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Menstrual cycle in women who co-use marijuana and tobacco

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Abstract

Objectives—Marijuana is the most commonly used illicit drug in the United States and co-use with tobacco is increasing. Preliminary studies have indicated that marijuana may suppress luteinizing hormone (LH) or shorten the luteal phase. Although the literature is mixed, these sex hormones may play a role in smoking cessation outcomes. This secondary subgroup analysis aims to explore the menstrual cycle of females who co-use marijuana and tobacco compared to females who only use tobacco in a sample of tobacco treatment-seeking individuals.

Methods—Female participants, aged 18-50 who self-reported regular menstrual cycles and co-use of marijuana and tobacco were matched 1:3 by age to participants who only use tobacco. Length of the follicular and luteal phases were determined using First Response Urine LH tests. Wilcoxon two-sample T-tests were used to determine differences in phase lengths between groups.

Results—Thirteen women who co-use marijuana and tobacco and 39 women who only use tobacco were included in this analysis. Overall, participants were 37.3 ± 8.0 (SD) years of age, mostly Caucasian (67%) and smoked 12.6 ± 5.2 (SD) cigarettes per day. The luteal phase length among participants who co-use marijuana and tobacco (11.4 days ± 2.2 [SD]) was significantly shorter than among participants who only use tobacco (16.8 days ± 11.3 [SD]; $p=0.002$). No differences were found in follicular phase length or menstrual cycle length.

Conclusions—These data suggest that females who co-use marijuana and tobacco may have a shortened luteal phase in comparison to females who only use tobacco. Further studies are needed to better understand how marijuana use may impact the menstrual cycle and affect smoking outcomes.

Keywords

Marijuana; Co-Use; Menstrual cycle; Sex hormones

Introduction

Marijuana is the most commonly used illicit drug in the United States (Azofeifa et al., 2016; Schauer et al., 2015). The prevalence of co-using marijuana and tobacco continues to increase and approximately 5% of US adults have indicated co-use in the past month

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(Schauer et al., 2015). The use of marijuana is expected to continue to rise as many states have legalized marijuana for medicinal or recreational use and more states are likely to follow suit in the coming years (Hall and Lynskey, 2016; Hall and Weier, 2015; Schauer et al., 2015). The public health consequences of this increased acceptability and use remain unclear among women.

The menstrual cycle is characterized by sex hormones and events signifying two main phases; the follicular phase and the luteal phase. The follicular phase begins with the onset of blood flow (menses). Estradiol rises for approximately 10 days followed by a surge in luteinizing hormone (LH) which stimulates ovulation. Ovulation occurs approximately halfway through the menstrual cycle and the onset of the luteal phase follows. The luteal phase is marked by a peak in progesterone and a secondary peak in estradiol (Strauss and Barbieri, 2013). The pre-clinical literature suggests that marijuana affects these sex hormones. In animal models, administration of cannabis has been shown to reduce LH levels (Chakravarty et al., 1975; Dalterio et al., 1983), as well as prevent LH surge in female rats (Ayalon et al., 1977; Dixit et al., 1975). However, unlike the animal models, clinical studies are less clear in the association of marijuana use and sex hormones. A small study of sixteen healthy females between the ages of 21 and 33 with regular menstrual cycles evaluated the immediate effects (within 180 minutes) of smoking a marijuana cigarette and LH levels. Among women in the luteal phase, smoking a 1-gram marijuana cigarette containing 1.8% THC resulted in a significant reduction in LH compared with those who smoked a 1-gram placebo cigarette. However, this study found that marijuana use had no effect on estradiol or progesterone levels in either the follicular or luteal phase (Mendelson et al., 1986). Another double-blind crossover study by the same investigator found that marijuana had no effect on the LH surge among ten healthy menopausal women (Mendelson et al., 1985). Alternatively, a larger and more recent study of 201 women enrolled in the North Carolina Pregnancy Study found that occasional marijuana use (up to three times in the previous 3 months) and frequent marijuana use (more than three times in the previous 3 months) was associated with a 3.5 and 2 day increase, respectively, in follicular phase length compared to participants who did not use marijuana (Jukic et al., 2007).

While the bio-behavioral basis for how sex hormones may affect tobacco cessation is still evolving, pre-clinical literature strongly suggests progesterone is protective against drug seeking behaviors whereas estrogen promotes drug abuse behaviors (Carroll and Anker, 2010; Donny et al., 2000; Lynch, 2009). The clinical literature, however, is less clear. Previous work, including our own, have shown more favorable smoking outcomes in the luteal phase (low estradiol/high progesterone) compared to the follicular phase (high estradiol/low progesterone) (Allen et al., 2008) and smokers reported better cognition and a diminished nicotine response in the luteal phase as compared to the follicular phase (DeVito et al., 2014). Also, increased progesterone has been shown to be protective against tobacco relapse (SS Allen et al., 2016; Saladin et al., 2012), whereas lower levels of progesterone have been shown to increase tobacco smoking behavior, including increased puff intensity, number of puffs, and weight of cigarettes (Schiller et al., 2012). Conversely, however, a more recent meta-analysis concluded there were no differences in smoking outcomes between the luteal phase and follicular phase (Weinberger et al., 2015). The reason for these seemingly conflicting results may be due to differences in methodology or a lack of

distinction between withdrawal symptoms and premenstrual symptoms (Carpenter et al., 2006). Untangling how marijuana use may impact the menstrual cycle and therefore affect smoking cessation remains unresolved.

The objective of this secondary subgroup analysis is to explore the menstrual cycle of premenopausal females who co-use marijuana and tobacco compared to females who only use tobacco in a sample of tobacco treatment-seeking individuals. We hypothesize that in participants who co-use marijuana and tobacco, the LH surge may more likely be suppressed and that the luteal phase will be shortened, ultimately affecting smoking behavior and cessation outcomes.

Methods

Parent Study

Data for this secondary subgroup analysis were obtained from an ongoing parent study (P50-DA033942; PI: Sharon Allen) at the University of Minnesota. All procedures were approved by the University of Minnesota Institutional Review Board and all participants provided informed consent. The parent study is a double-blind, placebo-controlled randomized clinical trial investigating sex differences in the effect of exogenous progesterone on impulsivity and smoking outcomes. Participants (males and females) who are interested in quitting are enrolled during ad libitum smoking. Females are enrolled during the follicular phase of the menstrual cycle (days 1 through 7 following the onset of menses) while males are enrolled at any time. Participants are then invited to attend a baseline visit where they are randomized to receive either 200mg twice a day of progesterone or placebo for 12 weeks. For females, this visit is scheduled during the luteal phase of the menstrual cycle (following an increase in luteinizing hormone (LH surge)). For males, this visit is scheduled approximately two weeks after the screening visit (see procedures section below for further details on female LH testing). After one week on study medication, participants are assigned a quit date and then followed for 12 weeks to assess relapse. This secondary subgroup analysis only includes data from female participants prior to randomization and were collected from December, 2012 through June, 2016. The parent study is still ongoing and main results are forthcoming.

Participants

Participants were female smokers aged 18 to 50 who were in stable physical/mental health, smoked 5 cigarettes per day for at least one year, were motivated to quit smoking cigarettes (7 on a Likert-type scale) and had self-reported regular menstrual cycles for the past three months (premenopausal). Marijuana use was assessed by self-reported current use at the time of screening using a yes or no response. Participants were excluded if they met DSM-IV criteria for psychotic disorders, bipolar, ADHD or MDD in the past 3 months, used nicotine replacement therapies or varenicline, other types of tobacco or nicotine, used illicit drugs other than marijuana, used hormonal contraceptives, were currently pregnant or breastfeeding or had any conditions contraindicated to the use of progesterone.

Since differences in menstrual cycle length may be confounded by age, participants who co-use marijuana and tobacco were matched to participants who only use tobacco based on age category. Three participants who only use tobacco per one participant who co-uses marijuana and tobacco were randomly selected and matched by age category (18 to <30; 30 to <40; and 40 to 50). Twenty-five percent of the total sample was comprised of participants who co-use marijuana and tobacco while 75% was comprised of participants who only use tobacco.

Procedures

In order to time a female's baseline and quit date during the luteal phase of the menstrual cycle, participants were provided with 10 First Response Ovulation tests (LH tests; Church & Dwight Co., Inc., Ewing, NJ) following successful completion of the screening visit. These tests are 99% accurate in detecting an LH surge in a laboratory setting (First Response Package Insert). Participants were asked to perform an LH test each morning using their first morning urine and to call study staff when they detected an LH surge (two dark lines on the testing stick). This was then recorded by study staff as the start of the luteal phase. If a participant was not able to detect an LH surge during the first month of testing, she was allowed to try again for up to two additional menstrual cycles before being disqualified due to no LH surge and dropped from the study. In order to determine when a participant should start performing the 10 LH tests, study staff took their average menstrual cycle length and asked them to begin approximately five days prior to anticipated ovulation. For instance, a participant with a 28-day cycle started LH testing on day 9 while a participant with a 36-day cycle started on day 18.

Measures

Demographics and smoking behavior were collected at the screening visit. Marijuana use was defined as self-reported current use (yes or no). No additional information was collected on frequency or quantity of marijuana use. Start of the follicular phase was defined as the first day of vaginal bleeding (AM Allen et al., 2016). Although ovulation occurs 24-36 hours after the LH surge (Strauss and Barbieri, 2013), without the use of sonography, identifying ovulation was not feasible in this study (AM Allen et al., 2016). Therefore, we used the LH surge to define the start of the luteal phase. Additionally, follicular phase length was defined as the number of days between the onset of menses and the date of LH surge. Luteal phase length was defined as the number of days between the LH surge and date of the onset of the following menses. Menstrual cycle length was defined as number of days between two sequential dates of onset of menses.

Analyses

Descriptive statistics were used to describe the demographics and smoking behavior of both groups. Fisher's exact test was used to compare categorical variables and Wilcoxon two-sample T-tests were used to compare numeric variables and outcomes between groups. P-values < 0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Participant Characteristics

Thirteen participants who co-use marijuana and tobacco were identified from the cohort of the parent study (n=99). Thirty-nine participants who only use tobacco were randomly selected (based on age matching) from the remaining cohort. Overall, participants were 37.3 ± 8.0 (SD) years of age, mostly Caucasian (67%) and smoked 12.6 ± 5.2 (SD) cigarettes per day. Nicotine dependence, based on the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991), was moderately low (FTND score = 4.1 ± 1.9 [SD]). No significant differences were found between groups (see Table 1).

Menstrual Cycle Phases

Follicular phase length, luteal phase length and menstrual cycle length were calculated for all participants. Compared to participants who only use tobacco, participants who co-use marijuana and tobacco had a shorter luteal phase $16.8 \text{ days} \pm 11.3$ (SD) vs. $11.4 \text{ days} \pm 2.2$ (SD), respectively, $p=0.002$. No other significant differences were found in follicular phase or total menstrual cycle length (see Table 2).

Luteinizing Hormone Surge (LH surge)

Participants were given up to three months to detect an LH surge. Three out of 13 participants who co-use marijuana and tobacco (n=3, 23%) were unable to detect an LH surge during the first month of testing. Two out of 39 participants who only use tobacco (n=2, 5%) were unable to detect an LH surge during the first month of testing. This trend, however, did not reach statistical significance ($p=0.09$).

Discussion

This study examined differences in menstrual cycle phase lengths of premenopausal female smokers who co-use marijuana and tobacco (n=13) and those who only use tobacco (n=39). These data indicate a shortened luteal phase in participants who co-use marijuana and tobacco. In fact, the luteal phase among participants who co-use marijuana and tobacco was 5.4 days shorter ($p=0.002$) than participants who only use tobacco. However, no difference was found in follicular phase length or menstrual cycle length. In addition, this study examined differences in luteinizing hormone surge (LH surge) between participants who co-use marijuana and tobacco and participants who only use tobacco. Interestingly, we found that three out of 13 participants who co-use marijuana and tobacco (n=3, 23%) were unable to detect an LH surge during the first month of testing while only two out of 39 participants who only use tobacco (n=2, 5%) weren't able to detect a surge during the first month of testing, however, this trend did not reach statistical significance.

Few studies, to date, have examined the effects of marijuana on the human menstrual cycle with most studies being conducted during the 1980s. An early study by Mendelson et al. using a double-blind, cross-over, within subject design found that among premenopausal women, acutely smoking a 1-gram marijuana cigarette during the luteal phase suppressed the luteinizing hormone blood level by 30% compared to placebo (Mendelson et al., 1986).

This study was well-controlled, using an inpatient setting and was carefully timed as to when participants were administered marijuana and when the blood samples were collected for LH analysis. Our study, in contrast, was a between subject design and did not account for timing and dosing of marijuana. This difference in methodology may provide context as to why we did not see a significant difference in suppression of LH surge between our two groups. A more recent study by Jukic et al. found that in a cohort of premenopausal women, occasional or frequent marijuana use was associated with a 2.75 day increase in follicular phase length compared to participants who did not use marijuana (Jukic et al., 2007). Our study, however, found that participants who co-use marijuana and tobacco had a shortened luteal phase compared to participants who only used tobacco. These conflicting results may also be due to differences in methodology. Jukic et al. estimated ovulation by assaying urine specimens for estrone 3-glucuronide (a metabolite of estrogen) and pregnanediol 3-glucuronide (a metabolite of progesterone) while we used LH tests. Further, all studies described in this manuscript, including ours, contain small sample sizes. This undoubtedly impacts the power of the study to detect differences between groups.

Also of great interest to the researchers is how marijuana use may impact a female's ability to quit using tobacco. Our previous work shows more favorable quit smoking outcomes in the luteal phase of the menstrual cycle (Allen et al., 2008) and since co-use of marijuana and tobacco may limit this time period, it may make quitting smoking more difficult. Further, prevalence of smoking among females has historically been shown to be lower compared to males and females have been shown to experience fewer successful cessation attempts (Perkins, 2001; Satcher et al., 2002), however, this sex difference has more recently been disputed (Jarvis et al., 2013). The use of marijuana among females may disproportionately affect their ability for successful smoking cessation and warrants further study. These findings may also be of clinical significance. A shortened luteal phase may result in the production of less progesterone which is essential to fertility. Women who produce inadequate progesterone may have difficulties getting pregnant and maintaining a healthy pregnancy (Blacker et al., 1997).

Although our study is strengthened by age matching the control group and by biochemically confirming LH surge, there are some limitations worth noting. First, marijuana use was defined as self-reported current use at the time of screening using a simple yes or no response. No data was collected on timing or frequency of marijuana use. Previous research has shown that frequency of use may affect the length of the follicular phase (Jukic et al., 2007) while acute exposure to marijuana may suppress LH levels (Mendelson et al., 1986). Additionally, our sample of participants who co-use marijuana and tobacco was small (n=13). A larger study would be better powered to detect differences in menstrual cycle length and follicular phases between participants who co-use marijuana and tobacco compared to participants who only use tobacco. Finally, although sex hormones (progesterone and estradiol) are being collected for the parent study, the hormone levels were not available for this analysis. Having actual hormone levels could better confirm menstrual cycle phase and reduce user error with the LH testing kits.

In conclusion, these data provide evidence that marijuana may affect the menstrual cycle, specifically, by shortening the luteal phase. Future studies should ascertain frequency,

timing, and dosage of marijuana in order to determine menstrual cycle differences between participants who co-use marijuana and tobacco and participants who only use tobacco. These observations may help to inform future, larger-scale studies in understanding the association between marijuana use and menstrual cycle in females who also use tobacco. Addressing this co-use during treatment may ultimately help female smokers to quit.

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Table 1
Demographics and Smoking Characteristics

	All Participants	Participants Who Co-Use Marijuana and Tobacco	Participants Who Only Use Tobacco	p-value
N (%)	52 (100)	13 (25)	39 (75)	
Age (years), mean (sd)	37.3 (8.0)	37.3 (9.3)	37.2 (7.6)	0.94
Race, N (%)				
Caucasian	35 (67)	9 (69)	26 (67)	1.00
African American	8 (15)	2 (15)	6 (15)	
Other	9 (17)	2 (15)	7 (18)	
Cigarettes per day, mean (sd)	12.6 (5.2)	12.6 (5.1)	12.6 (5.3)	0.92
FTND Score, mean (sd)	4.1 (1.9)	4.2 (2.4)	4.0 (1.8)	0.68
Quit Attempts, mean (sd)	5.0 (5.3)	4.2 (4.7)	5.2 (5.6)	0.46
Weight, mean (sd)	183.2 (48.1)	185.8 (51.2)	182.3 (47.7)	0.77

Table 2
Menstrual Cycle Phase Lengths

	Participants Who Co-Use Marijuana and Tobacco	Participants Who Only Use Tobacco	p-value
N	13	39	
Phase Lengths, mean (SD) [Min – Max]			
Follicular Phase Length (days) ^a	15.0 (5.1) [7 – 44]	14.7 (6.3) [1 – 22]	0.230
Luteal Phase Length (days) ^b	11.4 (2.2) [8 – 16]	16.8 (11.3) [3 – 70]	0.002
Total Menstrual Cycle Length (days) ^c	26.4 (5.7) [13 – 34]	31.5 (13.3) [20 – 85]	0.540

^aFollicular Phase Length: Number of days between the onset of menses and the date of LH surge

^bLuteal Phase Length Number of days between the date of LH surge and date of the onset of the following menses

^cTotal Menstrual Cycle Length: Number of days between two sequential dates of onset of menses.