 months post trial) *	Placebo vs. progesterone (change from baseline to 12 weeks)	16.65	1.18 to 235.52	0.04
	Placebo vs. progesterone (change from baseline to 3-months follow-up)	30.39	3.18 to 290.04	0.01
Percentage of positive urines per week (12 weeks)	Placebo vs. progesterone per week	1.00	0.87 to 1.15	0.99
Percentage of positive urines per week (baseline, 12 weeks, 3 months post trial) **	Placebo vs. progesterone (change from baseline to 12 weeks)	1.18	0.24 to 5.84	0.84
	Placebo vs. progesterone (change from baseline to 3-months follow-up)	1.34	0.23 to 7.88	0.75

Post-hoc Analyses				
Outcome	Comparison	Hazard Ratio	95% Confidence Interval	P value
Relapse For Participants Abstinent at Intake During Trial (Hazard Ratio)	Placebo vs. Progesterone	4.71	1.09 to 20.5	0.05
Relapse For Participants Abstinent at Intake Including 3 Month Follow Up (Hazard Ratio)	Placebo vs. Progesterone	3.50	0.92 to 13.3	0.06

* Overall model for days of cocaine used per week (baseline, 12 weeks, 3 months) X^2 (df,2)=5.16; P=.08.

** Overall model for percentage of positive urines per week (baseline, 12 weeks, 3 months post trial) was X^2 (df,2)=0.11; P=.95