Original investigation

Progesterone and Postpartum Smoking Relapse: A Pilot Double-Blind Placebo-Controlled Randomized Trial

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Abstract

Introduction: Pregnancy is a strong motivator to quit smoking, yet postpartum relapse rates are high. Growing evidence suggests a role of sex hormones in drug abuse behavior and given the precipitous drop in sex hormones at delivery, they may play a role in postpartum relapse. This pilot study evaluates the feasibility and potential role of exogenous progesterone in postpartum smoking relapse.

Methods: This 12-week double-blind placebo-controlled randomized pilot trial randomized 46 abstinent postpartum women to active progesterone (PRO; 200 mg twice a day) versus placebo (PBO) for 4 weeks. Participants were followed for relapse for 12 weeks. Main study outcomes include abstinence (point prevalence), feasibility (compliance per number of clinic visits attended, pill counts and Electronic Data Capture [EDC] completed) and self-reported acceptability. Safety was also measured by depressive symptom scores, adverse events, and breastfeeding.

Results: Overall retention rate was 87% at week 12. At week 4, abstinence rates were 75% in the PRO group and 68.2% in the PBO group (*p* = .75). Medication adherence was 68% and clinic visit attendance was 80%, with no differences by randomization. Depressive symptom scores, adverse events, and breastfeeding did not vary by randomization.

Conclusions: Although the study was not powered to evaluate abstinence rates, we did observe a higher prevalence of abstinence at week 4 in the PRO group. Further, exogenous progesterone was well tolerated and did not adversely affect depressive symptoms or breastfeeding. Thus, the results of this pilot study indicate further investigation into progesterone as a postpartum relapse prevention strategy is warranted.

Implications: This innovative pilot trial determined the feasibility of delivering exogenous progesterone as a potential prevention of postpartum smoking relapse. We observed high retention and moderate adherence rates, as well as high acceptability among participants. Further, though not statistically significant, more women in the treatment group remained abstinent from smoking during follow-up. This project adds to the growing body of literature on the role of sex hormones in smoking relapse and also provides support for a fully powered clinical trial.

Introduction

Pregnancy is a strong motivator to quit smoking with 23% of women successfully able to quit while pregnant.[1] Unfortunately over half relapse within 6 months of delivery and up to 90% relapse after 1 year.[2] Postpartum relapse negatively affects not only maternal health, but also infant health through secondhand smoke exposure (SHS). SHS increases health risks ranging from early death (eg, Sudden Infant Death Syndrome) to acute (eg, pneumonia and ear infections) and chronic conditions (eg, asthma) in children.[3] To date, effective interventions to prevent postpartum smoking relapse are lacking.

Many postpartum interventions are predominantly psychosocial, such as support groups,[4] telephone sessions,[5] and web-based interventions.[6,7] Others are based on financial incentives[8–10] and nicotine replacement therapy.[11–13] While some of these interventions have improved cessation during pregnancy, they lack effectiveness for the prevention of postpartum relapse.

There is growing evidence suggesting sex hormones may play an important role in drug abuse behavior. This is strongly supported by preclinical work[14,15] but clinical studies are mixed.[16–20] In pregnancy, progesterone increases by more than 10 fold and certain estrogen levels increase by up to 1000 fold, then within the first few hours postpartum levels drop to near pre pregnancy levels.[21] Sex hormone levels remain low until women begin naturally cycling and sex hormones become more balanced.[22] The precipitous drop in progesterone, which is thought to be protective against drug abuse behavior, may play an important role in postpartum relapse. Unfortunately, few studies have explored the potential role of progesterone during this time. Therefore, this pilot double-blind placebo-controlled randomized trial evaluated the safety and feasibility of administering exogenous progesterone (PRO) compared to placebo (PBO) in the postpartum period for smoking relapse prevention. The specific aims were to (1) determine feasibility (compliance and acceptability) with study procedures and the safety of administering progesterone in the postpartum period (adverse events, depressive symptoms and breastfeeding) and (2) collect preliminary information on the role of progesterone (exogenous delivery and serum levels) on postpartum smoking relapse. We hypothesized there would be no significant differences between participants randomized to PRO versus PBO in terms of compliance and acceptability, as well as adverse events, depressive symptoms or breastfeeding. Although this pilot study was not fully powered to detect significant differences in smoking outcome, we also expected to see higher rates of smoking relapse at 4 and 12 weeks postpartum in PBO group compared to the PRO group. Finally, we expected that, regardless of randomization, women who relapse to smoking would have on average a lower level of serum progesterone.

Methods

This study was approved by the University of Minnesota's Institutional Review Board before any procedures completed.

Participants

Recruitment occurred between June 2013 to February 2015 in Minneapolis/St Paul, Minnesota. Recruitment consisted of presentations at OB/GYN clinics, flyers and advertising on social media. Eligibility included: women 18–35 years old; stable physical/mental health; uncomplicated, single gestational pregnancy with established prenatal care; a signed letter from their OB physician confirming no pregnancy-related complications (ie, gestational diabetes, fetal growth restriction, pregnancy hypertension, history of ≥3 miscarriages, known congenital anomaly); self-report of no smoking for 4 weeks prior to study enrollment (at 32–35 weeks gestation), confirmed with carbon monoxide (CO) < 5 ppm[23]; previous history of five cigarettes per day (CPD) for at least 6 of the past 12 months; motivated to remain abstinent after delivery (≥7 on 10-point Likert-type scale); willing to use nonhormonal birth control during the postpartum follow-up period of the study; English fluency; and ability to provide informed consent. Ineligibility items included: self-reported use of illicit drugs, nicotine replacement therapy, smoking cessation medications, or medications contraindicated to progesterone use (ie, drugs that may inhibit CYP3A4 functioning); contraindications to progesterone treatment (ie, history of thrombophlebitis, deep vein thrombosis, pulmonary embolus, clotting/bleeding disorders, stroke, heart disease, diabetes, liver dysfunction or disease, or an allergy to peanuts (progesterone capsules contain peanut oil).

Procedures

Participants were assessed via phone then invited to a screening visit between 32–35 weeks gestation where informed consent was obtained. Once enrolled, participants attended a baseline visit at 36 weeks gestation and completed several questionnaires, provided a blood sample for hormone measurement (progesterone), had their vital signs assessed (height, weight, blood pressure, heart rate) and were trained on Electronic Data Capture (EDC).

Between 36 weeks gestation and delivery, participants completed EDC daily using either their own or a study-supplied smartphone. Participants were prompted once daily to complete a short assessment at random times between 8 AM and 10 PM. Assessment items included daily Subjective State Scale[24,25] for measurement of positive and negative affect, weekly Edinburgh Postnatal Depression Scale[26,27] for assessment of depressive symptoms, and in the event of a smoking "slip," the modified Cigarette Evaluation Questionnaire[28] measuring the degree to which subjects experienced the reinforcing effects of smoking (results of the Subjective State Scale and modified Cigarette Evaluation Questionnaire analyses are forthcoming). Weekly phone calls were made to troubleshoot issues, further collect data regarding smoking status and offer brief relapse prevention counseling. Participants also used EDC to alert staff when they went into labor, delivered the baby and completed postpartum daily breastfeeding and vaginal bleeding logs.

At 4 days postpartum (week 0), participants were randomized (1:1) to either oral micronized progesterone (200 mg twice daily) or placebo. This visit occurred in their homes, at the research clinic or a location of their choice. At this visit, participants completed questionnaires; provided a blood sample for progesterone and cotinine; did breath CO measurement, had vital signs assessed, were given study medication and instructed to start medication that evening at 8 PM. Participants were instructed to take the medication at 8 AM and 8 PM for the next 4 weeks. Four days postpartum was chosen since breast milk is established by that time.[29] Administering progesterone too early can inhibit prolactin and thereby affect breast milk production.[30] The readiness to start medication was assessed with a self-report breastfeeding questionnaire.[31] If the participant reported delayed onset of lactation the medication start date was postponed. If a participant reported no plans of breastfeeding, the assessment was waived and medication was started on day 4 per protocol.

Over the next 12 weeks, participants were seen at the research clinic four times (weeks 2, 4, 8, and 12). At each visit, participants

completed the Edinburgh Postnatal Depression Scale,[26] blood samples (progesterone, cotinine) were drawn, breath CO measurement and vital signs were taken, adverse events assessed with a change in general health question including the Columbia-Suicide Severity Rating Scale,[32] smoking status (Timeline Followback),[33,34] medication compliance (pill count), and a brief (15 minute) relapse prevention counseling session (or cessation counseling if indicated). For the nonclinic week visits (weeks 1, 3, 5, 6, 7, 9, 10, and 11), phone calls were made by study staff to check on EDC progress, troubleshoot EDC issues, collect data regarding smoking status, assess adverse events and offer brief relapse prevention or cessation counseling.

Participants were compensated at each clinic visit in cash plus a $30 gift card to Target or a gift bag for themselves or baby. Gift bags included baby items (weeks 0, 4, and 12) or spa-like gifts for the mother (baseline, weeks 2 and 8). Participants were paid $10 cash for each clinic visit, $1 for each completed EDC, $5 for each weekly phone call with study staff and a cash bonus ($300) upon study completion. Thus, maximum compensation was $782.

Study Medication

Participants were randomized to receive either active (200 mg twice a day) or placebo progesterone. The active medication was micronized progesterone capsules manufactured by Teva Pharmaceuticals. It is synthesized from a plant source and chemically identical to progesterone of human ovarian origin. The drug was purchased through Investigational Drug Services at the University of Minnesota, Fairview Medical Center and encapsulated along with an identical placebo. After oral administration, 50%–60% of micronized progesterone is absorbed; it is metabolized by the liver to several steroids. The elimination half-life is 3–4 hours. The study dose (200 mg of oral micronized progesterone) provides serum concentrations comparable to the luteal phase of the menstrual cycle (3–25 ng/ml).[35,36] Common side effects include fatigue, nausea, breast tenderness, spotting, and weight gain.[37]

Measures

Study data were collected in several ways. First, data from clinic visits (CO, vitals, Timeline Followback, adverse events, pill counts, and study questionnaires) were managed using Research Electronic Data Capture (a secure, web-based application for research studies).[38] Next, blood samples at clinic visits were collected using standard venipuncture technique and preparation. Frozen samples were transported to internal labs for the analysis of progesterone and cotinine. Progesterone was analyzed using a solid phase enzyme-linked immunosorbent assay (ELISA) based on the principle of competitive binding. The assay sensitivity is 0.045 ng/ml with a standard range of 0–40 ng/ml.[39] Cotinine was analyzed by liquid chromatography tandem mass spectrometry. The limit of quantitation for these analyses was 0.4 ng/ml, and the coefficient of variation 6%.[40] Finally, daily data collection at home (EPDS, vaginal bleeding and breastfeeding) was done using EDC.

Baseline Characteristics

The following measures were collected at the Screening Visit: demographics (ie, age, parity, race), previous smoking behavior (CPD, number of previous quit attempts) and environmental exposure to smoking (ie, partner smoking).

Feasibility

Feasibility was defined by compliance and acceptability. Specifically, compliance was measured as the number of visits attended (maximum of five), number of medication pills taken (maximum of 56) and number of EDCs completed (maximum of 84). Acceptability was measured with a nine-item study satisfaction questionnaire where each item was measured via a four-point Likert-type scale (with higher scores indicating higher acceptability). This questionnaire, done at each clinic visit, assessed study protocol, study medication, collateral factors, and EDCs.

Safety

Adverse events were assessed weekly at clinic visits or through phone calls with a single open-ended question about changes in general health. If a participant experienced an adverse event that was "possibly" or "definitely" related to the study medication, this was discussed with the medical personnel and appropriate action was taken (medication decreased/stopped or mental health referral). Participants were encouraged to contact study staff if they experienced any serious medical problems between assessments.

Depression

Depression screening was done with the Edinburgh Postnatal Depression Scale.[26] This 10-item instrument is commonly used to screen for postpartum depressive symptoms but is not diagnostic. It has also been validated for prepartum use.[27] This item was completed weekly via EDC from 36 weeks gestation through 12 weeks postpartum, and at each clinic visit using Research Electronic Data Capture. In addition, the Columbia-Suicide Severity Rating Scale[32] was administered weekly (phone or study staff) since depression was a side effect of progesterone.

Breastfeeding and Vaginal Bleeding

Breastfeeding was initially assessed using the Breastfeeding Assessment Form[31] completed by staff at the week 0 visit. Study drug was delayed if breast milk was not yet established. Participants continued to record breastfeeding status daily using EDC. Vaginal bleeding was reported daily by participants via EDC.

Smoking Status

Smoking status or abstinence was confirmed by breath CO measurements (CO < 5 ppm indicating abstinence)[23] serum cotinine (<4.47 ng/ml indicating abstinence)[41] analysis and self-report via the Timeline Followback procedure[33,34] at each clinic visit. Cotinine levels for weeks 0, 4, and 12 were analyzed. Smokers were considered to have relapsed if: (1) they smoked a single puff or more of a lit cigarette anytime after randomization (defined as no longer achieving continuous abstinence [CA]) (2) if they had a single puff or more of a lit cigarette during 7 days prior to a specific time point (defined as no longer achieving 7-day point prevalence abstinence [PP]) or (3) if they had seven consecutive slips without a 24-hour period between any slip (defined as no longer achieving prolonged abstinence).[42] For CA and prolonged abstinence relapse days can range from 0 (smoking on randomization date) to 84 days (not smoking at the end of the study). If participants did have a single puff or more from a lit cigarette, they were instructed to immediately initiate an EDC to capture the event.

Analysis

Descriptive statistics (means and standard deviations for continuous variables and totals/percentages for categorical variables) were used to summarize demographics by randomization group. Feasibility and

relapse outcomes were compared between groups. Two group *t* tests were used to compare continuous variables or outcomes (compliance and acceptability at weeks 4 and 12) between groups. Fisher's exact tests were used to compare categorical variables or outcomes (PP at weeks 4 and 12) between groups. CA was compared between groups using a log-rank test (participants without a relapse prior to 84 days were censored). A two group *t* test was used to compare week 0 EPDS scores between groups and a paired *t* test was used to assess change in EPDS scores from week 0 to week 12. For EPDS scores, a group by time interaction was examined using a linear model with a random subject effect. The associations between baseline demographics and characteristics (listed in Table 1) and outcomes were explored using simple logistic regression (for PP) or simple linear regression (for compliance and acceptability). Associations between outcomes and serum progesterone were assessed with logistic regression (PP) or Cox's regression (CA). All randomized participants were included in the analysis, however, one participant's serum cotinine (>4.47 ng/ml) indicated current smoking at week 0. Thus, she was excluded as smoking relapse had occurred prior to the delivery of the study intervention, in only the modified intent-to-treat analysis.[41] SAS V9.3[43] was used for the analysis. *p* Values less than .05 were considered statistically significant. There were no adjustments for multiple comparisons in this pilot study.

Results

Baseline Characteristics

A total of 134 pregnant women were initially assessed for eligibility by phone. Of those, 83 (62%) were not interested or ineligible (smoking <5 CPD prior to quitting, pregnancy complications or unwilling to use nonhormonal birth control for the study duration). Our target *N* was 40 randomized postpartum women. A total of 51 pregnant women were enrolled between 32–35 weeks gestation. Of the 51 enrolled during pregnancy, five women (10%) were either lost to follow-up or withdrew participation and were labeled "dropouts." The remaining 46 delivered live babies and were randomized. Participants who were lost to follow-up or withdrew participation after randomization were labeled "incompleters" (Figure 1).

Overall, participants (*n* = 46) were 26.5 (±5.2) years of age, mostly non-Hispanic white (62%), with at least some college education (83%). They smoked a mean of 10.1 (±4.5) CPD prior to quitting, reported a mean of 17.4 (±2.6) years of age when they became a regular smoker, a mean of 4.3 (±4.8) quit attempts throughout their lifetime and a median of 180 days for their longest quit attempt. No differences were observed by randomization (Table 1).

Feasibility

Retention

Study retention after randomization was 87% (40/46) at 12 weeks. This did not differ by randomization (PRO 21/24 and PBO 19/22). Incompleters represented 13% (6/46) and there was no difference by randomization (*p* = 1.00). Participants cited the following reasons for not completing the protocol: wanting to start hormonal birth control prior to completing the study (*n* = 3), clinic visits with a new baby were too burdensome (*n* = 2) and concerns regarding milk production and vaginal bleeding (*n* = 1).

Table 1. Demographics and Baseline Characteristics (*N* = 46)

Variable	Total	Progesterone *n* = 24	Placebo *n* = 22	*p*[a]
Age, mean (*SD*)	26.5 (5.2)	26.2 (5.5)	26.7 (5.0)	.7403
Non-Hispanic, *n* (%)	42 (91)	21 (88)	21 (95)	.6093
Race, *n* (%)				
White	28 (62)	14 (61)	14 (64)	1.0000
Black	12 (27)	6 (26)	6 (27)	
Native American	2 (4)	1 (4)	1 (5)	
>1 race	3 (7)	2 (9)	1 (5)	
		1 missing		
Education, *n* (%)				.6702
Graduate	1 (2)	1 (4)	0	
College graduate or higher	7 (15)	2 (8)	5 (23)	
Some college	30 (65)	17 (71)	13 (59)	
High school	6 (13)	3 (13)	3 (14)	
<High school	2 (4)	1 (4)	1 (5)	
Marital status, *n* (%)				.3785
Never married	30 (65)	17 (71)	13 (59)	
Married	9 (20)	3 (13)	6 (27)	
Divorced	6 (13)	4 (17)	2 (9)	
Remarried	1 (2)	0	1 (5)	
Smoker in household, *n* (%)	21 (46)	10 (42)	11 (50)	.7675
CPD, mean (*SD*)	10.1 (4.5)	10.1 (4.7)	10.0 (4.4)	.9776
Age regular smoker, mean (*SD*)	17.4 (2.6)	17.7 (2.8)	17.0 (2.4)	.3472
Quit attempts, mean (*SD*)	4.3 (4.8)	4.1 (3.1)	4.6 (6.2)	.7101
Longest quit in days, median (IQR)	180 (30–300)	120 (21–365)	195 (90–270)	.6805
Weight concern scale, mean (*SD*)	2.7 (1.2)	2.5 (1.0)	2.9 (1.4)	.3888
Week 0 Progesterone ng/ml	0.82 (0.52)	0.71 (0.40)	0.97 (0.66)	.1925
# of Pregnancies	2.11 (1.30)	2.25 (1.45)	1.95 (1.13)	.4487
# of Children	0.67 (0.90)	0.88 (1.08)	0.45 (0.60)	.1060

CPD = cigarettes per day; IQR = interquartile range.

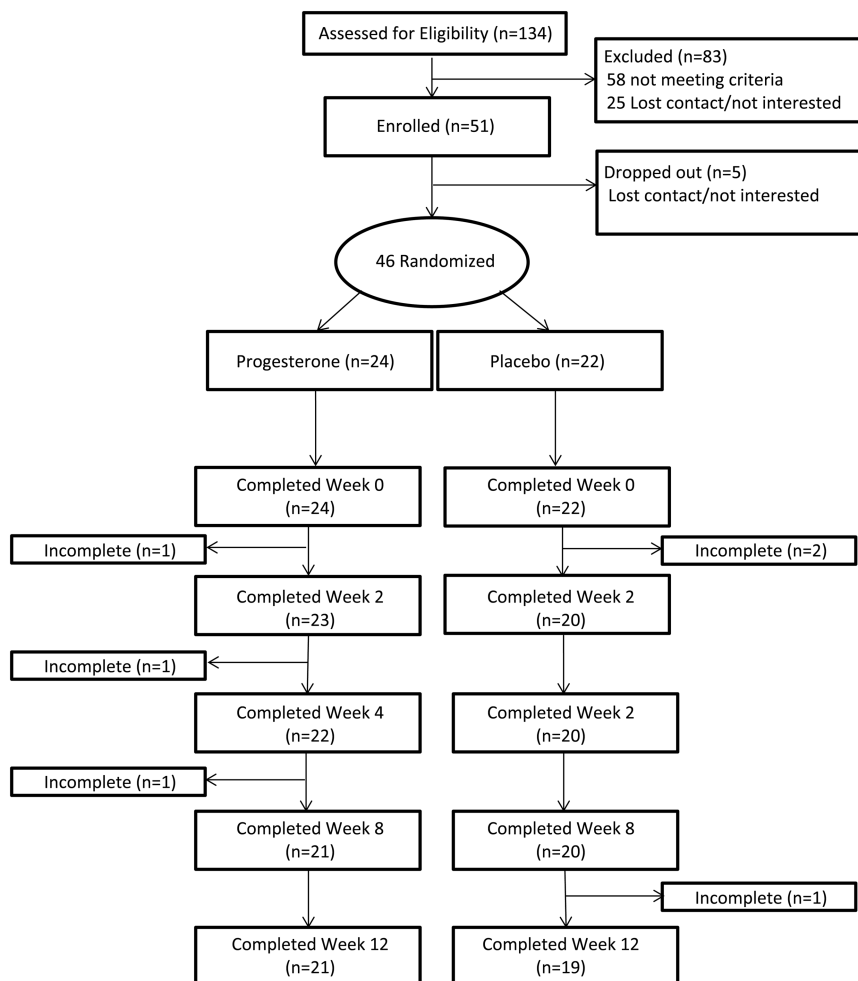[a]Two group *t* test or Fisher's Exact tests

Figure 1. CONSORT diagram.

Compliance

Results indicated number of clinic visits, pill counts and EDC's completed did not differ by randomization. Adherence rate of medication was 68% (Table 2). The mean (*SD*) progesterone levels at week 2 for the PRO and PBO groups were 12.72 ng/ml (21.01) and 0.21 ng/ml (0.33), respectively; *p* = .0217. However, progesterone levels in 33% (6/18) of participants in PRO were lower than 1.0 at week 2. The majority of participants 72% (33/46) began study medication per protocol on day 4 postpartum. Subsequently, 27% (12/46) were delayed starting medication due to nursing or scheduling issues and one participant refused medication due to breastfeeding complications but remained in the study (1/46).

Acceptability

There were no differences in the acceptability scores by randomization (PRO: 3.6 ± 0.3 vs. PBO: 3.5 ± 0.3; *p* = .22). Higher acceptability was associated with older age at which they became a regular smoker (*r* = 0.55; *p* = .0005) and with having more children (*r* = 0.30; *p* = .0659).

Safety

Adverse Events

No adverse events were determined "definitely related" to study drug. Medication was not reduced for any participant. Two participants (4%) reported adverse events that were "possibly related." These included dizziness (*n* = 1) and depressed mood with anxiety (*n* = 1). One serious adverse event, not related to study participation, was reported in the PBO group (hospitalization for a postpartum infection). During the 4 weeks of treatment, 22% (10/46) participants reported daily vaginal bleeding: three PRO (with all three breastfeeding) and seven PBO (with only six breastfeeding).

Depression

At week 0, depressive symptoms scores were similar in the two randomization groups (PRO: 5.6 ± 3.8 vs. PBO: 7.3 ± 4.4, respectively; *p* = .17). Regardless of randomization, depressive symptoms scores significantly decreased by −2.4 (±3.8) from week 0 to week 12 (*p* = .0023). A group by time interaction was not significant (*p* = .88). No participants endorsed suicidal ideation during the study.

Breastfeeding

The initiation of study medication was delayed by up to 6 days for 11 participants due to low milk supply or other breastfeeding complications. One additional woman was delayed 13 days for similar reasons. Number of days reported to last breastfeeding were similar (PRO 51 ± 35; PBO 54 ± 35, *p* = .83).

Table 2. Feasibility of Study Protocol (*N* = 46)

	Total	Progesterone *n* = 24	Placebo *n* = 22	*p*[c]
Compliance (mean ± *SD*)				
Number of postpartum visits attended (range: 0–5)	4.5 (1.1)	4.5 (1.1)	4.4 (1.2)	.5990
Doses of medication taken (range: 0–56)	38.2 (20.3)	38.9 (22.3)	37.5 (18.3)	.8154
EDCs completed (range: 0–84)	61.3 (22.7)	60.9 (21.8)	61.8 (24.3)	.9002
Acceptability (mean ± *SD*)				
Acceptability score[a] at week 4, *n* = 38	3.6 (0.3)	3.6 (0.3)	3.5 (0.3)	.2205
Acceptability score[a] at week 12, *n* = 39	3.5 (0.3)	3.6 (0.3)	3.5 (0.4)	.1354
Individual questions[b] *n* (%)				
1. How willing would you be to participate in a study like this again?	37 (80.4)	20 (83.3)	17 (77.3)	
2. Overall, how much of a burden was it to participate in this study?	6 (13.0)	2 (8.3)	4 (18.2)	
3. Overall, how much did participating in this study interfere with your usual activities?	1 (2.2)	0	1 (4.5)	
4. How difficult was it to use the cell phone to complete the study questionnaires?	1 (2.2)	1 (4.2)	1 (4.5)	
5. Overall, how much were you annoyed with the number of times the cell phone beeped during the day?	1 (2.2)	0	1 (4.5)	
6. How difficult was it to take the study-supplied medication?	6 (13.0)	2 (8.3)	4 (18.2)	
7. How difficult was it to notify the study staff of your child's birth?	3 (6.5)	2 (8.3)	1 (4.5)	
8. Overall, how much do you think this study has helped you stay smoke-free after your baby was born?	32 (69.6)	20 (83.3)	12 (54.5)	
9. Overall, how difficult was it to work with study staff?	0 (0)	0 (0)	0 (0)	

EDC = electronic data capture.

[a]Defined as the average of nine questions (1 and 8 reversed). Scores range between 1–4 with 1 = low acceptability and 4 = high acceptability.

[b]Responses of "moderately" or "extremely" on week 12 satisfaction survey.

[c]Two group *t* test.

Table 3. Summary of Postpartum Smoking Relapse by Point Prevalence

Outcome	Total	Progesterone *n* = 24	Placebo *n* = 22	*p*[a]
PP abstinent at 4 weeks, *n* (%)				
ITT				.7462
Yes	33 (71.7)	18 (75.0)	15 (68.2)	
No	13 (28.3)	6 (25.0)	7 (31.8)	
Modified ITT[b]				1.0000
Yes	33 (73.3)	18 (75.0)	15 (71.4)	
No	12 (26.7)	6 (25.0)	6 (28.6)	
PP abstinent at 12 weeks, *n* (%)				
ITT				.3945
Yes	22 (47.8)	13 (54.2)	9 (40.9)	
No	24 (52.2)	11 (45.8)	13 (59.1)	
Modified ITT[b]				.5544
Yes	22 (48.9)	13 (54.2)	9 (42.9)	
No	23 (51.1)	11 (45.8)	12 (57.1)	

ITT = Intent to treat; PP abstinence = 7-day point prevalence (a single puff or more of a lit cigarette during the 7 days prior to a specific time point is defined as relapse).

[a]Fisher's exact test.

[b]One participant excluded due to smoking at week 0.

Progesterone Association With Relapse

Postpartum Smoking Relapse

Based on point prevalence, 71.7% (33/46) of participants remained abstinent at week 4, with 75.0% (18/24) PRO and 68.2% (15/22) PBO (*p* = .75). At week 12, 47.8% (22/46) of participants were still abstinent: 54.2% (13/24) PRO and 40.9% (9/22) PBO (*p* = .39; Table 3). Based on CA, the median days to relapse was 81 (PRO: 81 days, PBO: 65 days; *p* = .95). Of those who relapsed prior to 4 weeks and 12 weeks,

the mean days to relapse were 13.6 ± 7.5 days (PRO: 13.4 ± 7.0 days; PBO: 13.8 ± 8.4 days) and 30.0 ± 25.6 days (PRO: 34.2 ± 27.7 days; PBO: 25.2 ± 23.2 days), respectively. Similar results were found using prolonged abstinence whereas 85% had not relapsed prior to week 12 and there were no differences by randomization (*p* = .067). CPD, age became a regular smoker, smoker in household, number of quit attempts and longest quit attempts were not found to be statistically significantly associated with relapse at weeks 4 and 12.

Association of Serum Progesterone Levels and Postpartum Smoking Relapse

Serum progesterone level was not associated with PP at week 4 (*OR* = 1.00, 95% confidence interval [CI] = 0.95–1.04, *p* = .85) or at week 12 (*OR* = 1.03, 95% CI = 0.97–1.09, *p* = .41). Progesterone level was also not associated with time to first slip (hazard ratio = 1.00, 95% CI = 0.98–1.02, *p* = .89). For the PRO group (with levels greater than 1.0 at week 2 indicating medication compliance) and for the PBO group, the change in progesterone from baseline to week 2 was not associated with relapse as measured by PP.

Discussion

This double-blind randomized controlled pilot study was designed to determine feasibility of administering exogenous progesterone to women in the immediate postpartum period as a relapse prevention strategy. Given the preclinical[14,15] and clinical literature[16–20] which supports the role of progesterone as attenuating addictive behavior and given the erratic change of gonadal hormones in the postpartum period we hypothesized that administering exogenous progesterone to postpartum women could potentially prevent postpartum relapse. Our observations indicate that there was moderate to high compliance and high acceptability of administering exogenous progesterone to women in the immediate postpartum period. These observations

did not differ by randomization. Further, while this study was not powered to assess progesterone effects on quit outcomes, women randomized to the active progesterone group had a higher prevalence of abstinence at 4 weeks postpartum.

Overall, participants were highly compliant with this protocol regardless of randomization. Clinic visit attendance (>80%) was comparable to previous clinical trials including postpartum studies.[44–46] Study retention (87%) was also comparable to previous cessation studies for addiction.[44,47–50] Number of pills taken (69%) or adherence rate to study medication was moderate compared to previous pharmacological clinical trials.[45,46,51] Of note, 33% of the progesterone group at week 2 had low progesterone blood levels suggesting missing pills. Possible reasons include the burden of twice daily dosing or busy with their newborn. This lower adherence rate could contribute to lack of differences in abstinence between randomized groups. This could be improved by novel reminders of dosing or alternate methods of progesterone delivery. Abstinent rates at end of treatment for progesterone versus placebo (75% vs. 68%) and end of study (54% vs. 41%) respectively, were comparable for treatment groups in other pharmaceutical cessation trials for addiction in the general population. For example, in a study comparing varenicline and placebo abstinence rates at 12 weeks were 50% versus 12%, respectively[45] and in a comparison of bupropion versus placebo abstinence rates were 29% versus 19%, respectively at 7 weeks.[52] A third study compared varenicline plus nicotine replacement therapy (patch) to placebo and observed abstinence rates of 55% versus 41% at 12 weeks.[53] One must keep in mind that even though our placebo group had higher abstinence rates this is a limited comparison given the different populations. Our participants were postpartum and other factors could play a role such as new mothers and more concern about passive smoke and influence of breastfeeding. Although the reasoning behind breastfeeding supporting substance abstinence is not completely understood, some hypotheses include more maternal bonding and personal investment in baby's health, or more time spent with baby equals less time spent smoking.[54] Breastfeeding has been highly associated with postpartum cigarette abstinence and duration of breastfeeding is proven to positively correlate with duration of smoking abstinence.[55,56] This warrants further study.

Progesterone was well tolerated by participants. Serum levels of progesterone were comparable to previous studies administering similar doses (200 mg twice daily) of exogenous progesterone.[57] No participants required alteration of dosage. Daily vaginal bleeding was reported in 22% of participants, regardless of randomization, or breastfeeding status and is a common occurrence with progesterone treatment. Drug was not discontinued for any participant because of side effects compared to a large randomized 12-week cessation trial, where study drug was discontinued due to adverse events: for varenicline (8.6%) for bupropion Sustained Release (15.2%) and for placebo (9.0%).[45]

The pharmaceutical literature indicates that depressive symptoms and lactation problems may be side effects of progesterone administration.[37] Given we were administering a safe but high dose of progesterone, there were concerns that participants may experience these adverse effects, but none developed. In the United States, 41% of women report exclusive breastfeeding at 3 months, 19% at 6 months with 79% of women reporting have ever-breastfed.[58] Participants who breastfed in this study at 12 weeks were comparable: 42% for PRO and 50% for PBO with 66% reporting progesterone had no effect on breastfeeding and were not delayed in starting study medication. Further, progesterone did not negatively affect breastfeeding once milk was established. Interestingly participants experienced decreased depressive symptoms over the 12 weeks regardless of randomization. Exogenous progesterone effect on postpartum depressive symptoms seemed minimal and consistent with other studies.[36,44] However, our study sample was not depressed. In fact, our study sample reported less depressive symptoms than in the general population of women (18.5%)[59] and during the postpartum period (7%–13%).[60] Therefore, future research should explore how progesterone may alter postpartum smoking behavior in women who are at high risk of developing depressive symptoms as they may receive additional benefit from progesterone treatment.

Finally, participants indicated high levels of acceptability for this study protocol at both week 4 (end of treatment) and at week 12 (end of study) regardless of randomization. Most (70%) felt that this study helped them stay smoke free and the majority (80%) indicated they would be willing to participate in the study again. Few (6/46; 13%) participants reported that it was a burden to participate.

A large proportion of participants in this trial remained abstinent during follow-up; 71.1% at week 4 (75.0% in PRO and 68.2% in PBO) and 47.8% at week 12 (54.2% in PRO and 40.9% in PBO). Though not statistically significantly, the PRO group had a higher prevalence of abstinence. While the current project was a feasibility study and not powered to determine a statistically significant difference, if our observations are valid, a sample size of 231 per group would be needed to detect this difference at 80% power.

Although this project has several strengths (randomized double-blind control trial design, use of EDC), it does have some limitations. First, while consistent with the goals of assessing feasibility and collecting preliminary data, this study included a small homogenous sample. Thus, we are not able to fully assess the effect of progesterone on postpartum smoking relapse nor can we generalize our observations to the general population. Second, low levels of serum progesterone in the progesterone group at week 2 suggests participants were missing pills, limiting the potential effect of progesterone. Further, because there is considerable inter-subject variability in the absorption of oral progesterone,[36] non-oral administration may provide a more stable dose from participant to participant and should be considered in future work. Third, history of depression, a strong predictor of postpartum smoking relapse, was not assessed. Future work should assess both a history of depression in the past, as well as postpartum depression, as both limit the likelihood of maintaining abstinence.[61–63] Thus, these observations are limited. Future work should consider focusing on women who are at high risk for postpartum relapse due to a history of depression, and/or not breastfeeding.

In summary, postpartum relapse is a major public health problem that may be related to the erratic fluctuation of hormones. Given the encouraging literature, pre-clinical and clinical, regarding progesterone and its dampening effect on addictive behavior, the potential therapeutic value of exogenous progesterone in a larger clinical trial is important. Given the acceptable and feasible results of this study, a fully powered trial to explore the effect of exogenous progesterone on postpartum smoking relapse is warranted.

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Declaration of Interests

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