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Progesterone for Smoking Relapse Prevention Following Delivery: A Pilot, Randomized, Double-Blind Study

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1. Introduction

Among the 13 million female smokers of reproductive age in the US (CDC, 2004), pregnancy and the postpartum period present unique possibilities and challenges. Close to half of women who were smokers prior to conception are able to quit smoking in pregnancy (Colman and Joyce, 2003). Unfortunately, nearly 50% (Polanska et al., 2011; Reitzel et al., 2010) relapse within the 2–6 months after delivery and 70–80% relapse within a year (Forray et al., 2015). Smoking in the mother places her at increased risks for cancer, heart disease, and chronic pulmonary disease. Also of concern are the deleterious health effects of second-hand smoke on newborns, which include increased risk for respiratory and ear infections, sudden infant death syndrome, behavioral dysfunction and cognitive impairment (DiFranza et al., 2004). In addition, women who smoked pre-pregnancy may cease breastfeeding early in order to restart smoking (Joseph et al., 2017).

While many psychosocial and environmental factors (Fang et al., 2004; Hymowitz et al., 2003) contribute to postpartum relapse to smoking, biological factors should not be ignored. A particularly important factor to consider is the role of progesterone in pregnancy and after delivery. Progesterone levels are greatly elevated in pregnancy and peak in the third trimester

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(200–400 nM), when they are nearly 150 times higher than during the luteal phase of the menstrual cycle (1–3 nM) (Schumacher et al., 2014). This peak in the third trimester corresponds to the time many women discontinue smoking (Forray et al., 2015). Levels drop precipitously after delivery to perimenopausal levels (Schumacher et al., 2014).

Progesterone and its active metabolites, allopregnanolone and pregnanolone, regulate neuronal signaling via genomic and non-genomic mechanisms of action. The therapeutic effect of progesterone is likely mediated by allopregnanolone's modulation of GABA_A neurotransmission (Biggio et al., 2009; Turkmen et al., 2011). As neuroactive steroids, progesterone and allopregnanolone participate in a wide range of CNS activities including cognitive function as well as dampening stress and reward responses (Bali and Jaggi, 2014; Schumacher et al., 2014; Thakre et al., 2013). In animals, progesterone diminishes nicotine self-administration (Lynch, 2009) and is known to block nicotinic receptors, including the $\alpha 4\beta 2$ subunit, implicated in nicotine addiction (Bertrand and Gopalakrishnan, 2007; Pereira et al., 2002). Human data, although limited, show that exogenous administration of progesterone attenuates both craving for cigarettes and the subjective rewarding effects of smoking in recently abstinent female smokers (Allen et al., 2008; Sofuoglu et al., 2001; Sofuoglu et al., 2009). Blockage of nicotinic receptors and reductions in activity in the orbito-frontal cortex, ventral striatum and amygdala during craving or reward anticipation are properties shared by progesterone and the smoking cessation medications, varenicline and bupropion (Culbertson et al., 2011; Franklin et al., 2011; Henningfield et al., 2009). In fact, there is evidence that higher levels of endogenous progesterone are associated with an increase in the odds of being abstinent in female smokers undergoing medication-based treatment (nicotine patch or varenicline) (Saladin et al., 2015).

Other than contingency management (Heil et al., 2008; Higgins et al., 2010), effective treatments for smoking in postpartum women are limited. Psychotherapeutic interventions are only modestly effective (Agboola et al., 2010; Reitzel et al., 2010), and the efficacy and safety of pharmacologic treatments for smoking are not yet established in pregnant and postpartum women (Agboola et al., 2010). Thus, new and efficacious interventions are needed for postpartum women.

Progesterone has many unique features as a relapse prevention intervention in postpartum women; it is a natural hormone commonly used by obstetricians and nurse practitioners/midwives, and is safe and well tolerated in this population, including those who are breastfeeding (Goletiani et al., 2007). The aims of this pilot study were to: 1) assess the feasibility, in terms of recruitment, use and acceptability of postpartum progesterone replacement for women with a history of pre-pregnancy smoking, 2) collect data to estimate the parameters required to design a definitive randomized controlled trial (RCT), and 3) preliminarily test the efficacy of progesterone in preventing relapse to smoking postpartum. We anticipated adequate randomization of women who screened eligible, and retention of at least 70% in the progesterone group. We predicted that the relapse rate, as biochemically verified at the end of the trial and the 3-month follow-up assessment, would be lower for those assigned to progesterone than those assigned to placebo.

2. Methods

2.1. Design

This was a stratified (for age and severity of nicotine dependence, with equal randomization), double-blind, placebo-controlled, parallel-group pilot trial. Women were given medication or placebo for 8 weeks following delivery and were re-evaluated three months after the end of the trial. In this pilot study, we randomized 41 participants to either progesterone or placebo. Recruitment began January 2014 and final data collection occurred August 2016. The study was approved by the Yale School of Medicine institutional review board and included a certificate of confidentiality from the National Institutes of Health.

2.2. Participants

Women were eligible to participate if they: 1) were within 3 weeks of delivery because relapse to smoking happens early after childbirth; 2) aged 18 to 42 years; 3) were abstinent from smoking in the final two months of pregnancy and at delivery; 4) had biologically confirmed abstinence from tobacco and other nicotine products at randomization (breath carbon monoxide (CO) levels ≤ 8 ppm and urine cotinine levels ≤ 200 ng/ml (Benowitz et al., 2002)). 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, or untreated abnormal pap smear (cervical intraepithelial neoplasia II or III since cellular atypia may be worsened by progesterone treatment); 2) had current or past history of bipolar disorder or schizophrenia, current diagnosis of major depression, panic disorder or post-traumatic stress disorder, or the presence of suicidal or homicidal ideation either at study baseline during the evaluation process or during participation in the trial; 3) dependence on and/or abuse of alcohol or other illicit drugs (e.g., cocaine, opiates, benzodiazepines, etc.) in the month prior to randomization into the trial (based on clinical evaluation including self-report, and confirmed by positive urine toxicology screen); 4) had a known allergy to progesterone or peanut oil (vehicle for micronized progesterone); 5) currently undergoing treatment with another pharmacological agent for smoking cessation; 6) did not speak English; 7) had plans to move out of the area within 8 months after study screening; 8) lacked capacity to understand the study or provide informed consent; 9) were incarcerated or pending incarceration; 10) were unwilling to accept randomization; 11) were hospitalized or pending hospitalization; or 12) had subsequent pregnancy since this would be another source of progesterone; 13) were planning on using progestin containing birth control in the first two months after delivery.

2.3. Recruitment Procedures

We accepted study referrals and conducted on-site clinic screening assessments in three academic obstetrics clinics associated with Yale New Haven Hospital. Two of the clinics serve the urban population in the greater New Haven, CT area, and the third was the maternal fetal medicine clinic that serves as a referral center for women throughout the state. We screened 170 pregnant women for a history of smoking. 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. Current smokers that intended to quit prior to delivery and had not reached 32 weeks' gestation at the time of screening were monitored monthly for abstinence via telephone calls and/or at prenatal visits. Abstinence was confirmed via a urine cotinine analysis (<100 ng/ml) and a breath CO analysis (<8 ppm) by 32 weeks' gestation and again prior to randomization. Intake occurred between 32 and 36 weeks' gestation.

2.4. Randomization

Randomization occurred within four days after delivery. The study statistician prepared a computerized urn randomization program to ensure balance between the two groups for age and severity of nicotine dependence. The strata for age were 1) 18 to 25 years or 2) >25 years. Age was a stratifying factor because older postpartum women are more likely to achieve abstinence (Colman and Joyce, 2003). For severity of nicotine dependence, the strata were smoking 1) < 10 cigarettes per day or 2) ≥ 11 cigarettes per day, in the month before conception. The statistician generated a randomization list that included identification numbers and treatment condition. The list was given to a technician with no involvement in the study other than preparation of study medication bottles. The technician 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 all study staff remained blind to allocation.

2.5. Test Drug

Oral micronized progesterone and identical appearing placebo capsules were prepared by Rockwell Compounding, Rye, NY and compounded with riboflavin, which causes the urine to change color, as a check for adherence. Typically, 50–60% of micronized progesterone is absorbed after oral administration; it reaches its peak plasma levels in two to three hours and has an elimination half-life of three to four hours (McAuley et al., 1996). A total daily dose of 200 mg of micronized progesterone results in serum progesterone levels slightly higher to those found in the mid-luteal phase of the menstrual cycle (Evans and Foltin, 2006; Sofuoglu et al., 2011). For this study, we utilized 200 mg of oral micronized progesterone, and due to its short half-life, it was given twice daily to maintain stable plasma level of progesterone. We did not measure serum levels of progesterone in the study, thus we speculated a total daily dose of 400 mg of progesterone in conjunction with endogenous progesterone production will net progesterone levels between 10–20 ng/L (Sofuoglu et al., 2011). The placebo pill contained an inert ingredient and was identical in appearance to the oral micronized progesterone pill.

2.6. Study Measures

The SuCal is based upon the Timeline Followback (TLFB) (Sobell and Sobell, 1992) and includes information about daily smoking. It is a valid and reliable method for collection of information about the quantity and frequency of all substances used each day. The following PhenX Toolkit measures were used for screening: General Psychiatric Assessment (120101), Substance Abuse and Dependence measure for alcohol (510401), drugs (510402) and tobacco (510403), and the Tobacco Protocols (030602, 030702, 030802, 030902) (Hamilton

et al., 2011). The Fagerstrom Test for Nicotine Dependence (FTND) was used to determine the severity of nicotine dependence (Heatherton et al., 1991) was also used at the time of screening. At each treatment visit the ten-item Questionnaire on Smoking Urges (QSU-brief) (Cox et al., 2001) was administered to assess for cravings and factors that may reinforce smoking. For urine cotinine analysis, we utilized Reditest Smoke Cassette (Redwood Toxicology) a rapid immunoassay for the qualitative detection of cotinine in urine at 200 ng/ml. For CO monitoring we utilized the Covita piCO+ Smokerlyzer. CO levels above 8 ppm were considered positive. To screen for substance use we utilized a one-step six panel chromatographic immunoassay for the qualitative detection of amphetamines, benzodiazepines, cocaine metabolites, cannabinoids (THC), oxycodone and other opiates (Redwood Toxicology Reditest Panel-dip). The Systematic Assessment for Treatment Emergent Events (SAFTEE) (Johnson et al., 2005) was used to assess adverse events, and includes guidelines and standard questions for gathering information on the frequency and severity of adverse events.

2.7. Study visits

2.7.1. Intake and Randomization Visit—The intake assessment was computerized and included questions on smoking and other substance use, the PhenX Toolkit measures listed in section 2.6, the Edinburgh Postnatal Depression Scale (EPDS), the FTND, breastfeeding intention and social support. Smoking abstinence was confirmed with urine cotinine analysis (<100 ng/ml) and a breath CO analysis (<8 ppm). Participants also completed a SuCal administered by the RA. At randomization women once again completed a SuCal, had abstinence confirmed via urine cotinine analysis and breath CO, and completed a computerized assessment that included the EPDS, QSU-brief, and questions on breastfeeding intentions.

2.7.2. Weekly Follow-up Visits—Participants were assessed each week (seven +/- three days) for eight weeks. At each visit, the RA obtained the SuCal, a urine sample and measured expired CO. The urine was checked for cotinine, illicit drugs, temperature (between 92 and 98 degrees), and β human chorionic gonadotropin level. Pills were counted to determine the number taken. Participants completed a computer assessment that included the QSU-brief, EPDS, and questions about side effects. After these procedures, if desired, participants met with a study therapist. The therapy was based upon motivational enhancement therapy and cognitive behavioral therapy for smoking and was adapted for use in pregnant and postpartum women (Yonkers et al., 2012). It included six modules that addressed smoking, healthy behaviors and relapse prevention. Women could receive up to \$270 for completing the entire study, stratified by individual visit type as follows: \$40 for their initial assessment, \$20 for each of 7 study visits (visits 1,3–8), \$40 for the week 2 visit, and \$50 for the 3-month follow-up visit.

2.7.3. Three-month Post-Trial Visit—This visit included the assessments described in 2.7.2, including a SuCal covering the period from the end of the 8-week trial until the day of follow-up, urine cotinine analysis and breath CO.

2.8. Outcomes variables

The primary outcome was study feasibility as shown by: 1) a participation rate of 50% for eligible women between screening and randomization, and 2) retention of at least 70% in the progesterone group. Our secondary outcomes were 7-day point prevalence of abstinence at week 8 and time in weeks to relapse. Abstinence was defined as self-report of no smoking in the past 7 days and a negative urine cotinine test. Women who reported smoking or had a positive urine cotinine test were coded as not abstinent, and women with both missing urine and self-report week 8 data were imputed as not abstinent (Altman, 2009; Moher et al., 2010). Five women missed the week 8 visit and did not provide a urine, but they did complete their 3-month follow-up visit and thus their abstinence was defined per their self-reported use as reported in the SuCal. For the time in weeks to relapse outcome, relapse was defined as the first week of seven consecutive days of smoking or the second of two consecutive weeks of between 1 and 6 days, inclusive, of smoking (Hughes et al., 2003). Estimates of effect sizes for both secondary outcomes were calculated to inform power analysis and sample size calculations for a future definitive RCT. Another secondary analysis was smoking craving as measured by the QSU-brief over the 8-week trial period.

As a pilot, the study was not powered to detect a significant difference on our outcomes. We used the guidelines for Stage 1b studies, suggesting 15–30 participants per cell (Rounsaville et al., 2001). For abstinence at week 8, with 20 subjects per condition and a 2-tailed alpha of 0.05 we calculated 62% power to detect an effect size similar to the effect size found in a study using varenicline to prevent smoking relapse, in which continuous abstinence rate was 49.4% with varenicline and 11.6% with placebo (Oncken et al., 2006).

2.9. Data Analysis

Data analyses were conducted using the intent-to-treat principle and used all randomized participants. Descriptive statistics were calculated overall and by treatment group for baseline demographics and other characteristics and were compared visually to check for any clinically meaningful differences between groups. The binary outcome of 7-day point prevalence of abstinence (i.e., no smoking in the past 7 days, verified by urine cotinine) at week 8 was analyzed using logistic regression to compare the odds of abstinence between progesterone and placebo groups, adjusting for stratifying variables, age (18–25 years versus >25 years) and pre-quit smoking level (<10 versus >10 cigarettes per day). Results were reported as odds ratios with 95% confidence intervals. To aid with further interpretation and inform power analyses for future RCT's, the probability of 7-day point prevalence abstinence at week 8 for each treatment group was modeled using a generalized estimating equation (GEE) with a binomial distribution and identity link. The probability of abstinence for each group and the difference in probabilities between groups ($p_{\text{progesterone}} - p_{\text{placebo}}$) with 95% confidence intervals were reported. To see how imputation influenced our results, we compared results from models in which missing week 8 data were imputed as not abstinent to models that included complete cases only (N=34) and models that used the last observation carried forward method of imputation.

To compare time to relapse from baseline (date of delivery) through 20-weeks postpartum between progesterone and placebo groups, we used Kaplan-Meier survival estimates and

Cox proportional hazards regression, adjusted for stratifying variables of age and pre-quit smoking level. Data were censored when relapse did not occur before participants completed the study at week 20 (N=9) or dropped out of the study before week 20 (N=7). The assumption of proportional hazards was checked by testing the time-dependent covariate, treatment x time in weeks. The exact method was specified to handle ties in observed survival times, assuming ties arose from grouping continuous, untied data. Results were reported as median time to relapse and hazard ratios (HR) with 95% confidence intervals.

To compare changes in QSU-brief total scores over time between groups, we used GEE, specifying a gamma distribution (due to the positively skewed distribution of these scores), log link and autoregressive correlation structure. The independent variables included treatment group, setting placebo as the reference group, time in weeks as a continuous variable, and treatment by time interaction, as well as adjusting for age and pre-quit smoking level categories, as previously described. The main variable of interest was the treatment by time interaction term, which tests if the rate of change in score differed between treatment groups. Results were presented as incidence rate ratios (IRR's) with 95% confidence intervals for the treatment by time interaction term. IRR's were calculated by exponentiating the β -coefficients since score means were modeled on a log scale, and for the interaction term, they represent the percent difference in the weekly rate of change in mean score between treatment groups.

Analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC), and significance threshold was set at 0.05.

3. Results

Figure 1 shows the participant flow in the trial. Of the 170 pregnant women screened for a history of smoking, 90 reported a history of smoking in the last six months and were willing to be assessed for eligibility. A total of 41 women met entry criteria, agreed to participate and were randomized between February 2014 and April 2016.

3.1. Subject Characteristics

Table 1 shows the baseline characteristics and demographics of women enrolled in the study. The overall mean (SD) age of all women randomized was 25.8 (4.6) years and was similar for the women randomized to the progesterone, 26.2 (4.9) years, and placebo, 25.3 (4.3) years, groups. The mean (SD) number of cigarettes smoked per day at baseline for the two groups was similar, 6.2 (4.3) for the progesterone group and 7.1 (3.3) for the placebo group. The progesterone and placebo groups were similar in terms of age stratification, race/ethnicity, level of education, pre-pregnancy level of smoking, and proportion living with a smoker.

The number of women who intended to exclusively breastfeed at randomization was slightly higher in the placebo group. When actual feeding practices were evaluated two weeks following delivery, six women in the progesterone group and no women in the placebo group were exclusively breastfeeding. The number of women who elected to receive therapy did not differ between treatment groups, 15 (79%) in the placebo group and 15 (68%) in the

progesterone group, $\chi^2(1) = 0.602$, $p = 0.44$. The mean (SD) number of therapy sessions received was also similar with 3.5 (2.5) sessions in the placebo group and 2.7 (2.4) in the progesterone group, $t(39) = 1.04$, $p = 0.30$.

3.2. Feasibility

Of the 90 women screened for the study, 64 were eligible for participation of which 41 (64%) were randomized, meeting the anticipated participation goal of 50%. Overall, 32 (78%) participants completed the trial, 17 in the progesterone group and 15 in the placebo group. Of the 22 women allocated to progesterone, three did not receive the intervention and two were lost to follow-up, resulting in 77% ($n = 17$) retention at the 3-month follow-up. The placebo group had 79% retention at the 3-month follow-up, with two participants lost to follow-up and two who did not receive allocated treatment. Medication adherence was similar between the two treatment groups, with women in the progesterone group taking an average (SD) of 76.0 (42.0) doses and 84.5 (38.3) doses by women in the placebo group ($p = 0.46$). In addition, 35 women (85%) had positive urines for riboflavin in 70% of samples collected and six (15%) did not, three in each treatment group. The urine results were consistent with the pill count data.

3.3. Smoking Outcomes

3.3.1. Seven-day point prevalence—The 7-day point prevalence of abstinence at week 8 was achieved by 45% ($n = 10$) of women in the progesterone group and 32% ($n = 6$) of women in the placebo group, using raw data. Results from the logistic regression model (see Table 2) showed that, independent of age and pre-quit smoking level, women in the progesterone group had 1.77 higher odds of abstinence at week 8 as women in the placebo group, although this difference did not reach statistical significance (OR = 1.77; 95% CI = 0.48 to 6.52; $p = 0.39$). After adjusting for age and pre-quit smoking level, the probability of 7-day point prevalence abstinence at week 8 was 46% (95% CI = 22% to 70%) and 33% (95% CI = 7% to 58%) for progesterone and placebo, respectively, for a difference of 13% (95% CI = -17% to 44%). Age and smoking level pre-pregnancy were not associated with relapse.

The sensitivity analysis for imputation showed consistent results across all methods. For the complete case analysis ($N=34$), the unadjusted OR was 2.08; 95% CI = 0.53 to 8.23; $p = 0.30$, and the adjusted OR was 1.99; 95% CI = 0.49 to 8.06; $p = 0.33$. For the last observation carried forward ($N=41$), the unadjusted OR was 1.61; 95% CI = 0.47 to 5.54; $p = 0.45$, and the adjusted OR was 1.68; 95% CI = 0.47 to 6.04; $p = 0.43$.

3.3.2. Time to relapse—At the end of 20 weeks, five women (23%) remained abstinent in the progesterone group versus four (21%) in the placebo group. Median time to relapse from baseline to 20 weeks postpartum was four weeks for the placebo group and 10 weeks for the progesterone group (Wilcoxon rank sum test $p = 0.28$). Figure 2 shows the Kaplan-Meier survival curves by treatment group, which did not differ significantly from each other (log-rank chi-square $p = 0.40$). For the Cox regression model, no evidence against the assumption of proportional hazards was found ($\beta = 0.14$; SE = 0.11; $p = 0.22$), and the placebo group was 39% more likely to relapse compared to the progesterone group over the 20 weeks,

although this difference did not attain statistical significance (HR = 1.39; 95% CI= 0.66 to 3.38; $p = 0.41$).

3.3.3. Effect on craving—We assessed the impact of the intervention on cravings across the 8-week trial by evaluating the association of QSU-brief scores with the interaction between treatment group and time. Results of the GEE modeling QSU-brief scores are shown in Figure 2. The rate of change in QSU-brief scores differed significantly between treatment groups, with a 9.2% greater decline per week in mean QSU-brief score in the progesterone versus placebo group (IRR = 0.91; 95% CI= 0.86 to 0.96; $p < 0.001$).

3.4. Adverse Events

Five women reported an adverse event, three in the placebo group and two in the progesterone group. The women in the placebo group reported: headache ($n = 1$, at one visit); feeling warm ($n = 1$, at two consecutive visits); and itching ($n = 1$, at one visit). The women in the progesterone group reported: abnormal pap smear ($n = 1$; repeat pap smear was negative); and heavy menses during first cycle following delivery ($n = 1$). No serious adverse events occurred during the trial. We measured EPDS scores to detect depressive symptoms as a possible adverse event. Mean EPDS score at baseline was 3.7 in the placebo group and 3.0 in the progesterone group. In the placebo group, baseline EPDS scores ranged from 0.0 to 21.0 with a median score of 3.0 and an interquartile range of 0.0 to 6.6. In the progesterone group, baseline EPDS scores ranged from 0.0 to 16.0 with a median score of 0.5 and an interquartile range of 0.5 to 5.0. Median scores were fairly stable across follow up visits, ranging from 2.0 to 4.0 in the placebo group and 0.0 to 3.0 in the progesterone group.

3.5. Assessment of the blind

When subjects were asked to guess what treatment they were allocated to, four of 27 women who provided responses, stated they did not know. Of the remaining 23 participants who attempted to guess their treatment, nine women (39%) in the progesterone group correctly guessed their treatment allocation compared with two in the placebo group (9%). Conversely, nine women (39%) in the placebo group thought they had received progesterone, while three women (13%) in the progesterone group thought they had received placebo.

4. Discussion

In this pilot trial on the use of progesterone as a smoking relapse intervention we demonstrated that such a trial is feasible in terms of adequate randomization, trial retention and acceptability among postpartum women. At the end of the 8-week trial, the smoking outcomes showed a trend in the expected direction with a higher proportion of women in the progesterone group maintaining abstinence with a slower rate of relapse over the 3-month follow-up period, compared to women in the control group; although these findings were not statistically significant. Another main objective was to estimate inputs for sample size calculations for the future definitive RCT, which were obtained for both the 7-day point prevalence (risk difference of 13%) and the time to relapse (HR = 1.39).

Women in the progesterone group exhibited significantly lower smoking craving scores than women in the placebo group. This finding is in line with previous work, which found that progesterone treatment, as compared to placebo, attenuates craving and the subjective-rewarding effects of cigarette smoking among non-perinatal female smokers (Sofuoglu et al., 2001; Sofuoglu et al., 2009; Sofuoglu et al., 2011). This significant difference in smoking cravings is particularly important clinically for this population, as intense cravings often lead to smoking lapses, and in turn, relapse (Kassel et al., 2003). Furthermore, postpartum women frequently give up breastfeeding to return to smoking (Joseph et al., 2017). Differences in breastfeeding practices between treatment groups should be explored further in a definitive RCT.

Progesterone was well tolerated by postpartum women. No serious adverse events occurred during the trial, and no differences were observed between groups with respect to mood changes. These findings are consistent with other studies (McAuley et al., 1996; Yonkers et al., 2014) that indicate progesterone does not have the same side effect profile as progestins derived from androgens. This provides further support of progesterone as a safe and acceptable pharmacological intervention for postpartum smokers. Both women and their physicians struggle with the decision to use antismoking medication after delivery. While it is optimal for mothers to remain abstinent the risks and benefits of currently available smoking cessation medications during lactation are not clear. Progesterone, on the other hand, has particular appeal for obstetrical providers who are accustomed to the use of hormonal treatments. Given that young women, including postpartum women, are more likely to see an obstetrical provider than other medical professionals, the uptake of this promising therapeutic intervention may be enhanced compared to current interventions.

Our findings are in line with the only two other studies evaluating the role of progesterone in postpartum women for substance use relapse prevention. In a 12-week trial conducted by our group, we found that postpartum women with a cocaine use disorder who were randomly assigned to progesterone reported significantly less cocaine use and had a slower rate of relapse among those who were abstinent at baseline compared to women randomized to placebo (Yonkers et al., 2014). A recent pilot trial of progesterone in postpartum smokers showed more women remained abstinent after 4 weeks of progesterone treatment compared to women receiving placebo, although this difference did not reach statistical significance (Allen et al., 2016). In both studies, as in the current one, progesterone was well tolerated.

The neurobiological mechanisms by which progesterone might reduce smoking craving and relapse is not fully understood, but likely involve enhancement of GABA transmission, allosteric modulation of nicotinic receptors, and interactions with various receptors involved in the dampening of stress and reward responses (Bali and Jaggi, 2014; Bertrand and Gopalakrishnan, 2007; Schumacher et al., 2014; Thakre et al., 2013). Further, progesterone has been shown to improve response inhibition in both preclinical and clinical studies. In a Go/No-Go food task, rats treated with progesterone showed decreased impulsivity (Swalve et al., 2016). In clinical laboratory studies, our group has demonstrated that progesterone, both endogenous, in abstinent female smokers in luteal phase, and exogenous, 200 mg/day in current female smokers, improves cognitive performance on a Stroop task (DeVito et al., 2014; Sofuoglu et al., 2011). When one considers the importance of impulsivity or response

inhibition in relapse to smoking, such cognitive effects may contribute to progesterone's proposed efficacy for smoking cessation (Schepis et al., 2011; VanderVeen et al., 2008). Future studies that investigate the mediating effects might help to elucidate the mechanism of progesterone's effect on smoking.

Our trial has several strengths. The main strength is that it was a randomized double-blind, placebo-controlled, parallel-group pilot trial with eight weeks of active treatment in the immediate postpartum period, when the risk of relapse is highest. Furthermore, we had weekly follow-up during the intervention and 3-month post-trial follow-up with biological verification of smoking status. The study population was diverse. Finally, the results of our primary smoking outcome remained robust under different imputation methods.

The main limitation of our study was that as a pilot trial it was not sufficiently powered to detect significant differences between the two groups or determine the role of possible moderators, such as breastfeeding. We also did not collect blood samples to measure serum progesterone levels. While we had good follow-up, missed visits might have biased our results since women who missed visits might have temporarily lapsed or relapsed. As a pilot trial the generalizability of the findings is limited. The sample population was small and consisted of women attending hospital-based prenatal clinics with moderate levels of smoking. A future RCT with larger sample in more than one clinical setting is needed to enhance generalizability and address the current limitations. The feasibility demonstrated by this pilot trial along with the collection of preliminary data on effect size that can be utilized to inform such a future definitive RCT.

5. Conclusion

These preliminary findings support the feasibility and acceptability of progesterone treatment in postpartum smokers. If these preliminary findings can be evaluated and in a larger study with sufficient power, this may constitute a promising and safe smoking relapse prevention strategy for use during lactation.

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Highlights

- Female smokers frequently quit smoking in pregnancy when progesterone levels are high.
- Relapse postpartum is common when progesterone levels drop.
- Progesterone replacement in postpartum women decreased craving for cigarettes.
- Progesterone showed a trend toward increased abstinence and slower relapse.
- Findings support the promise of progesterone treatment in postpartum smokers.

Figure 1.
Participant flow in the trial.

*Self-reported substance use captured at 3-month follow-up visit.

**Missing data imputed as having used cigarettes.

Figure 2. Time to Relapse after Delivery. Kaplan-Meier estimates of the time (weeks) to smoking relapse among the progesterone and placebo groups from delivery (randomization) through the 3-month follow-up after the 8-week intervention. Included on the bottom of the figure is the number of women at risk for relapse in each group at each time point. HR = hazard ratio.

Figure 3.

Change in the brief Questionnaire on Smoking Urges (QSU-brief) score over time by treatment group. Graphs depict modeled means from generalized estimating equation, specifying a gamma distribution, log link, and autoregressive correlation structure and modeling association of QSU-brief with treatment, time, and treatment*time, adjusted for age (18–25 years vs. over 25 years) and pre-pregnancy smoking level (≤ 10 vs. >10 cigarettes/day). Treatment x time interaction (reference = placebo group) Incidence Rate Ratio = 0.91, 95% CI = 0.86 to 0.93, $p < 0.001$. QSU-brief has a possible range from 10 to 70, with higher scores indicating more severe smoking urges.

Table 1**Baseline Characteristics of Participants**

Variable	Overall (n=41) N (%)	Progesterone (n=22) N (%)	Placebo (n=19) N (%)
Age			
>25 years	19 (46.3)	9 (40.9)	10 (52.6)
≤25 years	22 (53.7)	13 (59.1)	9 (47.4)
Race/Ethnicity			
Hispanic	15 (36.6)	11 (50.0)	4 (21.1)
Black, non-Latino	22 (53.7)	9 (40.9)	13 (68.4)
White, non-Latino	3 (7.3)	2 (9.1)	1 (5.3)
Multi-racial	1 (2.4)	0 (0.0)	1 (5.3)
Education			
< High school degree	9 (22.0)	6 (27.3)	3 (15.8)
High school degree	22 (53.7)	13 (59.1)	9 (47.4)
Some college (no degree)	10 (24.4)	3 (13.6)	7 (36.8)
Lives with spouse or partner			
Yes	20 (48.8)	10 (45.5)	10 (52.6)
No	21 (51.2)	12 (54.6)	9 (47.4)
Parity			
1	11 (26.8)	8 (36.4)	3 (15.8)
2	12 (29.3)	4 (18.2)	8 (42.1)
3	11 (26.8)	7 (31.8)	4 (21.1)
4+	7 (17.1)	3 (13.6)	4 (21.1)
Pre-quit smoking level			
10 cigarettes/day	34 (82.9)	17 (77.3)	17 (89.5)
>10 cigarettes/day	7 (17.1)	5 (22.7)	2 (10.5)
Lives with smoker			
Yes	18 (51.4)	10 (47.6)	8 (50.0)
No	19 (48.6)	11 (52.4)	8 (50.0)
Missing	4	1	3
Breastfeeding intentions			
Breastfeed exclusively	13 (31.7)	9 (40.9)	4 (21.1)
Breastfeed and formula feed	21 (51.2)	11 (50.0)	10 (52.6)
Formula feed exclusively	6 (14.6)	2 (9.1)	4 (21.1)
Unsure	1 (2.4)	0 (0.0)	1 (5.3)
Feeding method at week 2 visit			
Breastfeed exclusively	6 (14.6)	6 (27.3)	0 (0.0)
Breastfeed and formula feed	8 (19.5)	5 (22.7)	3 (15.8)
Formula feed exclusively	21 (51.2)	7 (31.8)	14 (73.7)
Missing	6 (14.6)	4 (18.2)	2 (10.5)
Fagerstrom Test for Nicotine Dependence			

Variable	Overall (n=41)	Progesterone (n=22)	Placebo (n=19)
	N (%)	N (%)	N (%)
Low dependence	13 (31.7)	7 (31.8)	6 (31.6)
Low to moderate dependence	20 (48.8)	11 (50.0)	9 (47.4)
Moderate dependence	8 (19.5)	4 (18.2)	4 (21.1)
High dependence	0 (0.0)	0 (0.0)	0 (0.0)
	Mean (SD)	Mean (SD)	Mean (SD)
Baseline number of cigarettes per day	6.6 (3.9)	6.2 (4.3)	7.1 (3.3)
Edinburgh Postnatal (EPDS) Depression Scale *	3.4 (4.7)	3.0 (4.5)	3.8 (4.9)
Brief Questionnaire of (QSU-brief) Smoking Urges **	16.9 (13.7)	18.0 (12.2)	15.6 (15.4)

* Scale is scored from 0 to 30. Higher scores indicate more severe symptoms.

** Scale is scored from 10 to 70. Higher scores indicate more severe symptoms.

Table 2
Logistic regression model predicting 7-day point prevalence of abstinence at week 8 (N=41)

Explanatory variables	N (%) Abstinent	Unadjusted OR		Adjusted OR	
		(95% CI)	p-value	(95% CI)	p-value
Treatment					
Progesterone	10 (45)	1.81 (0.50, 6.50)	0.37	1.77 (0.48, 6.52)	0.39
Placebo	6 (32)	1.00		1.00	
Age					
>25	9 (41)	1.19 (0.34, 4.19)	0.79	1.11 (0.31, 4.00)	0.87
25 years	7 (37)	1.00		1.00	
Pre-quit smoking level					
10 cigarettes/day	13 (38)	0.83 (0.16, 4.29)	0.82	0.93 (0.17, 5.03)	0.94
>10 cigarettes/day	3 (43)	1.00		1.00	

OR= odds ratio, CI= confidence interval

Stratifying variables: age (18–25 years versus >25 years) and pre-quit smoking level (<10 versus >10 cigarettes per day)