Circadian patterns of ad libitum smoking by menstrual phase

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Abstract

Objective—Recent research suggests nicotine metabolism may be influenced by sex hormones. Thus, we hypothesized that circadian smoking patterns would vary by menstrual phase.

Methods—Healthy female smokers (n = 31) between the ages of 18 and 40 with regular menstrual cycles, and not using hormones or psychotropic medications, were recruited for a randomized clinical study. Subjects recorded the time of each cigarette smoked and their menstrual phase with daily diaries prospectively for one complete menstrual cycle of ad libitum smoking. Analyses included Poisson regression to assess variations in the rate of smoking during waking hours (i.e., 6:00 a.m. and 12:00 midnight) and circadian smoking patterns by menstrual phase.

Results—Participants were 29.61 ± 5.44 years of age and smoked 16.93 ± 5.37 cigarettes per day. Participants had a lower rate of smoking during waking hours in the follicular phase as compared to the menses phase. There were no significant menstrual phase differences in the circadian smoking patterns.

Conclusions—These results offer further support for the influence of sex hormones on smoking behavior, but not on circadian patterns of smoking. Additional research is needed to study the direct relationship between nicotine metabolism, sex hormones, menstrual phase, and smoking behavior.

Keywords
women; smoking; menstrual cycle; circadian patterns

INTRODUCTION

Research indicates female smokers may be more likely to relapse after an attempt at smoking cessation compared to men (Bjornson et al., 1995). Recent research has indicated that the menstrual cycle may play a role in undermining quit attempts (Carpenter et al., 2006; Franklin et al., 2004; Allen et al., 2008; Allen et al., 2009). Although the precise mechanism of this relationship remains unknown, it has been suggested that ovarian hormones alter nicotine metabolism. A recent study by Benowitz et al. (2006) indicated post-menopausal females and males had slower metabolism of nicotine compared to pre-menopausal females. Further, females using combined estrogen–progesterone contraceptive
pills had faster nicotine metabolism than females using progesterone-only contraceptives (Benowitz et al., 2006). These findings suggest that sex hormones may affect smoking behavior across the menstrual cycle. However, the clinical literature on this topic is mixed. A number of studies have observed no differences in cigarettes smoked per day by menstrual phase (Allen et al., 2009; Allen et al., 1996; Allen et al., 1999; Franklin et al., 2004), whereas other studies have noted an increase in cigarettes smoked per day during the luteal phase (Craig et al., 1992; Snively et al., 2000; Marks et al., 1994). All these studies are limited since their evaluation was on the total number of cigarettes smoked per 24 h day, without regard to the circadian patterns in which these cigarettes were smoked (e.g., the hourly rate of smoking over the 24 h day). Gender differences in smoking topography (Eissenberg et al., 1999; Perkins, 1999) have been identified, suggesting sex hormones may play a role in smoking behavior on a more refined level than absolute number of cigarettes smoked per day.

To our knowledge, the present report is the first to longitudinally investigate ad libitum circadian smoking patterns by menstrual phase using a within subject design. The current study aims are to: (1) assess circadian patterns of smoking for the four menstrual phases: menses (M), follicular (F), luteal (L), and late luteal (LL), and (2) investigate the rate of smoking during waking hours (i.e., 6:00 a.m. to 12 midnight) for the same four menstrual phases. Numerous research studies in the last 30 years indicate that smokers show a characteristic steep rise in smoking upon waking, reflecting efforts to restore plasma nicotine levels depleted during sleep (e.g., Mooney et al., 2006). We hypothesized this typical circadian pattern of smoking would differ by menstrual phase. Since estrogen is suspected to stimulate nicotine metabolism, we anticipated a steeper rise in the number of cigarettes smoked during the morning hours of F phase (when estradiol is at its peak) as compared to the other phases of the menstrual cycle. Further, we hypothesized that the rate of smoking during waking hours would not vary by menstrual phase, given previous work by our group which indicated no differences in total number of cigarettes smoked per 24 h day (Allen et al., 1996; Allen et al., 1999; Allen et al., 2009).

**METHODS**

**Study participants**

Thirty-three participants were enrolled in this study, 31 (93.9%) were included in these analyses and two (6.1%) were excluded due to lost-to follow-up after study enrollment. To be eligible for the study, participants had to be between the ages of 18 and 40, smoke at least 10 cigarettes per day for at least the past year, have regular menstrual cycles, not be using any hormones or psychotropic medications, and be motivated to quit smoking (see Allen et al., 2008 for details on inclusion/exclusion criteria).

**Study procedures**

This study was approved by the University of Minnesota Institutional Review Board. Participants were recruited through local advertising. The screening process included assessment of study eligibility using self-reported medical, menstrual, and smoking histories, measurement of breath carbon monoxide (≥ 5 ppm indicative of current smoking),
and completion of demographic and smoking history forms, including the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Informed consent was obtained before study enrollment and data collection.

Following screening, participants were instructed to prospectively record the time each cigarette was smoked on a daily paper diary provided to the participants at the screening visit. The diary included 20 blank lines for the subject to write down the time each cigarette was smoked. Subjects were instructed to carry the diary with them at all times. To discourage inaccurate retrospective reporting, they were told there was no penalty for missing forms. Participants attended weekly visits prior to their assigned quit date at which study staff collected completed smoking and menstrual diaries, verified smoking status (by CO levels), and encouraged participants to continue smoking at their baseline level until their assigned quit date. Participants were followed for one complete menstrual cycle of ad libitum smoking and one complete menstrual cycle of attempted smoking cessation (results of smoking intervention are reported elsewhere; Allen et al., 2009). Study participants were compensated for participation.

To control for an order effect, participants were randomized to begin data collection during either the F phase (day 4–8) or the L phase (6–8 days after ovulation), with day 1 defined as the onset of menses. Menstrual cycle was monitored via menstrual calendars and urine lutenizing hormone (LH) testing (for further details see Allen et al., 2008 for details). For the purposes of these analyses, menstrual phases were defined as follows: M phase includes the days of self-reported active bleeding (range of 3–8 days). L and LL phases are days 8–14 and 1–7, respectively, prior to the onset of the next self-reported menses. F phase was defined as the days between M and L phases up to a maximum of 10 days since the follicular phase (dependent on when the follicle starts to develop) has the most variability in the menstrual cycle.

Statistical analysis

All analyses were conducted using the statistical analysis system version 9.1.3 (SAS, 2008). Values of $p < 0.05$ were considered statistically significant, based on two-tailed tests. Seven of the 31 (22.5%) participants enrolled had one or more phases of missing data. Given these missing data, the sample size for each menstrual phase is as follows: M ($n = 24$), F ($n = 28$), L ($n = 29$), and LL ($n = 25$). Demographics and baseline smoking behavior was computed using data collected at the screening visit. Self-recorded smoking counts are summarized in 2 h intervals or bins (i.e., the day was divided into 12, 2 h bins; Frederiksen and Frazier, 1977). These bins were then used to describe the circadian pattern of smoking. Counts were analyzed with the GLIMMIX procedure. This mixed effects approach accommodates correlated data, induced by repeated observations of the same participants. More specifically, conditional upon the random effects (e.g., intercepts, slopes, quadratic terms, etc.), the outcome measure is Poisson distributed. A Poisson regression model was developed that included effects of menstrual phase, time of day during waking hours (from 6:00 a.m. to midnight), a quadratic term for time of day, and the interactions between phase and the two time of day terms.
RESULTS

Demographics and smoking behavior

Study participants \((n = 31)\) were, on average, 29.61 (standard deviation [S.D.] ± 5.44) years of age with an average of 13.90 ± 1.85 years of education and 29% were non-white. They smoked a mean of 16.93 ± 5.37 cigarettes per day. Their average FTND score was 4.68 ± 2.08.

Circadian smoking patterns by menstrual phase

Pattern of cigarette smoking across the 24 h day (averaged in 2 h bins) by menstrual phase are displayed in Figure 1. Because relatively little smoking occurred in the over night hours, analyses were restricted to the waking day (6:00 a.m. to midnight). Significant linear, \(F(1, 31) = 6.71, p = 0.0145\), and quadratic \(F(1, 835) = 5.55, p = 0.0187\) effects were observed, reflecting a steep rise in smoking rate in early morning hours, followed by stable rate of smoking across the balance of the day.

Waking smoking rate by menstrual phase

Significant differences in smoking rate (cigarettes/2 h bin) as a function of phase were observed: \(M (M = 1.61, SE = 0.08)\), \(F (M = 1.45, SE = 0.07)\), \(L (M = 1.51, SE = 0.07)\), and \(LL (M = 1.54, SE = 0.07; F(3, 835) = 5.44, p = 0.0010)\). Post hoc comparisons, using a Tukey-Kramer adjustment to maintain Type I error rate, showed a lower rate of smoking occurred in the F phase as compared to the M phase during the waking day \(t(835) = 4.02, p = 0.0004\).

DISCUSSION

The results of the current study indicate the overall circadian pattern of smoking did not vary by menstrual phase. As expected, we observed a sharp rise in number of cigarettes smoked in the early morning, followed by a stable smoking pattern during the remainder of the day. Contrary to our hypothesis, we also observed a lower rate of smoking during waking hours in the follicular phase as compared to the menses phase.

This study raises a number of questions with regards to the impact of sex hormones on smoking behavior. Our results suggest that sex hormones may not play a role in the circadian smoking patterns. This agrees with previous results (Mooney et al., 2006), which showed no gender differences in smoking patterns. However, gender differences and role of sex hormones may present as differences in nicotine withdrawal symptomatology, rather than changes in smoking behavior as hypothesized. Differences in withdrawal by menstrual phase have been observed (Allen et al., 1996; De Bon et al., 1995), where withdrawal during ad libitum smoking has been observed to be higher in the late luteal and menses phases compared to the follicular and ovulatory phases. A confounding issue here might be premenstrual symptoms which are prevalent in the late luteal phase and correlate with withdrawal symptoms (Allen et al., 1996). Research is mixed on gender differences of craving and withdrawal symptoms. Some studies (Pomerleau et al., 2005; Svikis et al., 1986) show no gender difference while others indicate women experience greater
withdrawal during smoking cessation than men (Leventhal et al., 2007; Hogle and Curtin, 2006).

When examining the rate of smoking during waking hours we observed significant phase effects; specifically, the follicular phase was associated with a lower rate than menses phase. Albeit the magnitude of this difference is small and the clinical importance may not be significant. Since by nature the follicular phase is the most variable in length, perhaps a tighter window for follicular phase i.e., 4–5 days right before ovulation when estradiol is higher, might provide more information about the role of estrogen. Further, daily estradiol measurements are needed to determine if this hormone effects the metabolism of nicotine and hence the smoking rate. Lastly, the accuracy of paper records is limiting, although we did not have electronic data collection at the time of the study.

While this study has several strengths, including its prospective nature and randomized design, there are several study limitations. These limitations include a relatively small and homogenous study sample, the collection of self-reported data using paper diaries, and no measurement of sex hormones.

CONCLUSION

Our results indicate that while the menstrual phase does not appear to play a role in circadian smoking patterns, there may be a relationship between menstrual phase and ad libitum rate of smoking during waking hours which varied by phase (i.e., lower in follicular compared to menses). Additional studies should include a larger, more diverse study sample, pharmacokinetic measurements of sex hormones and nicotine levels, as well as electronic capture of smoking patterns. This would help define the relationship between smoking patterns and sex hormones which could lead to the development of more effective smoking cessation interventions for women.

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Figure 1.
Circadian pattern of smoking by menstrual phase