

THE EFFECTS OF MENSTRUAL PHASE AND NICOTINE ABSTINENCE ON NICOTINE INTAKE AND ON BIOCHEMICAL AND SUBJECTIVE MEASURES IN WOMEN SMOKERS: A PRELIMINARY REPORT

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SUMMARY

Nicotine intake, menstrual and smoking withdrawal symptomatology, and baseline cortisol and MHPG were assessed in nine women smokers under conditions of *ad lib* smoking and overnight abstinence in three menstrual phases (early follicular, mid-to-late follicular, and late luteal). A trend towards higher nicotine intake ($p < 0.10$) was observed in the mid-to-late follicular phase. Although menstrual symptomatology was not significantly elevated during the smoking abstinence condition overall, abstinence appeared to prevent the normal reduction in symptomatology during the mid-to-late follicular phase that occurred under conditions of *ad lib* smoking. Menstrual and withdrawal symptoms were highly correlated, and both were most pronounced during the late luteal/abstinence condition. The smoking-specific item "craving" reflected this pattern, though in attenuated form, suggesting that the observed exacerbation of withdrawal symptomatology was not simply due to generalized dysphoria, as queried in both instruments. MHPG was significantly elevated in the late luteal phase, whereas cortisol was significantly higher during *ad lib* smoking than during abstinence and tended to be highest in the mid-to-late follicular phase. Further investigation will be needed to determine the functional significance of these findings for understanding and treating smoking in women.

INTRODUCTION

OVER THE PAST SEVERAL YEARS, there has been growing recognition that systematic hormonal fluctuations associated with the menstrual cycle have an impact not only on reproductive biology but also upon numerous other aspects of mood, behavior, and cognitive function (e.g., Magos, 1987). Because psychoactive substances, by definition, alter mood or performance, the idea that discretionary drug use may vary as a function of menstrual phase has considerable face validity. But, although several investigators have attempted to demonstrate such a phenomenon for a variety of drugs, including caffeine (Schechter *et al.*, 1989), alcohol (Mello, 1986; Schechter *et al.*, 1989), and marijuana (Griffin *et al.*, 1986), the only persuasive evidence advanced to date has been in the presence of the premenstrual syndrome (PMS) (Mello, 1986).

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Other appetitive responses, however, most notably craving for food and food intake (Pliner & Fleming, 1983; Tomelleri & Grunewald, 1987; Laessle *et al.*, 1990), have been convincingly demonstrated to increase during the premenstrual phase of the normal menstrual cycle in healthy volunteers.

Attempts to test the hypothesis that nicotine self-administration varies systematically in response to menstrual phase have produced mixed results: (1) Steinberg and Cherek (1989) studied nine women during 2-hr sessions conducted 5 days/week over two consecutive menstrual cycles. Based on automated measures, most subjects increased mean puff number and/or total puff duration per session during menses, compared with the premenstrual phase (the 5 days immediately preceding onset of flow) and with all other days combined (with no further phase distinctions). (2) Mello *et al.* (1987) studied cigarette smoking in 24 women given access to alcohol for 21 days in an inpatient setting. Seventeen of the 24 (70%) increased smoking, indicated by a decreased inter-cigarette interval during the premenstruum (undefined). When the analysis was limited to the 19 women who had concurrent access to alcohol during the premenstruum (to eliminate access/lack of access to alcohol as a possible confound), 14 (74%) exhibited increased smoking during that period. All women reported increased psychological discomfort during the premenstruum. (3) O'Hara *et al.* (1989) studied withdrawal symptoms in 22 premenopausal smokers enrolled in a behavioral smoking cessation program. For nine of these women, the scheduled "quit day" happened to fall during the follicular phase of the cycle (day 1 to day 15). For the remaining 13, it fell during the luteal phase (day 15 through the day prior to onset of menses). Subjects who quit during the luteal phase showed significantly higher scores on a questionnaire rating withdrawal symptoms 24 and 72 hr after quitting. For the group overall, highly significant correlations were found at 24, 48, and 72 hr between withdrawal scores and ratings of menstrual distress.

Unfortunately, because of design limitations and discrepant definitions of phase, these studies raise as many questions as they answer. Although two of the three (Mello *et al.*, 1987; O'Hara *et al.*, 1989) suggest increased smoking and increased withdrawal symptomatology during the latter part of the cycle, it is difficult to specify the phase associated with increases in smoking or to relate these studies to one another. By contrast, the study by Steinberg and Cherek (1989) showed the highest level of smoking to occur during menses rather than during the premenstruum. Since day 1 of the menstrual cycle was not separated out from the remainder of the menses, however, it is unclear how much smoking in response to dysmenorrhea might have contributed to this effect. (It has been suggested that nicotine may relieve menstrual cramps [Andersch & Milsom, 1982; Backon, 1989], a phenomenon that deserves study in its own right.) Interpretation of the study by Mello *et al.* (1987) is complicated by their simultaneous manipulation of the availability of alcohol. O'Hara *et al.* (1989) compared absolute post-cessation withdrawal scores, without correcting for pre-cessation scores. Moreover, the failure of the withdrawal scale to be sensitive to abstinence effects calls the validity of the main dependent variable into question. None of these three studies (Mello *et al.*, 1987; O'Hara *et al.*, 1989; Steinberg & Cherek, 1989) included any attempt to verify menstrual phase with hormonal measures, an omission that may have some bearing on the conflicting findings. For example, in the study by O'Hara *et al.* (1989), women who quit smoking on days 12–17 may have been pre- or post-ovulatory, depending on their average cycle length, bringing the follicular and luteal ascriptions into question. Furthermore, measures of plasma nicotine were not taken in the studies on smoking, and topographical parameters are known to be inadequate indices of nicotine intake (Pomerleau *et al.*, 1989b).

In an effort to clarify and extend our understanding of these issues, we studied nine women

smokers under conditions of *ad lib* smoking and abstinence, in three hormonally verified phases of the menstrual cycle: (1) The early follicular (EF) phase, during which most women are in menses and when estrogen and progesterone are usually low, was chosen as a test of the findings of Steinberg and Cherek (1989). (2) The mid-to-late follicular (M/LF) phase was chosen because it was regarded as likely to be affectively and behaviorally "neutral" (Schechter *et al.*, 1989; Mitchell *et al.*, in press). (3) The late luteal phase (LL), when estrogen and progesterone levels are beginning to drop and "premenstrual" symptoms tend to occur, was chosen as a stringent test of the findings of Mello *et al.* (1987) and O'Hara *et al.* (1989). Menstrual symptomatology, withdrawal symptomatology, and, on the *ad lib* smoking days, nicotine intake after smoking a single cigarette were assessed. Our hypothesis was that menstrual phase would affect nicotine intake and smoking-related affective variables (e.g., nicotine withdrawal). Although the mixed findings in the literature regarding the nature and existence of differences in either intake or symptomatology precluded extensive speculation about the underlying hormonal mechanisms, we also measured basal levels of cortisol and 3-methoxy-4-hydroxyphenylglycol (MHPG) in an effort to assess whether corticosteroid and/or central noradrenergic activity (using MHPG as a marker; Peyrin, 1990) were associated with menstrual phase, smoking condition (abstinence vs. *ad lib* smoking), and/or subsequent nicotine intake.

SUBJECTS AND METHODS

Subjects

Nine female smokers were recruited from the community through local newspaper advertisements to participate in this study. To be eligible, a subject was required (1) to be between 20 and 39 yr old, (2) to smoke an average of at least 15 cigarettes per day, (3) to be in good health and not on any prescription medications, (4) to be neither underweight nor markedly obese (Body Mass Index [BMI] between 18 and 27 kg/m²; Kraemer *et al.*, 1990), (5) not to be using oral contraceptives or an IUD, (6) not to be pregnant or at risk for becoming pregnant, (7) to have no complaints or history of treatment for PMS; and (8) to menstruate on a regular basis, with monthly cycles averaging between 26 and 35 days. Subjects also were excluded for recent psychiatric illnesses. Over 100 women responded to our advertisements, 24 of whom met the eligibility requirements with respect to age, BMI, cycle length, smoking rate, etc. Of these 24 women, 15 were excluded because of scheduling difficulties, failure to keep appointments, or our inability to establish a patent line for blood withdrawal.

Definition and verification of menstrual phase

Subjects were studied twice during each of three menstrual phases known to vary in terms of ovarian steroid milieu and menstrual symptomatology: (1) The EF phase was defined as day 2 through day 5 of the menstrual cycle. Day 1 was avoided because of the potential confounding effect of dysmenorrhea. (2) The M/LF phase was the time period following menses and prior to the pre-ovulatory luteinizing hormone (LH) surge. Subjects were scheduled between day 6 and day 11. (3) The LL phase was defined as the 4 days prior to menses. A home test kit developed to aid in achieving or avoiding pregnancy (either OvuQUICK, Monoclonal Antibodies, San Diego, CA, or Clearplan Easy, Whitehall Laboratories, New York, NY) was used to pinpoint the LH surge, which precedes ovulation by 24–36 hr and the onset of next menses by approximately 14 days, and the subjects were scheduled accordingly. To verify that the cycle under investigation was indeed ovulatory, the subjects were asked to bring first morning urine samples to the laboratory on days 7–9 following the LH surge, and a qualitative assay of pregnanediol glucuronide, a progesterone metabolite, was performed.

Definition and verification of abstinence from smoking

At the beginning of each session, subjects were tested for expired carbon monoxide with the VITALOGRAPH-ECS0 monitor to determine compliance with the abstinence requirement. On non-smoking days, values above 15 ppm would have disqualified subjects for that day's session. Compliance was subsequently verified by nicotine assay.

Subjective instruments

The Hughes-Hatsukami Withdrawal Scale (Hughes & Hatsukami, 1986) was modified by inclusion of bipolar endpoints, to minimize the bias towards dysphoria inherent in the unipolar version. Each of the 16 items was rated on a scale of -5 through +5, with possible total scores ranging from -80 to +80. The Woods Menstrual Symptom Severity List (Mitchell *et al.*, in press) identifies 33 items that contribute to phase differences in symptom severity. Items are scored on a scale of 0 (none) through 4 (severe); overall score can range from 0–132. In the version used in our study, the 33 scored items were embedded in a 51-item questionnaire designed to downplay our interest in specifically “premenstrual” symptomatology.

Assays

Blood samples were collected in Vacutainer tubes containing EDTA to prevent clotting and immediately stored in crushed ice. Following the session, samples were centrifuged at 4° C. Plasma aliquots were frozen at -80° C. Nicotine, cotinine, MHPG, and cortisol were analyzed by M. Hariharan, Ph.D., in the Psychiatry Department Research Assay Support Laboratory. Estradiol (E) and progesterone (P) were analyzed in the Pediatric Endocrine Laboratory of C. S. Mott Children’s Hospital under the supervision of Inese Beitins, M.D.

Assays of nicotine and cotinine were performed by high performance liquid chromatography (HPLC) (Hariharan *et al.*, 1988). This method requires about 1 ml of biological sample. The isocratic HPLC unit utilized a C₁₈ reverse-phase column and a mobile phase of citric acid-phosphate buffer and phenylimidazole as the internal standard. Average coefficient of variation (CV) for the assay was 6.5% for nicotine, with a lower detection limit of 1 ng/ml.

Plasma cortisol was measured by competitive protein binding assay. Average interassay CV was 6.3%, and intrassay CV was 5.95%, with a 0.5 µg/dl lower limit of detection.

MHPG was analyzed by an HPLC method (Hariharan *et al.*, 1989) that employs coulometric detection with iso-MHPG as the internal standard. The detection limit of the assay is 0.1 µg/l. The interassay CV for a sample with a mean MHPG concentration of 3.84 µg/l was 5.2%, and the average recovery was 37%.

Plasma E (England *et al.*, 1974) and P (Niswender, 1973) were measured by radioimmunoassay (RIA). For E, the interassay CV averaged 8%, the intraassay CV averaged 4%, and the sensitivity was 5 pg/ml. For P, the interassay CV averaged 5%, the intraassay CV averaged 5%, and the sensitivity was 20 pg/ml.

Urinary test kits

OvuQUICK provides a qualitative home test of LH in late morning urine. In a clinical study of 191 specimens in 25 cycles reported by the manufacturer, OvUQUICK was compared to both a qualitative EIA and a quantitative RIA in detecting the LH surge. OvUQUICK identified the LH surge the same day as did EIA 96% of the time (one day earlier for the remaining 4%), and the same day as did RIA 98% of the time. Clearplan Easy is a similar home test of LH in urine collected at least 4 hr after previous urination. In a clinical study of 54 consecutive patients, Clearplan predicted ovulation within one day of the serum LH surge as measured by RIA in 82–88% of cases and within 2 days in 89–96% of cases (Gudgeon *et al.*, 1990). ProgestURINE (Monoclonal Antibodies, San Diego, CA) is a qualitative assay of pregnanediol glucuronide (PDG) in the first morning urine during the mid-luteal phase. The assay sensitivity is 3 µg/ml. In a study of 324 urine specimens from 28 menstrual cycles reported by the manufacturer, overall correlation with urinary PDG measured by RIA was 92%. In a similar comparison with 92 samples from 28 menstrual cycles, overall correlation with serum P by RIA was 93%.

Procedure

Each subject attended an orientation session during her M/LF phase, during which the requirements of the study were reviewed, written informed consent was obtained, instruction in the use of the urine test kits was provided, the subject’s height and weight were measured, and baseline questionnaires were completed. The subjects were not informed of the purpose of the study. Although they were clearly aware of our interest in the menstrual cycle, smoking, and smoking abstinence, queries made following each subject’s participation in the study gave no indication that they brought any expectations to the study regarding possible interactions of these variables. Study sessions were conducted at mid-day (starting between 1000h and 1230h, standard for each subject, so that each subject’s test time varied by less than an hour across the 6 study days) on two consecutive weekdays (*ad lib* smoking vs. overnight abstinence sessions) in each of the three identified menstrual phases. For three of the six sessions, once in each menstrual phase, the subject smoked *ad lib* prior to that day’s session.

For the other three sessions, the subject was asked to abstain from smoking for 12 hr preceding the session. To minimize the impact of possible order effects, subjects were randomly assigned to one of two smoking condition sequences (*ad lib* smoking day first vs. abstinence day first) and one of three menstrual phase sequences (EF first, M/LF first, LL first), a total of six possible sequences.

The subjects was seated in a reclining chair separated from the experimenter by a 5'×4' partition. An indwelling catheter was inserted into a forearm vein and connected to a heparinized 1-m long infusion-exfusion tubing. This line was run through a 3-in hole in the partition. On smoking days only, to standardize the nicotine deprivation period, the subjects smoked one usual-brand cigarette immediately after insertion of the line (min 0). Between min 0 and 30, the subjects completed the smoking withdrawal and menstrual symptomatology questionnaires. When they finished, they were permitted to read magazines. At min 30, the subjects were asked to smoke one usual-brand cigarette.

Blood withdrawal occurred as unobtrusively as possible at 1 min, 15 min, 30 min, and 35 min following insertion of the line (min 0). The samples taken at 1 min, 15 min, and 30 min were later pooled for assay of baseline E and P (to control to some degree for episodic secretion). Blood withdrawn during the 30-min sampling period was also assayed for cortisol, MHPG, and, on smoking days only, pre-smoking nicotine levels. Blood withdrawn at 35 min was assayed for nicotine, providing post-smoking levels on smoking days and "baseline" levels on abstinence days. Following completion of the session and withdrawal of the line, the subjects participated in a brief taste-testing procedure to provide data for a larger database on sweet taste preference in women smokers, exsmokers, and nonsmokers (Pomerleau *et al.*, 1991).

The data were analyzed by two-way repeated measures factorial ANOVA, with two levels of smoking condition (*ad lib* smoking vs. overnight abstinence) and three levels of menstrual phase (EF, M/LF, and LL). Nicotine intake was assessed only once during each phase and was analyzed by one-way ANOVA. Pearson product-moment correlation coefficients were calculated for the major variables. Because too little is known about most of the variables under investigation to permit the formulation of directional hypotheses, two-tailed significance tests were used throughout.

RESULTS

The subjects ranged in age from 23 to 34 yr (mean±SD=27.2±4.1 yr) and had a BMI ranging from 19–27 (mean±SD=22.4±2.6). They scored a mean (±SD) of 6.6 ± 1.8 on the Fagerstrom Tolerance Questionnaire, an index of nicotine dependence (Fagerstrom, 1978; Fagerstrom & Schneider, 1989), characterizing them as moderately dependent smokers (Pomerleau *et al.*, 1989a). No subject exceeded an average daily intake of 600 mg caffeine or an average weekly intake of 150 g ethanol (10 drinks).

Confirmation of abstinence and menstrual phase

All subjects succeeded in meeting the criteria for overnight abstinence, as measured by CO and subsequently verified by plasma nicotine levels of <10 ng/ml. Mean baseline nicotine levels for the three abstinence days (mean±SEM) were 2.0±0.6, 1.6±0.9, and 2.6±0.7 ng/ml. Comparable values for the three *ad lib* smoking days were 20.8±2.6, 20.9±2.4, and 21.6±2.1 ng/ml. As expected, significant differences emerged for smoking condition (abstinence vs. *ad lib* smoking), but not for menstrual phase ($F_{2,16}=0.30$, $p=NS$). No interaction effects were detected ($F_{2,16}=0.03$, $p=NS$).

Difficulties in predicting and scheduling the 18 LL sessions (two LL sessions for each of nine subjects) resulted in the following protocol deviations: (1) Four of the 18 LL sessions subsequently proved to have been scheduled slightly earlier than intended (7 to 5 days prior to the onset of menses). (2) A fifth LL session was anomalous, because onset of menses occurred earlier than predicted 2 mo in a row. Since insurmountable logistical problems prevented further rescheduling, the session had to be run shortly after the onset of menses. (3) Because one subject was unable to attend her LL/abstinence session as originally scheduled, it had to be

postponed until the next month, again following the prediction and verification procedures described above. Thus, means for the LL phase actually include data for four sessions that fell 1–3 days earlier than specified by the protocol, one session that fell a few hours later than specified, and one LL/abstinence session that, though falling within the prescribed interval, was run during a different cycle from her LL/smoking session. All data were included in the analysis. There was a significant main effect of phase for P and a trend towards a significant phase effect for E. No smoking condition or interaction effects were detected. Fig. 1 presents the mean hormone levels of the three pooled samples for each session.

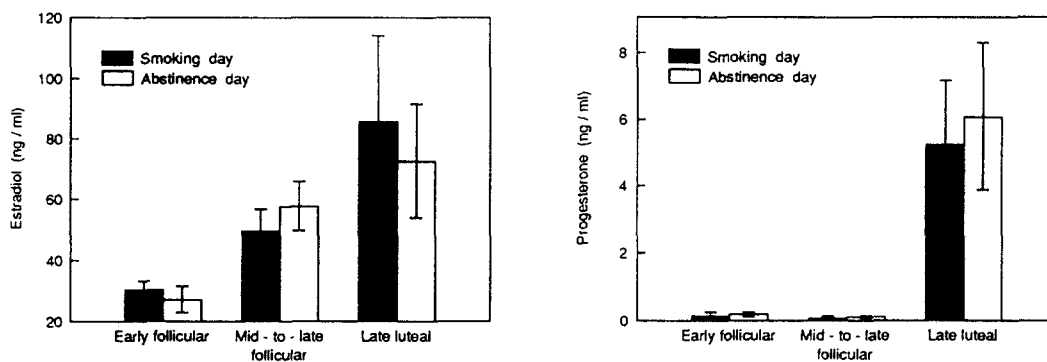


FIG. 1. Levels of estradiol and progesterone measured in three pooled plasma samples after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n = 9$).

Nicotine intake

Mean nicotine increments (post- minus pre-smoking levels) on smoking days were 9.0 ± 1.7 , 11.5 ± 1.8 , and 9.4 ± 2.2 ng/ml for the EF, M/LF, and LL phases, respectively. There was a trend toward a significant difference among these means ($F_{2,16} = 2.86$, $p < 0.10$). The nicotine increments for the three smoking days were highly correlated, with coefficients ranging from 0.80 ($p < 0.05$) to 0.88 ($p < 0.01$).

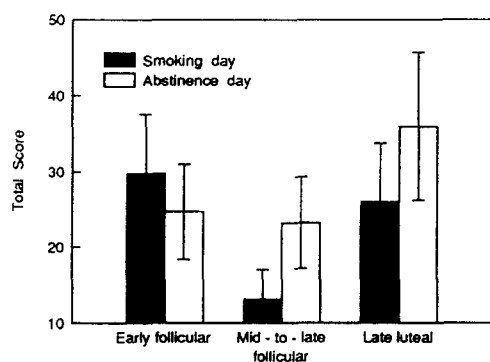


FIG. 2. Scores on Woods Menstrual Symptom Severity Checklist (total of 33 items, each scored 1–4) after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n = 9$).

Menstrual and withdrawal symptomatology

Scores on the menstrual symptomatology questionnaire are presented in Fig. 2. These data place six subjects in the range of high symptom severity for the M/LF phase and five for the LL phase, as defined by Mitchell *et al.* (in press), with six subjects showing phase differences suggestive of PMS. No significant main effect for smoking condition was detected. A trend toward a significant main effect for menstrual phase emerged ($F_{2,16} = 2.82$, $p < 0.10$), as did a trend towards a significant phase \times smoking condition interaction ($F_{2,16} = 3.23$, $p < 0.10$).

Scores on the nicotine withdrawal questionnaire are presented in Fig. 3. A highly significant main effect for smoking condition was

detected for withdrawal scores ($F_{1,8}=11.93, p<0.05$), as expected, with scores in the overnight abstinence condition consistently exceeding those in the *ad lib* smoking condition. A trend toward a significant main effect for menstrual phase emerged ($F_{2,16}=3.15, p<0.10$), as did a trend toward a significant phase \times smoking condition interaction ($F_{2,16}=3.32, p<0.10$).

For all sessions, the menstrual symptomatology and withdrawal symptomatology questionnaires were highly correlated, with coefficients among the 6 study days ranging from 0.64 ($p<0.10$) to 0.95 ($p<0.001$). For most subjects, a high degree of within-subject correlation between these two scales was observed as well, with correlation coefficients for the nine subjects across the six study conditions being -0.31 (NS), -0.14 (NS), 0.67 (NS), 0.80 ($p<0.10$), 0.80 ($p<0.10$), 0.81 ($p<0.05$), 0.90 ($p<0.05$), 0.91 ($p<0.05$), and 0.97 ($p<0.01$). For both scales, overall menstrual and withdrawal symptoms were most pronounced during the LL phase under conditions of abstinence. As shown in Fig. 4, the smoking-specific item of craving, in addition to the expected significant elevations for smoking condition ($F_{1,8}=18.84, p<0.01$), also showed the pattern described above, though it fell short of significance ($p=0.10$).

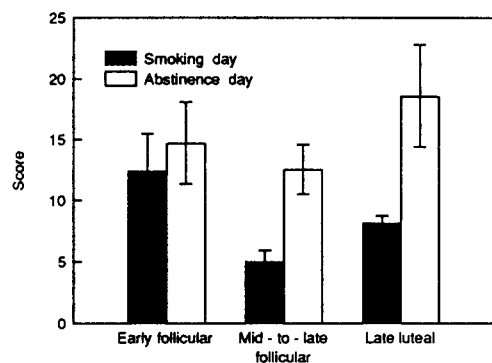


FIG. 3. Scores on a bipolar version of the Hughes-Hatsukami Smoking Withdrawal Scale (modified) (range of possible scores: -80 to +80) after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n=9$).

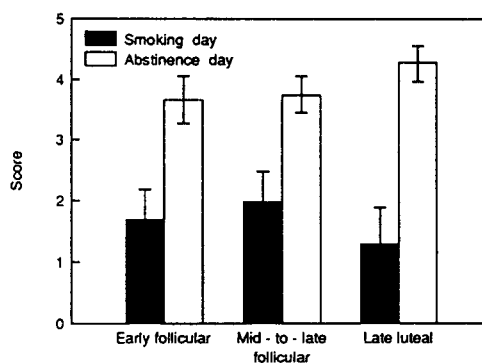


FIG. 4. Scores on the craving item (range of possible scores: -5 to +5) in the bipolar version of the Hughes-Hatsukami Smoking Withdrawal Scale (modified) after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n=9$).

MHPG and cortisol

MHPG levels for the six sessions are presented in Fig. 5 (complete data available for eight subjects). Statistical analysis showed a significant main effect for menstrual phase ($F_{2,14}=5.45, p<0.05$). Newman-Keuls tests revealed that LL levels were significantly higher than EF levels ($p<0.05$) and M/LF levels ($p<0.001$), with no significant difference between the latter two phases. No significant effects for smoking condition or phase \times smoking condition interaction were detected. MHPG levels for the 6 days were highly correlated, with coefficients ranging from 0.64 ($p<0.10$) to 0.95 ($p<0.001$).

Cortisol levels for the six sessions are shown in Fig. 6 (complete data available for eight subjects). Analysis revealed significant effects for smoking condition ($F_{1,7}=15.17, p<0.01$), with *ad lib* smoking levels (30 min after the previous cigarette) exceeding those under conditions of overnight abstinence. A trend towards a significant menstrual phase effect also emerged ($F_{2,14}=2.97, p<0.10$). No significant phase \times smoking condition interaction was detected. Unlike for MHPG, no systematic pattern of intercorrelations among the 6 days was detected for cortisol.

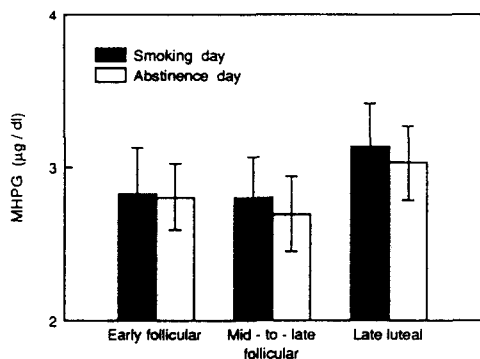


FIG. 5. Plasma MHPG levels after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n = 8$).

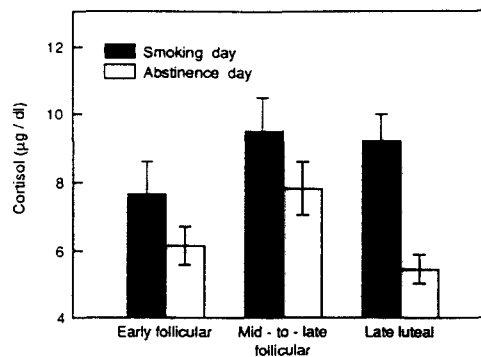


FIG. 6. Plasma cortisol levels after *ad lib* smoking and overnight abstinence for each of three menstrual phases (mean \pm SEM; $n = 8$).

Correlation among variables

Correlation coefficients were calculated in an effort to determine the possible relationship between baseline variables and subsequent nicotine intake. Basal MHPG levels were negatively correlated with subsequent nicotine intake, with correlation coefficients for the EF, M/LF, and LL phases being -0.63 ($p < 0.10$), -0.67 ($p < 0.05$), and -0.60 ($p < 0.10$), respectively. No significant or systematic correlations of basal cortisol level, menstrual symptomatology, or withdrawal symptomatology with subsequent nicotine intake were detected. Neither MHPG nor cortisol showed any consistent pattern in predicting menstrual or withdrawal symptomatology. Plasma E and P levels were not systematically correlated with any other dependent variable.

DISCUSSION

As expected, marked phase effects were observed for E and P. Consistent with the fact that several subjects were tested 1–3 days earlier than planned in the LL phase, mean p values exceeded the expected values for day -4 through onset of menses (usually < 2 ng/ml). Consequently, ascription of our findings (or in some instances our lack of findings) to specifically “premenstrual” factors must be made with caution.

Unfortunately, our study amplifies rather than resolves inconsistencies already in the literature regarding differential smoking in response to menstrual phase (Mello *et al.*, 1987; O’Hara *et al.*, 1989; Steinberg & Cherek, 1989), since our findings suggest the possibility of a slight increase in nicotine intake during the M/LF phase, a phase characterized by the smallest degree of menstrual symptomatology. Unlike ours, none of the previous studies included biochemical verification of nicotine intake. On the other hand, our sample was small, the observed differences in intake were modest and fell short of significance, and our measures were based on the results of smoking a single, nondiscretionary cigarette.

It is worth noting that nicotine intake on a given day is one of the best predictors of nicotine intake on any other day, as indicated by the strong intercorrelations observed for nicotine intake for the 3 smoking days. The consistency with which smokers self-administer nicotine has been demonstrated (Benowitz, 1988) but is sometimes forgotten in attempts to uncover situational determinants of smoking. In fact, situational variations in smoking are probably best understood as superimpositions on the addictive cycles manifested by individual smokers.

Our subjects' overall menstrual symptomatology ratings were high in comparison with those reported by Mitchell *et al.* (in press). Since treatable PMS was an exclusion criterion, however, we attribute these findings to extensive differences in the circumstances under which the test was administered, rather than to any unexpected incidence of PMS in our subjects. Ratings of menstrual symptomatology on the smoking days showed the expected "on/off" pattern, with the lowest scores prevailing during the M/LF phase. Though no significant elevation in symptomatology was observed for the abstinence condition overall, our data can be interpreted to suggest that the "on/off" pattern is disrupted by the stressful effects of smoking abstinence, resulting in more constant and chronic symptomatology across the cycle.

The strong correlations between menstrual symptomatology and withdrawal symptomatology replicate those of O'Hara *et al.* (1989) and similar findings noted briefly by Allen *et al.* (1991). Though this finding is to some extent an artifact resulting from the extensive overlap between the individual items on the questionnaires, it may be that women smokers themselves confuse withdrawal symptoms with menstrual symptoms, or experience them in an additive or potentiated manner. Both menstrual and withdrawal symptoms were most pronounced during the LL/abstinence condition. The smoking-specific item "craving" also reflected this pattern in attenuated form, suggesting that the observed exacerbation of withdrawal symptomatology during the LL/abstinence condition was not simply a result of generalized dysphoria queried in both instruments. These results, taken together, may have treatment implications in that cessation may produce more discomfort, or possibly require more "inoculation" against relapse, during the LL phase.

The finding of elevated MHPG levels in the LL phase is consistent with the pattern reported in the literature for normal subjects whose smoking status was not reported (DeLeon-Jones *et al.*, 1978) and for women with PMS (Parry *et al.*, 1991). Overnight abstinence from smoking did not significantly affect MHPG levels. The apparent ability of MHPG levels to predict subsequent nicotine intake, with lower levels being associated with higher nicotine intake, is in keeping with the idea that smokers may "use" nicotine to stimulate catecholamine release (Westfall & Watts, 1964; Carruthers, 1976; McCarty, 1982), and that catecholamine depletion as reflected in reduced levels of MHPG may trigger increased smoking. The fact that MHPG levels did not differ between the smoking and nonsmoking conditions, however, indicates that a few hour of nicotine abstinence does not produce noticeable differences in catecholamine metabolic activity. Moreover, there was no evidence of an increase in smoking in response to the "stress" of premenstrual or withdrawal symptomatology.

Studies of the effects of abstinence on cortisol levels in smokers have produced conflicting results, with some investigators having reported an increase and others a decrease (cf. Hughes *et al.*, 1990, for review). The present study showed a consistent decrease in cortisol following approximately 12-hr abstinence, though the difference reached significance only in the LL phase. Since the cortisol sample in the present study was withdrawn 30 min after the previous cigarette, however, the possibility that the observed elevation on the *ad lib* smoking days was an acute response to a recent cigarette, rather than to chronic exposure to nicotine, cannot be ruled out. The trend toward a significant phase effect for cortisol, with levels being highest in the M/LF phase, is consistent with previous findings for nonsmokers (Gennazini *et al.*, 1975; Tam *et al.*, 1985) and for women with PMS (Parry *et al.*, 1991). The coincidence of peak smoking with peak cortisol is consistent with the hypothesis that smokers increase nicotine intake under conditions when cortisol is elevated to compensate for corticosteroid-mediated decreases in the sensitivity of the nicotine receptor (Pauly *et al.*, 1988; Pomerleau & Pomerleau, 1990). Since both "peaks" represent statistical trends only, and since no correlation between

cortisol and subsequent nicotine intake was detected, such an interpretation must be regarded with caution.

Because the present study was exploratory in nature, replication in larger samples and over multiple cycles, with stratification of subjects by degree of menstrual symptomatology and nicotine dependence, is desirable. Failure to detect significant correlations among various variables (e.g., cortisol and subsequent nicotine intake) must be interpreted with particular caution, as our sample was too small to provide adequate statistical power. Inclusion of non-smoking controls to provide baseline data might help clarify the chronic hormonal effects of nicotine in smokers.

The need for further investigation in this area is not academic. Since the release of Surgeon General Luther Terry's landmark report publicizing the hazards of cigarette smoking (USPHS, 1964), its prevalence in American men declined much more sharply (from 50.2% in 1965 to 31.7% in 1987) than in women (from 31.9% to 26.8%) (USDHHS, 1989). If current trends persist, smoking rates for women will exceed those for men by the mid-1990s (USDHHS, 1989). Rates of initiation have dropped much faster among men than among women (USDHHS, 1989). Women seem to quit with greater difficulty, possibly because they are treated with methods less appropriate to them (USDHHS, 1980; Stoto, 1986; Marlatt *et al.*, 1988; Blake *et al.*, 1989) and relapse more frequently than do men (Gritz, 1980). Although women, as major users of the health care system, have probably been adequately represented in treatment trials (e.g., Hooper, 1990), much of the basic behavioral and biological research on which these treatment strategies are based has been conducted in men. It is to be hoped that studies such as the present one will contribute to the identification of factors specific to smoking in women that could be used as the basis for the development of more effective, targeted treatment strategies.

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