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Progesterone for smoking relapse prevention following delivery: A pilot, randomized, double-blind study

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ABSTRACT

Introduction: Close to half of women who were smokers prior to conception quit smoking in pregnancy, when endogenous progesterone levels are high. However, at least half resume pre-pregnancy smoking levels within weeks after delivery and when progesterone levels drop. The current pilot study tested the feasibility and preliminary efficacy of postpartum progesterone replacement in preventing relapse to smoking in postpartum women with a history of pre-pregnancy smoking.

Methods: This was an 8-week, double-blind, parallel, randomized, placebo-controlled pilot trial of 41 women with a history of pre-pregnancy smoking who achieved abstinence by 32 weeks of gestation. Immediately following delivery women were randomized to oral micronized progesterone (200 mg twice daily) or placebo via computerized urn randomization program. The main outcome measures were descriptions of study feasibility: recruitment and retention. Secondary outcomes were 7-day point prevalence of abstinence at week 8, time to relapse and smoking cravings.

Results: The trial was feasible with adequate randomization, 64% (41/64) of eligible women, and trial retention, 78% (32/41) completed the trial. Women taking progesterone were 1.8 times more likely to be abstinent during week 8 and took longer to relapse (10 vs. 4 weeks) compared to the placebo group, although these differences did not reach statistical significance. After adjusting for age and pre-quit smoking level, the number needed to treat was 7. There was a 10% greater decline per week in craving ratings in the progesterone group compared to placebo ($\beta = -0.10$, 95% CI: -0.15, -0.04, $p < 0.01$). No serious adverse events occurred during the trial.

Conclusions: These preliminary findings support the promise of progesterone treatment in postpartum smokers and could constitute a therapeutic breakthrough.If these preliminary findings can be evaluated and replicated in a larger study with sufficient power, this may constitute an acceptable and safe smoking relapse prevention strategy for use during lactation.

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 (200–400 nM), when they are nearly

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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 α4β2 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, 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 18–42 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); 5) had a known allergy to progesterone or peanut oil (vehicle for micronized progesterone); 6) currently undergoing treatment with another pharmacological agent for smoking cessation; 7) did not speak English; 8) had plans to move out of the area within 8 months after study screening; 9) lacked capacity to understand the study or provide informed consent; 10) were incarcerated or pending incarceration; 11) were unwilling to accept randomization; 12) were hospitalized or pending hospitalization; or 13) had subsequent pregnancy since this would be another source of progesterone; 14) 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) 18–25 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