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The Effect of Combination Oral Contraceptives on Smoking-Related Symptomatology during Short-Term Smoking Abstinence

Katie Hinderaker,

Department of Family Medicine & Community Health, Medical School, University of Minnesota, 717 Delaware Street SE, Suite 400, Minneapolis, MN 55414

Alicia M. Allen, Ph.D., M.P.H.,

Department of Family Medicine & Community Health, Medical School, University of Minnesota, 717 Delaware Street SE, Room 422, Minneapolis, MN 55414, Phone: 612-624-0896

Nicole Tosun, M.S.,

Department of Family Medicine and Community Health, Medical School, University of Minnesota, 717 Delaware Street SE, Room 261, Minneapolis, MN 55414

Mustafa al'Absi, Ph.D.,

Department of Behavioral Sciences, Medical School, University of Minnesota, Duluth, 1035 University Drive, 236 SMed, D601A, Duluth, MN 55812

Dorothy Hatsukami, Ph.D., and

Department of Psychiatry, Medical School, University of Minnesota, 717 Delaware Street SE, Room 256, Minneapolis, MN 55414

Sharon S. Allen, M.D., Ph.D.

Department of Family Medicine & Community Health, Medical School, University of Minnesota, 420 Delaware Street SE, Room A682, Minneapolis, MN 55455

Katie Hinderaker: kehoff@umn.edu; Alicia M. Allen: alle0299@umn.edu; Nicole Tosun: tosun004@umn.edu; Mustafa al'Absi: malabsi@d.umn.edu; Dorothy Hatsukami: hatsu001@umn.edu; Sharon S. Allen: allen001@umn.edu

Abstract

Although an estimated 25% of premenopausal smokers report using oral contraceptives (OC), little is known about how OC use may influence smoking cessation. The purpose of this study was

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Correspondence to: Alicia M. Allen, alle0299@umn.edu.

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to examine the difference in smoking-related symptomatology during acute smoking abstinence between women on a standardized combination OC (Tri-Sprintec™) compared to women not on OCs (no-OC).

Participants were women aged 18-40 who smoked 5 cigarettes/day and reported regular menstrual cycles. Using a controlled cross-over design, participants completed two six-day testing weeks: Low Progesterone Week (LPW; Follicular (F) phase in no-OC or 1st week of pills in OC) and High Progesterone Week (HPW; Luteal (L) phase in no-OC or 3rd week of pills in OC). Each testing week included daily assessment of symptomatology and biochemical confirmation of smoking status.

During smoking abstinence, the OC group (n=14) reported significantly lower levels of positive affect (21.56 ± 7.12 vs. 24.57 ± 6.46 ; $\beta = 3.63$, $p = 0.0323$) than the no-OC group (n=28). Further significant interactions between group and testing week were observed as follows: Smoking satisfaction was higher during LPW in the OC group (LPW: 4.29 ± 1.30 vs. HPW: 4.10 ± 1.37) but higher during HPW in the no-OC group (LPW: 3.91 ± 1.30 vs. HPW: 4.23 ± 1.30 ; $\beta = -0.5499$, $p < 0.0001$). Similar interactions were noted in negative affect and psychological reward of smoking.

These results suggest that women on OCs may have different patterns of smoking-related symptomatology during short-term smoking abstinence as compared to women not on OCs. Additional work is needed to examine how this may affect smoking cessation efforts.

Keywords

Females; Nicotine; Hormones; Smoking; Withdrawal; Cessation; Oral Contraceptives

1. Introduction

Women face higher risks of smoking-related diseases and may also have greater difficulty quitting compared to men (Perkins & Scott, 2008; Allen, Oncken & Hatsukami, 2014a). Ovarian hormones potentially affect a woman's ability to quit. For instance, data suggests that the follicular (F) phase of the menstrual cycle is associated with more favorable smoking cessation outcomes when nicotine replacement therapy (NRT) is used (Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2004) and the luteal (L) phase is more favorable for smoking cessation when NRT is not used (Allen, Bade, Center, Finstad, & Hatsukami, 2008; Mazure et al., 2010). Greater menstrual phase variations in smoking-related symptomatology during ad libitum smoking (i.e., smoking as much and as often as desired) have also been associated with a greater increase in smoking relapse (Allen et al 2010; Carpenter et al 2006). The available literature is limited, however, as it only includes naturally cycling women.

Approximately 27% of premenopausal women who smoke report using oral contraceptives (OCs; McClave et al 2010), and little is known about how OC use may influence smoking cessation outcomes. Data from two cross-sectional studies indicate that smokers on combination OCs have faster nicotine metabolism than naturally cycling women (Benowitz et al, 2006; Berlin et al 2007). While these data may suggest OC users would have more

difficulty with cessation, another recent study (Dickmann, Mooney, Allen, Hanson, & Hatsukami, 2009) showed OC use was associated with lower levels of nicotine craving in adolescent girls during smoking cessation. However, these studies were limited due to their observational study designs, as well as a lack of uniformity in OC type and consideration for menstrual cycle timing.

The purpose of this exploratory study is to examine differences in smoking-related symptomatology (henceforth called ‘symptomatology’) during acute smoking abstinence at two time points in the menstrual cycle by women on a standard combination OC versus women who are not on OCs (no-OC). Given that OCs blunt the cyclical variation of endogenous hormone levels (e.g., progesterone and estradiol), we hypothesized that the OC group would experience different levels of symptomatology compared to the no-OC group. We also expected that the OC group would experience less menstrual cycle variation in symptomatology than the no-OC group.

2. Methods

2.1. Participants

This study is a secondary-data analysis on a subset of participants that participated in a larger study that aimed to examine the role of menstrual phase and depressive symptoms on short-term smoking abstinence outcomes (Allen et al 2014b). A convenience sample was recruited via mass and social media advertisements. To be eligible to participate in the parent study participants had to: (1) be between 18-35 years of age; (2) smoke 5 cigarettes/day for the last year, (3) have experienced premenstrual symptoms (as indicated by a score of 11 or higher on the Shortened Premenstrual Assessment form; (PAF; Allen, McBride, & Pirie, 1991) and (4) be in stable mental/physical health. Exclusion criteria included: (1) recent (<6 months) major depressive disorder (MDD), (2) lifetime history of premenstrual dysphoric disorder (PMDD), (3) current use of other nicotine sources, (4) recent (<3 months) use of psychotropic medication; and (5) recent (<3 months) breastfeeding and/or pregnancy. Two distinct groups of participants were included: OCs (n=14) and no-OC (n=28). The OC group included participants who were using combination OC for at least 3 months prior to study enrollment and were willing to switch to a study-supplied OC (Tri-Sprintec™). All OC users who completed the parent study protocol were included. The no-OC group participants reported regular menstrual cycles (24-26 days for 6 months) and no recent OC use (<3 months) prior to study enrollment. The no-OC group was a subset of participants who completed the parent study (n=147; Allen et al 2014b), who were identified by matching, with a 2:1 ratio, per the parent study's stratification variable (depressive symptoms) and by randomization variable (order of testing weeks), as well as race and time to first morning cigarette.

2.2. Procedures

All participants completed two six-day testing weeks with order randomly assigned. The testing weeks were timed to occur during low progesterone (LPW) or high progesterone (HPW). Specifically, LPW was defined as: (1) OC group: first week of Tri-Sprintec (ethinyl estradiol 35 mcg and norgestimate 0.18 mcg) or (2) no-OC group: follicular phase (days 2-7

of the menstrual cycle with day 1 determined by the onset of menses). HPW was defined as: (1) OC group: third week of Tri-Sprintec (ethinyl estradiol 35 mcg and norgestimate 0.25 mcg), or (2) no-OC group: luteal phase (2-7 days after luteinizing hormone surge identified by urine testing).

The testing week consisted of two days of ad libitum smoking (Days 1 and 2) followed by four days of abstinence (Days 3-6). At each visit, smoking abstinence was biochemically confirmed (CO <5ppm indicating abstinence), serum samples of estradiol and progesterone were collected (to retrospectively confirm phase in the no-OC group), and participants completed subjective questionnaires to assess symptomatology. Following the six-day testing week, participants then returned to ad libitum smoking for approximately six weeks before completing identical procedures in the alternate testing week. For additional details on screening, randomization and data collection, see Allen et al, 2014b.

2.3. Measures

At screening, participants reported their demographics (e.g. age, race, education) and baseline smoking behavior (e.g. cigarettes/day, quit history), as well as nicotine dependence via Fagerstrom Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The following four items were completed daily to assess symptomatology: (1) Minnesota Nicotine Withdrawal Scale (MNWS) assessed nicotine craving and withdrawal (Hughes & Hatsukami, 1986, 1998); (2) Brief Questionnaire of Smoking Urges (QSU-Brief; Tiffany & Drobes, 1991) measured intention and desire to smoke (Factor 1), and relief of negative affect (Factor 2), (3) Positive and Negative Affect Scale (PANAS) was used to assess positive and negative affect (Watson, 1988), and (4) Perceived Stress Scale (PSS; Cohen, Kamarch, & Mermelstein, 1983) measured total perceived stress. Finally, the Modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al 2007) was only completed during ad libitum smoking (Day 2) and assessed smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations and craving reductions. (For more information see Allen et al, 2014b.)

2.4. Statistical analysis

Descriptive statistics were calculated for demographics and smoking behavior variables. Differences between the study groups were assessed with chi-square and simple t-tests. Growth curve models with non-linear patterns and an unstructured matrix were used to examine the effect of OC on the pattern of change in symptomatology (separately, one for each of the 12 measures above) from Day 2 to Day 6. Two independent variables were investigated including group (OC vs. no-OC) and the interaction between group and testing week (LPW vs. HPW). All models were adjusted for age, baseline cigarettes/day, testing week (LPW vs. HPW), and order of testing weeks. P-values less than 0.05 were deemed statistically significant. No adjustments for multiple comparisons were made. SAS version 9.1.3 (SAS Institute, Cary, NC) was used to conduct the analyses.

3. Results

3.1. Sample characteristics

Participants (n=42) smoked, on average, of 10.4 ± 3.9 cigarettes/day with an average FTND score of 3.1 ± 1.9 . Most were non-Hispanic White (80.5%). Participants in the OC group (n=14) were significantly younger than the no-OC group (n=28; 23.4 ± 4.7 vs. 29.0 ± 6.2 , $p=0.005$). There were no other significant differences by group (Table 1).

3.2 Symptomatology by OC group

On the fourth day of abstinence (e.g. Day 6), the OC group had significantly lower levels of positive affect than the no-OC group (21.56 ± 7.12 vs. 24.57 ± 6.46 , $p=0.032$; respectively). A trend on the third day of smoking abstinence (e.g. Day 5) indicated that the OC group had lower craving as compared to the no-OC group (2.73 ± 1.00 vs. 3.02 ± 1.15 , $p=0.086$; respectively). No other significant differences were noted.

3.3 Symptomatology by OC group and testing week

Among the OC group, significantly greater smoking satisfaction and negative affect occurred during LPW, as compared to greater smoking satisfaction and negative affect during HPW for the no-OC group ($p<0.001$; Figure 1a and 1b). Both groups experienced greater psychological reward of smoking during LPW compared to HPW, however the OC group had a significantly greater menstrual cycle variation in psychological reward ($p<0.001$; Figure 1c).

4. Discussion

In this exploratory study, we observed several significant differences in smoking-related symptomatology between OC and no-OC users. First, during ad libitum smoking, we observed a significant interaction between OC use and menstrual cycle timing such that OC users experienced greater smoking satisfaction during the low progesterone week (e.g. lower norgestimate levels) whereas the no-OC group had greater satisfaction during high progesterone week (e.g. luteal phase). A second significant interaction was observed such that both groups had higher psychological reward during low progesterone week, but, contrary to our hypothesis, the OC group had a significantly greater decrease in psychological reward from the low progesterone week to the high progesterone week. Among the OC group, the exogenous progesterone levels increased from the low progesterone week (norgestimate 0.18 mcg) to the high progesterone week (norgestimate 0.25 mcg) whereas the exogenous estradiol maintained a steady dose (ethinyl estradiol 35mcg). Given progesterone is thought to protect against addictive behaviors (e.g. Lynch & Sofuoglu, 2014), this may be why the OC group experienced a decline in psychological reward. However, these data seem contradictory as OC users have blunted menstrual phase variation in endogenous levels of progesterone and estrogen, as compared to endogenous levels observed in the natural menstrual cycle. Therefore, one would expect a greater menstrual phase variation in physiological reward to occur in the no-OC group.

In terms of affect, we observed that the no-OC group experienced a minimal increase in negative affect during the high progesterone week as compared to the low progesterone week. This observation agrees with previous studies indicating higher depressive symptoms are experienced during the luteal phase (Perkins, et. al, 2000; Sakai & Ohashi, 2013). However, the OC group experienced greater negative affect during the low progesterone week as compared to the high progesterone week. Further, and contrary to our hypothesis, the negative affect levels experienced by the OC group during the low progesterone week are comparable to the negative affect level experienced by the no-OC group during both the low and high progesterone week. The OC group also experienced a greater decline in positive affect, regardless of testing week (LPW or HPW), as compared to the no-OC group. This may be related to the effect of exogenous progesterone on nicotine metabolism (Benowitz et al 2006). However, little research has been done to explore the relationship between nicotine metabolism and affect.

In summary, in this exploratory study, women who were on OCs experienced several notable differences in symptomatology during acute smoking abstinence as compared to women not on OCs. This study has several limitations including the small, homogenous sample resulting in limited generalizability and limited power to detect statistical differences. Further, confounding may be involved given the two study groups may not be exchangeable. For example, though not statistically significant, the educational level of the OC group is quite a bit higher than the no-OC group. It is likely that this confounding is not fully adjusted for in our analyses. However, this study also offers several strengths including the detailed measurements, biochemical confirmation of smoking status and crossover design, allowing for a within subject comparison of the menstrual cycle timing effect on our outcomes. Given our results OC use may influence smoking-related symptomatology and that an estimated 1 out of 4 premenopausal smokers report OC use (McClave et al 2010), additional research on the role of OCs during smoking cessation is warranted.

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Highlights

- We compared smoking-related symptomatology in women by oral contraceptive (OC) use.
- OC users had lower levels of positive affect during smoking cessation.
- Smoking satisfaction and psychological reward varied by OC use and menstrual cycle.
- OC users had more menstrual cycle variation in negative affect.

(c) Psychological Reward during Ad Libitum Smoking

Figure 1. Mean Smoking Satisfaction, Negative Affect, and Psychological Reward by OC Group and Testing Week

Smoking Satisfaction and Psychological Reward were assessed via the modified Cigarette Evaluation Questionnaire (Cappelleri et al 2007). Negative Affect was assessed via the Positive and Negative Affect Scale (Watson, 1988).

Table 1
Demographics & Smoking Behavior by Oral Contraceptive Group (n=42)

	All (n=42)	OC (n=14)	No-OC (n=28)	T / χ^2 (p)
Demographics				
Age	27.1 $\pm$ 6.3	23.4 $\pm$ 4.7	29.0 $\pm$ 6.2	2.99 (0.005)
Race (% White)	80.5%	78.6%	81.5%	2.46 (0.652)
Education (% Some College)	23.8%	14.3%	28.6%	4.09 (0.394)
Smoking Behavior				
Cigarettes/Day	10.4 $\pm$ 3.9	10.4 $\pm$ 5.2	10.5 $\pm$ 3.1	0.07 (0.944)
FTND Score	3.1 $\pm$ 1.9	2.8 $\pm$ 2.3	3.3 $\pm$ 1.8	0.61 (0.543)