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Review

Review

Systematic and Meta-Analytic Review of Research Examining the Impact of Menstrual Cycle Phase and Ovarian Hormones on Smoking and Cessation

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Abstract

Introduction: To determine the effect of ovarian hormones on smoking, we conducted a systematic review of menstrual cycle effects on smoking (i.e., ad lib smoking, smoking topography, and subjective effects) and cessation-related behaviors (i.e., cessation, withdrawal, tonic craving, and cue-induced craving).

Methods: Thirty-six papers were identified on MEDLINE that included a menstrual-related search term (e.g., menstrual cycle, ovarian hormones), a smoking-related search term (e.g., smoking, nicotine), and met all inclusion criteria. Thirty-two studies examined menstrual phase, 1 study measured hormone levels, and 3 studies administered progesterone.

Results: Sufficient data were available to conduct meta-analyses for only 2 of the 7 variables: withdrawal and tonic craving. Women reported greater withdrawal during the luteal phase than during the follicular phase, and there was a nonsignificant trend for greater tonic craving in the luteal phase. Progesterone administration was associated with decreased positive and increased negative subjective effects of nicotine. Studies of menstrual phase effects on the other outcome variables were either small in number or yielded mixed outcomes.

Conclusions: The impact of menstrual cycle phase on smoking behavior and cessation is complicated, and insufficient research is available upon which to conduct meta-analyses on most smoking outcomes. Future progress will require collecting ovarian hormone levels to more precisely quantify the impact of dynamic changes in hormone levels through the cycle on smoking behavior. Clarifying the relationship between hormones and smoking—particularly related to quitting, relapse, and medication response—could determine the best type and timing of interventions to improve quit rates for women.

Introduction

Tobacco use causes nearly half a million annual deaths in the United States[1] and more than five million annual worldwide deaths.[2] While there is evidence for increasing risk of mortality for smokers, especially for women,[3] smoking cessation can prevent and reduce many of the harmful consequences of smoking.[1] Despite being more likely to report a quit attempt than men,[4] women have more difficulty than men achieving smoking abstinence,[5–10] although see also Killen et al.[11] Moreover, women demonstrate differences in important smoking behaviors that may influence successful cessation outcomes including greater and more variable withdrawal symptoms[12–14] and greater cue-induced smoking cravings.[15,16]

Ovarian hormones and their fluctuations across the phases of the menstrual cycle may contribute to the greater difficulty that women experience when quitting smoking. Women with a natural monthly menstrual cycle (average length of 28–30 days) experience changes in ovarian hormone levels of estrogen and progesterone across the phases of the cycle.[17,18] Levels of both estrogen and progesterone are low at the beginning of the follicular phase (i.e., menses, days 1 to 4 where 4 is the average length of menses). Estrogen then increases during the follicular phase with a peak at the end of the phase at ovulation (~day 14). The peak estrogen is followed by a decrease and then a small increase in the middle of the luteal phase (~day 21). Progesterone levels are low throughout the follicular phase, begin to rise moderately at the end of the follicular phase, and peak in the middle of the luteal phase (~day 21). Both estrogen and progesterone levels decrease rapidly during the late luteal (i.e., premenstrual) phase.

Both estrogen and progesterone have actions on brain function, influencing multiple reward-circuitry neurotransmitter systems.[18,19] Estrogen has been shown in both preclinical and clinical research to increase the rewarding value of drugs of abuse[20] including nicotine.[21,22] For example, female rats demonstrate greater rewarding effects of nicotine compared to male rats when the females are intact, while ovariectomized female rats show no reward response to nicotine.[22] Women also metabolize nicotine more quickly, especially women who are pregnant or taking oral contraceptives, suggesting a link to increased estrogen levels.[23,24] A relationship between estrogen and nicotine metabolism has important clinical implications because quicker metabolism of nicotine is associated with more intense smoking,[25] greater reward from nicotine,[26] greater cravings to smoke after overnight smoking abstinence,[26] and poorer cessation outcomes.[27]

Similar to estrogen, progesterone appears to have an impact on smoking behavior, but with effects in the opposite direction. Preclinical studies demonstrate decreased motivation for nicotine when progesterone levels are high (see Lynch and Sofuoglu[18] for a review). For example, female rats demonstrate greater motivation for nicotine when progesterone levels are low and when there are greater estradiol levels relative to progesterone levels.[28] Self-administration of nicotine decreases in female rats that are pregnant, a time when progesterone levels are high.[29] Further, the administration of progesterone to non-human primates is associated with decreased nicotine self-administration.[30] Taken together, these studies suggest that estrogen may promote addictive behaviors through increased reward while progesterone may be protective against addictive behaviors through decreased reward value.

The preclinical evidence suggesting that ovarian hormones may be a critical factor in the rewarding effects of nicotine highlights the importance of further elucidating the nature of the relationship between hormones and smoking. One prior qualitative review summarized 13 studies of menstrual cycle phase, a proxy for ovarian hormone levels, and withdrawal and cravings.[17] While some studies found greater withdrawal and cravings during the luteal phase, compared to the follicular phase, there were limitations in the ability to draw conclusions because of mixed findings, small sample sizes, and variations across study methodologies. There has yet to be published a systematic examination of clinical, laboratory, and treatment studies that examine menstrual phase effects on a range of smoking behaviors and smoking-related symptomatology.

The purpose of this study is to conduct the first systematic and meta-analytic review of the literature on the relationship of ovarian hormones and menstrual cycle with smoking consumption-related behaviors (i.e., ad lib smoking, smoking topography, subjective effects of smoking) and smoking cessation-related behaviors (i.e., cessation and relapse, withdrawal, tonic craving, and cue-induced craving). The specific goals of this paper are to synthesize the current literature and to identify areas in need of additional research.

Methods

Systematic Review

A MEDLINE search was conducted in March 2014 to identify publications that included at least one menstrual cycle-related search term (e.g., "menstrual cycle," "ovarian hormones," "estrogen," "progesterone") and at least one smoking-related search term (e.g., "smoking," "tobacco," "cigarettes," "nicotine"). A previous review of studies on menstrual cycle phase differences in withdrawal and cravings[17] was examined for additional references. After removing duplicates and articles not published in English, the remaining publications were individually examined to determine whether they met inclusion criteria, namely that the study: (a) examined one or more types of behaviors related to smoking consumption or cessation (ad lib smoking, smoking cessation, smoking relapse, withdrawal, tonic cravings, cue-induced cravings, smoking topography, or subjective effects of smoking) and (b) examined differences in outcomes by menstrual cycle phase or by ovarian hormones. Information extracted from eligible papers included location of study (country), sample size, menstrual cycle phases assessed, whether biochemical confirmation of menstrual cycle phase occurred, whether women using oral contraceptives were included, and smoking-related outcome measures.

Meta-Analyses

After identifying studies for systematic review, articles were further evaluated for inclusion in meta-analyses. Studies were considered for inclusion if they met the following criteria: (a) provided estimates for both the follicular phase (or sub-phase) and the luteal phase (or sub-phase), and (b) provided the required statistical estimates for meta-analytic evaluation. The statistical estimates were extracted from published papers or obtained directly from the authors for two publications.[31,32] These relatively broad criteria resulted in the identification of studies using multiple methodologies (see Results section for details). For example, some studies randomly assigned participants to either follicular or luteal phase, and compared outcomes between phases (e.g., likelihood of successful cessation, withdrawal, ad lib smoking). Other studies followed participants across multiple menstrual cycle phases and conducted within-person evaluations of cycle differences. Studies also varied in the measures utilized for

each outcome. To generate commensurate effect size estimates, all comparisons between follicular and luteal phase were converted to Hedge's G statistic,[33] with corresponding standard error estimates. Studies were weighted based on 1/*SE*. Only outcomes with at least 5 Hedge's G estimates were included in meta-analyses. Fixed-effects only models were calculated first, with commensurate testing of effect size heterogeneity (Q-statistic). When Q was significant, a random effects model was also calculated. All analyses were conducted using the Metafor package in R.[34]

Results

Study Characteristics

Four hundred thirteen publications were identified through the literature search and 36 of these articles met all the criteria to be included in the review (see Table 1 for study details and measured outcomes). The average sample size of the female participants across studies was 50 (*SD* = 56). Menstrual cycle phase was assessed by self-report and 22 studies also biochemically confirmed cycle phases (e.g., surge of luteinizing hormone levels which occurs just before ovulation). The majority of papers included free cycling women with three papers reporting that samples included women taking oral contraceptives.[35–37] No study reported that they included women using an injectable contraceptive (e.g., Depo-provera).

Behavior Related to Smoking Consumption

Ad Lib Smoking

Seventeen papers examined ad lib smoking, smoking reduction, or nicotine levels by menstrual cycle phase or ovarian hormones (Table 2) but not enough papers met all of the criteria listed above to conduct a formal meta-analysis. The most commonly studied outcome variable was cigarette smoking and these studies yielded mixed results: six studies reported no differences in number of cigarettes smoked by menstrual cycle phase[49,59,60,63] or ovarian hormones,[41,43] three studies reported greater cigarette smoking during the luteal phase,[40,57,61] and five studies reported greater smoking during menses compared either to later in the follicular phase[47,62,67] or other phases (Table 2).[61,68]

Smoking Topography

Because only two studies were identified that examined smoking topography,[41,67] there were insufficient data for a meta-analysis. The first study[67] found significant differences in smoking topography measures (i.e., greater number of puffs, puff duration) by menstrual cycle phase while the second study[41] reported significant differences in smoking topography measures (i.e., greater number of puffs, intensity of puffs) by ovarian hormones (Table 2).

Subjective Effects of Smoking

Four separate laboratory studies by one research group examined differences in the subjective effects of nicotine by menstrual cycle phase[38] or for women receiving progesterone versus placebo.[43,50,55] There were insufficient data for meta-analysis so the individual studies are reviewed below. The first study[38] found lower reported positive subjective effects in response to intravenous (IV) nicotine (e.g., "high," "feel good," "want more") for women in the luteal phase compared to women in the follicular phase. The second study[55] included 12 women, all in the beginning of the follicular phase, who completed two laboratory sessions after overnight abstinence from cigarettes. During the laboratory sessions, participants were administered either 200 mg progesterone or placebo. Progesterone administration was associated with lower ratings of "good effects" after two puffs of a cigarette compared to placebo. Ratings for "strength" and "head rush" were lower in the progesterone condition as well but these differences did not reach significance. In the third study,[50] six women in the early follicular phase and six men participated in two laboratory sessions, each following overnight abstinence from smoking, during which they received either 200 mg progesterone or placebo. Across the full sample, the rating of the "bad effects" was greater and "like drug" was lower in the progesterone condition than the placebo condition in response to IV nicotine. Responses to progesterone versus placebo for just female participants were not reported. Finally, participants in the fourth study[43] were 30 women in the early part of the follicular phase and 34 men who were randomly assigned to receive 200 mg of progesterone, 400 mg progesterone, or placebo for four days. Participants were asked to abstain from smoking for the last three days of medication administration and then completed a laboratory session where subjective effects of smoking were rated after a 2-hr ad lib smoking period. Across the full sample, participants receiving placebo rated "drug strength" as greater compared to the other two conditions and participants who received 200 mg of progesterone rated "drug liking" as lower compared to the other two conditions. The sex by medication interactions were not significant. Across the studies, there was evidence for decreased positive subjective affects and greater negative subjective effects of nicotine with the administration of progesterone or during the luteal phase (the phase when progesterone is at its highest levels).

Behavior Related to Smoking Cessation

Smoking Cessation and Relapse

There were insufficient data to conduct meta-analysis of menstrual cycle phase effects on smoking cessation or relapse. As summarized in Table 3, three studies reported no menstrual cycle phase differences in quit rates[35,49] or time to smoking relapse,[48] two studies reported better outcomes for quitting during the follicular phase,[52,53] and three studies reported better outcomes for quitting during the luteal phase.[42,46,51] The majority of smoking relapse occurred during the same phase as the quit attempt (Table 3). With regard to oral contraceptive use, Epperson and colleagues[35] included 10 women taking oral contraceptives in their sample. Participants using oral contraceptives reported similar levels of negative affect as 47 participants not taking oral contraceptives during the first five days after attempting to quit smoking (M = 4.5, SD = 3.4 vs. M = 4.7, SD = 3.4). Quit outcomes for the subsample of participants using oral contraceptives versus participants not using oral contraceptives were not reported.

Withdrawal

Sufficient data were available to conduct meta-analysis of withdrawal symptoms by menstrual cycle phase (Table 4). Of the 19 studies that included withdrawal symptoms as an outcome measure, 11 were excluded from the meta-analysis. Five of these did not include estimates for follicular versus luteal phases or sub-phases.[36,51,55,56,65] Six studies[52,57–59,61,64] conducted comparisons for follicular versus luteal phases, but provided insufficient information for calculating Hedge's G effect size estimates and standard errors. The remaining eight studies were included in the meta-analysis.[31,32,37,38,44,49,60,66] Estimates from nicotine deprivation study conditions were used when available.

Table 1. Study Characteristics and Assessed Outcomes

							Outcomes assessed								
Reference	Country	Sample size—total	Sample size—women	% Caucasian	Number of menstrual phases assessed	Biochemical confirmation of phase?	Study design[a]	ad lib smoking	Smoking topography	Subjective effects of smoking	Smoking cessation	Smoking relapse	Withdrawal	Cravings—tonic	Cravings—cue induced
Allen et al.[31]	United States	147	147	56	2	Yes	W			X			X	X	
DeVito et al.[38]	United States	160	45	31	2	Yes	B			X			X	X	
Allen, Allen, et al.[39]	United States	47	47	53	2	Yes	W	X							
Sakai et al.[40]	Japan	29	29	–	3	Yes	W	X						X	
Schiller, et al.[41]	United States	98	98	79	See note[e]	Yes	–	X	X						
Mazure et al.[42]	United States	33	33	91	2	–	B				X				
Sofuoglu et al.[43]	United States	64	30	30	See note[d]	–	W	X		X				X	
Epperson et al.[35]	United States	385	185	87	2	–	B				X				
Allen et al.[44]	United States	202	202	82	2	Yes	B						X	X	
Gray et al.[45]	United States	387	37	78	4	Yes	W								X
Allen, Allen, Lunos, et al.[46]	United States	138	138	–	2	Yes	B				X				
Allen, Mooney, et al.[47]	United States	31	31	71	4	Yes	B	X							
Allen, Allen, Widenmier, et al.[48]	United States	38	38	–	2	Yes	B				X			X	
Allen, Allen, and Pomerleau[49]	United States	25	25	76	2	Yes	B	X			X		X	X	
Sofuoglu et al.[50]	United States	12	6	25	See note[d]	–	W						X	X	
Allen et al.[51]	United States	202	202	82	2	Yes	B				X	X	X	X	
Carpenter et al.[52]	United States	44	44	82	2	Yes	B				X		X	X	
Franklin et al.[53]	United States	102	37	65	2	–	B				X				
Franklin et al.[54]	United States	109	41	72	2	–	B			X					X
Sofuoglu et al.[55]	United States	12	12	–	See note[d]	–	W						X		
Allen et al.[32]	United States	30	30	80	2	Yes	W						X	X	
Pomerleau et al.[56]	United States	14	14	93	5	Yes	W	X					X	X	
Snively et al.[57]	United States	14	14	79	2	Yes	W	X					X	X	
Perkins et al.[37]	United States	78	78	–	2	–	B						X	X	
Marks et al.[58]	United States	12	12	–	4	Yes	W						X	X	
Allen et al.[59]	United States	21	21	86	2	Yes	W	X					X	X	
Masson and Gilbert[36]	United States	24	24	–	2	Yes	W						X		
Allen et al.[60]	United States	32	32	91	3	Yes	W	X					X	X	
DeBon et al.[61]	United States	30	30[b]	77	5	Yes	W	X					X		
Marks et al.[62]	United States	9	9[e]	100	5	–	W	X							
Pomerleau et al.[63]	United States	22	22	96	5	–	W	X							
Pomerleau et al.[64]	United States	9	9	–	3	Yes	W	X					X	X	
Craig et al.[65]	United Kingdom	30	20	–	2	–	B	X					X	X	
O'Hara et al.[66]	United States	36	22	–	2	–	B						X		
Steinberg and Cherek[67]	United States	9	9	–	3	–	W	X	X						
Mello[68]	United States	24	24	–	2	–	W	X							

– = not applicable, not reported, or unable to calculate from available data; B = between-subjects; TNP = transdermal nicotine patch; W = within-subjects; X = the outcome was assessed in the study.

[a]Between-subject or within-subject design for the comparison of menstrual cycle phase or ovarian hormones.

[b]15 female participants were smokers, and 15 female participants were non-smokers.

[c]Outcomes were examined by measurement of ovarian hormone levels.

[d]Study of progesterone vs. placebo; all women participated during the early follicular phase.

[e]All female participants met criteria for late luteal phase dysphoric disorder.

Table 2. Studies of Ad Lib Smoking/Smoking Topography and Menstrual Cycle Phase/Ovarian Hormones

Reference	Outcome measure	Type of measurement	Number of menstrual cycle phases	Menstrual cycle phases assessed	Primary findings
Allen et al.[69]	Nicotine levels	Response to nicotine nasal spray in the laboratory	2	Follicular, luteal	Trend level effect of greater maximum nicotine (p = .055) in follicular phase compared to luteal phase.
Sakai et al.[40]	CPD	Daily smoking log for two cycles	3	Follicular, luteal, menstrual	Greater smoking during luteal phase compared to follicular phase
Schiller et al.[41]	Number of cigarettes, smoking topography	1-hr ad lib smoking period in the laboratory	See note[a]	See note[a]	Number of cigarettes smoked not associated with estradiol, progesterone, or estradiol to progesterone ratio. A larger number of puffs were significantly associated with lower levels of progesterone relative to estradiol. Greater intensity of puffs was associated with larger decreases in progesterone and estradiol from the baseline assessment to the laboratory appointment (a 1–2 week period of time).
Sofuoglu et al.[43]	Number of cigarettes	2-hr ad lib smoking period in the laboratory	See note[b]	See note[b]	No significant differences for progesterone vs. placebo
Allen, Mooney, et al.[47]	Number of cigarettes	2-hr ad lib smoking period in the laboratory	4	Follicular, luteal, late luteal, menstrual	Greater smoking during menstrual phase compared to the follicular phase
Allen, Allen, and Pomerleau[49]	CPD	Daily smoking log for 4 weeks	2	Follicular, luteal	No significant differences by menstrual cycle phase
Pomerleau et al.[56]	CPD	Daily smoking log or 4 weeks	5	Post-menses, ovulation, post-ovulation, premenstrual, menstrual	Significant difference among phases in omnibus test, no post doc test reached significance, tread toward greater smoking in post-menses than postovulatory phase.
Snively et al.[57]	CPD	Daily smoking log for 8 weeks	2	Mid-to-late follicular, late luteal	Greater smoking in late luteal phase compared to mid-to-late follicular phase
	Nicotine boost	Inpatient observation	2	Mid-to-late follicular, late luteal	No significant differences in nicotine boost by menstrual cycle phase
Allen et al.[59]	CPD	Inpatient observation	2	Follicular, luteal	No significant differences by menstrual cycle phase
Allen et al.[60]	CPD	Daily smoking log for three days during each cycle phase	3	Follicular, luteal, late luteal	No significant differences by menstrual cycle phase
DeBon et al.[61]	CPD	Daily smoking log for one cycle	5	Follicular, ovulation, early luteal, late luteal, menstrual	Greater smoking during menstrual and luteal phases compared to ovulation
Marks et al.[62]	6-point scale: 1 (not at all) to 6 (extreme)	Daily smoking log for two cycles	5	Post-menses, ovulation, post-ovulation, premenstrual, menstrual	Greater smoking during menstrual phase than post-ovulation phase
Pomerleau et al.[63]	CPD	Daily smoking log for 6 weeks	5	Post-menses, ovulation, post-ovulation, premenstrual, menstrual	No significant differences by menstrual cycle phase
Pomerleau et al.[64]	Nicotine intake	Smoking one cigarette in the laboratory	3	Early follicular, mid-to-late follicular, late luteal	Trend level effect (p < .10) of phase on nicotine intake (mid-to-late follicular > early follicular and late luteal).
Craig et al.[65]	Smoking reduction (% change)	Percent reduction in smoking on "no smoking" days	2	Midcycle, premenstrual	Greater smoking reduction in participant asked not to smoke for two days during the midcycle phase (90%) compared to premenstrual (i.e., late luteal) phase (78%).

Table 2. Continued

Reference	Outcome measure	Type of measurement	Number of menstrual cycle phases	Menstrual cycle phases assessed	Primary findings
Steinberg and Cherek[67]	Number of cigarettes, smoking topography	2-hr ad lib smoking period in the laboratory	3	Premenstrual, menstrual, other	Greater smoking during menstrual phase compared to premenstrual and other phases. Participants took more puffs from their cigarettes and had longer puff durations when assessed during the "menstrual phase" (defined by the authors as a testing session on a day that "menstrual flow occurred" based on participant self-report; that is, the beginning of the follicular phase) compared to the "premenstrual" (5 days before menses onset) or "other" (any day that was not classified in one of the other two conditions) phases.
Mello et al.[68]	Change in CPD	Inpatient observation	2	5 days before premenstrual phase, premenstrual	The majority of participants (70%) increase d their smoking during premenstrual phase by an average of 2.68 (*SD* = 0.44) CPD

CPD = cigarettes per day. The menstrual phase (i.e., menses) occurs during the early portion of the follicular phase.
[a]Outcomes were examined by measurement of ovarian hormone levels.
[b]Study of progesterone vs. placebo; all women participated during the early follicular phase.

In a fixed effects-only model the mean weighted Hedges G effect size was 0.27 (95% CI = 0.15, 0.39; $p < .001$), with smokers exhibiting higher withdrawal scores in the luteal phase compared to the follicular phase. Given evidence for significant heterogeneity between studies ($Q = 14.52$, $p < .05$; $I^2 = 57.2\%$), a random effects model was also calculated (Figure 1). The Hedge's G statistic from this random effects model was 0.32 (95% CI = 0.10, 0.55; $p < .01$), with luteal phase demonstrating greater withdrawal symptoms than follicular phase.

This finding of greater withdrawal in the luteal phase compared to the follicular phase may be related to premenstrual symptomatology which is greater during the late luteal phase[40,60] and overlaps with withdrawal symptoms.[32] While five studies assessed premenstrual symptoms;[31,37,44,49,60] there were insufficient data to determine what impact premenstrual symptomatology may have on the relationship between menstrual cycle phase and withdrawal symptoms.

One study compared withdrawal symptoms in women currently using oral contraceptives ($n = 12$) and women not using oral contraceptives ($n = 12$).[36] After overnight abstinence, women using oral contraceptives did not report greater overall withdrawal symptoms but did report greater physical withdrawal symptoms (e.g., heart beat faster) than women not using oral contraceptives (mean and *SD* not reported, $p < .05$). Women using oral contraceptives also demonstrated larger increases in heart rate and blood pressure after smoking two cigarettes. In a second study,[37] results did not change when women taking oral contraceptives ($n = 15$ out of a total sample of 78) were excluded from the analyses.

Tonic Cravings

Sufficient data were available to conduct meta-analysis of cravings by menstrual cycle phase (Table 4). Of the 21 studies that included tonic craving as an outcome measure, 13 were excluded from the meta-analysis. Five of these did not include comparisons for follicular versus luteal phases.[43,50,55,56,65] Eight studies included comparisons for follicular versus luteal, but provided insufficient data for computing Hedge's G effect sizes and standard errors.[31,51,52,57–60,64] The remaining eight studies were included in the analysis.[32,37,38,40,44,48,49,61] Consistent with our methods for withdrawal, craving values were based on nicotine deprivation conditions when available. In a fixed-effects only model (Figure 1), there was a trend toward greater cravings during the luteal phase compared to the follicular phase but this difference did not reach significance (Hedge's G = 0.15, 95% CI = −0.01, 0.30; $p = .06$). There was no evidence for heterogeneity between effect size estimates ($Q = 13.50$, $p > .05$), therefore random-effects model estimates were not calculated.

Cue-Induced Cravings

In the first of two identified studies that examined cue-induced cravings to smoke by menstrual cycle phase,[54] women in the luteal phase reported a greater cue-induced increase in desire to smoke compared to women in the follicular phase. In the second study,[45] participants in the early follicular phase reported a greater increase in cravings compared to participants in the late luteal phase after exposure to smoking objects, although differences were no longer significant after controlling for exposure to non-smoking objects.

Discussion

Over the past few decades, a number of studies have identified that menstrual cycle and ovarian hormones influence smoking behavior. In the current study, we conducted a systematic review and meta-analysis, where possible, to examine menstrual cycle effects on seven aspects of smoking in order to synthesize research findings and ascertain areas in need of additional research. Thirty-six papers published over the past 30 years were identified that examined the impact of menstrual cycle phase or ovarian hormones on at least one

Table 3. Studies of Smoking Cessation/Relapse and Menstrual Cycle Phase/Ovarian Hormones

Reference	Reference note	Type of treatment	Length of treatment	Number of menstrual phases assessed	Menstrual cycle phases assessed	Random assignment to menstrual phase for quit attempt?	Primary findings
Mazure et al.[42]	–	Bupropion (300 mg)	6 weeks	2	Follicular, luteal	No	Greater point prevalence abstinence for participants who quit during the luteal phase (62.5%) compared to the follicular phase (29.4%, $p < .05$) at the end of the trial. No significant differences in quit rates by menstrual cycle phase at the three month follow-up (luteal phase, 18.8%; follicular phase, 11.8%; $p > .05$).
Epperson et al.[35]	–	TNP (21 mg/day), Naltrexone (0, 25, 50, 100mg)	6 weeks	2	Follicular, luteal	No	No significant differences in quit rates by menstrual cycle phase
Allen, Allen, Lunos, et al.[46]	Secondary analysis of Allen et al.[51]	Counseling	26 weeks	2	Follicular, luteal	No[a]	More participants relapsed during the follicular phase than the luteal phase (59.7% vs. 40.3%, $p < .05$). The majority of participants (65.9%) relapsed in the same phase in which they quit smoking.
Allen, Allen, Widenmier, et al.[48]	Secondary analysis of Allen et al.[51]	Counseling	26 weeks	2	Follicular, luteal	Yes	No significant differences in time to relapse to smoking by menstrual cycle phase
Allen, Allen, and Pomerleau[49]	Secondary analysis of Allen et al.[51]	Counseling	26 weeks	2	Follicular, luteal	Yes	No significant differences in quit rates by menstrual cycle phase
Allen et al.[51]	–	Counseling	26 weeks	2	Follicular, luteal	Yes	More participants who quit during the follicular phase had relapsed to smoking after 14 days (84%) and 30 days (86%) compared to the participants who quit during the luteal phase (14 days, 65%; 30 days, 66%; ps $< .001$). With regard to the outcome variable of days until seven slips, participants who quit smoking during the follicular phase relapsed to smoking in a fewer number of days ($M = 20.6$ days, $SD = 45.8$) than participants who quit in the luteal phase ($M = 39.2$, $SD = 59.0$, $p < .05$). The majority of participants relapsed in the same phase in which they quit smoking (Continuous abstinence, 88%–91%; prolonged abstinence, 69%–76%).

Table 3. Continued

Reference	Reference note	Type of treatment	Length of treatment	Number of menstrual phases assessed	Menstrual cycle phases assessed	Random assignment to menstrual phase for quit attempt?	Primary findings
Carpenter et al.[52]	–	TNP (21 mg/day), Counseling	6 weeks	2	Follicular, luteal	Yes	Non-significant trend of higher point prevalence abstinence after 2 weeks for participants who quit during the follicular phase (treatment initiators, 32%; intention to treat sample, 24%) compared to the luteal phase (19%, 16%).
Franklin et al.[53]	–	TNP (21mg/day), Counseling	8 weeks	2	Follicular, luteal	No	Greater abstinence for participants who quit during the follicular phase vs. the luteal phase after 3 days of treatment (81% vs. 48%, $p < .05$) and 1 week after the end of TNP treatment (69% vs. 29%, $p < .05$).

– = not applicable, not reported, or unable to calculate from available data; TNP = transdermal nicotine patch.
[a]Participants were women who had relapsed after a quit attempt and self-selected the timing of a second quit attempt.

aspect of smoking behavior. While there was evidence for menstrual cycle effects on all aspects of smoking behavior, some variables (e.g., cue-induced cravings, smoking topography) were studied by a small number of investigations and results were mixed for most variables. The research to date does not yet present a cohesive and clear picture of the relationship of menstrual cycle to smoking behavior.

Meta-analytic results found that women reported significantly greater withdrawal during the luteal phase compared to the follicular phase quantifying the findings of one previous qualitative literature review.[17] Additionally, there was a trend toward women reporting greater cravings during the luteal phase (marginally outside the criterion for statistical significance). Women report decreased positive and increased negative subjective effects of nicotine during the luteal phase[38] and with the administration of progesterone [43,50,55] also suggesting luteal phase effects on smoking as progesterone levels are the highest during this phase of the menstrual cycle. However, the findings of greater withdrawal and cravings during the luteal phase are difficult to reconcile with the suggestion that progesterone is protective against addictive behaviors[18] and preclinical evidence of decreased nicotine self-administration with higher progesterone in non-human primates and rats.[18] Progesterone levels vary across the luteal phase, reaching a peak in the mid-luteal phase and decreasing dramatically by the end of the luteal phase. Studies are needed that examine the association of smoking with changes in progesterone within the luteal phase more closely to clarify the role of progesterone in smoking behavior at different points during the phase.

Other smoking-related variables—including ad lib smoking, smoking topography, cue-induced craving, and cessation—failed to demonstrate consistent phase effects. Among studies of ad lib smoking, various studies demonstrated no differences, greater smoking in follicular phase, or greater smoking in the luteal phase. The few studies of cue-induced cravings and smoking topography also found inconsistent results. The small number of studies and their mixed results limit the ability to draw conclusions about menstrual cycle effects on ad lib smoking, cue-induced cravings, and smoking topography. Results are similarly mixed for smoking cessation with studies reporting no differences by menstrual cycle phase, preferential outcomes for luteal phase, and preferential outcomes for follicular phase.

These mixed results found for many of the studied variables may be related to variations in methodologies and interventions.[17,74] Many studies had small sample sizes and were based on retrospective rather than prospective trials. Across studies, the specific phases and sub-phases under investigation, methods to confirm cycle phase, and outcome variables have varied widely and in precision making cross-study comparisons difficult. The diverse methodology used in these studies also restricted the number of variables which could be examined using meta-analysis and limited the number of studies that could be included in the meta-analyses of withdrawal and cravings. These variations may have also impacted the meta-analytic outcomes, that is, the craving analysis did not reach statistical significance potentially due to variation in the measures of cravings (Figure 1) and the timing of craving measurement (e.g., early vs. late luteal). Further, smoking cessation studies differed in the type of interventions (behavioral vs. pharmacological treatment).[74] Participants received diverse treatments (counseling, transdermal nicotine patch [TNP], bupropion, naltrexone) which may have had differential impacts on outcome related variables such as withdrawal and craving relief. While the current findings suggest that pharmacological treatments for smoking cessation interact with ovarian hormones with regard to cessation outcomes, the nature of these relationships has yet to be fully elucidated.

Most studies collapsed participants into menstrual cycle phases, with menstrual cycle serving as a proxy for ovarian hormone levels. The majority of the studies included in the review (21 out of 36 studies) compared two phases: the luteal phase and the follicular phase. The meta-analyses also compared the luteal phase to the follicular phase, as the two-phase comparison was the most common,

Table 4. Studies of Withdrawal/Cravings and Menstrual Cycle Phase/Ovarian Hormones

Reference	Included in meta-analysis?	Treatment study?	Type of treatment	Number of menstrual phases assessed	Menstrual cycle phases assessed	Measure of withdrawal	Measure of cravings	Assessment setting	Primary findings
Allen et al.[31]	W	No	–	2	Follicular, luteal	MNWS	BQSU	Outpatient research clinic/lab	No significant differences in withdrawal by menstrual cycle phase during ad lib smoking. Greater withdrawal symptoms reported during luteal phase compared to the follicular phase during smoking abstinence. No significant differences in craving by menstrual cycle phase.
DeVito et al.[38]	W, C	No	–	2	Follicular, luteal	MNWS	BQSU	Outpatient research clinic/lab	No significant differences in withdrawal or cravings by menstrual cycle phase.
Sakai et al.[40]	C	No	–	3	Follicular, luteal, menstrual	–	VAS scale (0–100)	Diaries completed at home	Greater cravings to smoke during menstrual phase compared to follicular or luteal phases
Sofuoglu et al.[43]	–	No	–	See note[a]	See note[a]	–	BQSU	Outpatient research clinic/lab	Lower BQSU Factor 1 score for 400 mg progesterone compared to placebo and 200 mg progesterone
Sofuoglu et al.[50]	–	No	–	See note[a]	See note[a]	MNWS (modified, 0–100 scale)	BQSU	Outpatient research clinic/lab	No significant main effects of progesterone vs. placebo for withdrawal lower BQSU total score for 200 mg progesterone compared to placebo.
Allen et al.[44]	W, C	Yes	Counseling	2	Follicular, luteal	MNWS	QSU	Outpatient research clinic/lab	No significant differences in total withdrawal or cravings by menstrual cycle phase. Significantly greater report of increased appetite/weight gain (withdrawal symptom) for participants who quit during follicular phase compared to the luteal phase. Participants assigned to quit smoking during the follicular phase who reported higher anger and craving withdrawal symptoms were more likely to relapse to smoking at 14 days compared to those with lower anger and craving
Allen, Allen, Widenmier, et al.[48]	C	Yes	Counseling	2	Follicular, luteal	–	8-point scale (0 = not at all, 7 = very strong)	Outpatient research clinic/lab	Participants in follicular phase reported greater cravings to smoke at wake-up compared to participants in luteal phase. Difference was no longer significant after controlling for level of nicotine dependence.
Allen, Allen, and Pomerleau[49]	W, C	Yes	Counseling	2	Follicular, luteal	MNWS	MNSW-craving item	Diaries completed at home	Greater withdrawal reported during the luteal phase than the follicular phase. No significant differences in cravings by menstrual cycle phase.

Table 4. Continued

Reference	Included in meta-analysis?	Treatment study?	Type of treatment	Number of menstrual phases assessed	Menstrual cycle phases assessed	Measure of withdrawal	Measure of cravings	Assessment setting	Primary findings
Allen et al.[51]	–	Yes	Counseling	2	Follicular, luteal	MNWS	MNSW-craving item, QSU	Outpatient research clinic/lab	No significant differences in withdrawal or cravings by menstrual cycle phase.
Carpenter et al.[52]	–	Yes	TNP, Counseling	2	Follicular, luteal	MNWS	MNSW-Craving item	Outpatient research clinic/lab	Greater total withdrawal, cravings, and fatigue reported by participants assigned to quit in the follicular phase compared to participants assigned to quit in the luteal phase.
Sofuoglu et al.[55]	–	No	–	See note[a]	See note[a]	NWSC	NWSC-craving item	Outpatient research clinic/lab	No significant difference in overall withdrawal for progesterone vs. placebo. Lower cravings to smoke on progesterone condition before participants smoked a cigarette.
Allen et al.[32]	W, C	No	TNP[b]	2	Follicular, late luteal	MNWS	MNSW-craving item, QSU	Outpatient research clinic/lab	Greater withdrawal reported in late luteal phase compared to follicular phase. No significant main effect of menstrual cycle phase on cravings (MNWS-craving item; QSU). TNP reduced cravings to a greater degree in the late luteal phase compared to the follicular phase (MNWS-craving item).
Pomerleau et al.[56]	–	No	–	5	Post-menses, ovulation, post-ovulation, premenstrual, menstrual	MNWS	MNSW-craving item	Diaries completed at home	No significant differences in withdrawal by menstrual cycle phase. Greater cravings to smoke during post-menses phase compared to the premenstrual phase.
Snively et al.[57]	–	No	–	2	Follicular, luteal	SJTWQ	SJTWQ	Inpatient research clinic/lab	No significant differences in withdrawal or cravings by menstrual cycle phase.
Perkins et al.[37]	W, C	Yes	Counseling	2	Follicular, luteal	DSM-IV symptoms, 0–100 scale	Desire to smoke, 0–100 scale	Outpatient research clinic/lab	No significant differences in withdrawal by menstrual cycle phase during pre-quit period. Greater increase in total withdrawal and each withdrawal symptom for participants quitting during the luteal phase compared to the follicular phase. No significant differences in cravings by menstrual cycle phase.
Marks et al.[58]	–	No	–	4	Early follicular, mid-to-late follicular, mid-to-late luteal, late luteal	MNWS (modified; −50 to +50 scale, recoded to 0–50 for analyses)	VAS scale (−50 to +50, recoded to 0–50 for analyses)	Outpatient research clinic/lab	No significant differences in changes in withdrawal or cravings in response to nicotine by menstrual cycle phase.

Table 4. Continued

Reference	Included in meta-analysis?	Treatment study?	Type of treatment	Number of menstrual phases assessed	Menstrual cycle phases assessed	Measure of withdrawal	Measure of cravings	Assessment setting	Primary findings
Allen et al.[59]	–	No	–	2	Follicular, luteal	MNWS	QSU	Inpatient research clinic/lab	No significant differences in withdrawal or cravings by menstrual cycle phase.
Masson and Gilbert[36]	–	No	–	2	Early phase of cycle, menses/ late phase of cycle	SJTWQ	–	Outpatient research clinic/lab	No significant main effects of menstrual cycle phase for withdrawal. Oral contraceptive users reported more physical withdrawal than non-oral contraceptive users.
Allen et al.[60]	W	No	–	3	Follicular, luteal, late luteal	MNWS	MNWS craving item, QSU	Diaries completed at home	Greater withdrawal during the late luteal phase than the follicular or luteal phases. Greater cravings to smoke during the late luteal phase than the follicular phase on the NWSC Craving item. No differences in cravings to smoke by menstrual phase on the QSU.
DeBon et al.[61]	C	No	–	5	Follicular, ovulation, early luteal, late luteal, menstrual	MNWS (modified, added symptoms related to menstrual cycle, e.g., cramping)	–	Diaries completed at home	Greater smoking during menstrual phase compared to ovulation
Pomerleau et al.[64]	–	No	–	3	Early follicular, mid-to-late follicular, late luteal	MNWS (modified, −5 to +5 scale)	MNWS-craving item	Outpatient research clinic/lab	Trend ($p < .10$) toward main effect of phase on withdrawal scores. No significant differences in cravings by menstrual cycle phase.
Craig et al.[65]	–	No	–	2	Midcycle, premenstrual	TWQ	Frequency of urges to smoke, strength of urges to smoke	Diaries completed at home	No significant differences in withdrawal by menstrual cycle phase. Greater frequency and strength of urges to smoke for midcycle phase compared to premenstrual phase.
O'Hara et al.[66]	W	Yes	Counseling	2	Follicular, luteal	SJTWQ	–	Outpatient research clinic/lab	Greater withdrawal reported by women who quit during the follicular phase compared to the luteal phase 24, 48, and 72 hr after quitting.

– = not assessed, not applicable, not reported, or unable to calculate from available data; BQSU/QSU = (brief) questionnaire on smoking urges[70,71]; C = this study was included in meta-analysis of cravings; MNWS = Minnesota Nicotine Withdrawal Scale (also referred to as Nicotine Withdrawal Symptom Checklist; Hughes and Hatsukami[72]); SJTWQ = Shiffman–Jarvik Tobacco Withdrawal Questionnaire (also referred to as the Shiffman-Jarvik Withdrawal Questionnaire; Shiffman and Jarvik[73]); TNP = transdermal nicotine patch; TWQ = the withdrawal questionnaire (no reference provided); VAS = visual analog scale; W = this study was included in meta-analysis of withdrawal.

[a]Study of progesterone vs. placebo; all women participated during the early follicular phase.

[b]Participants were randomized to receive TNP or placebo patch over a seven day period for each of 2 menstrual cycle phases to assess changes in withdrawal symptoms by menstrual cycle and patch condition.

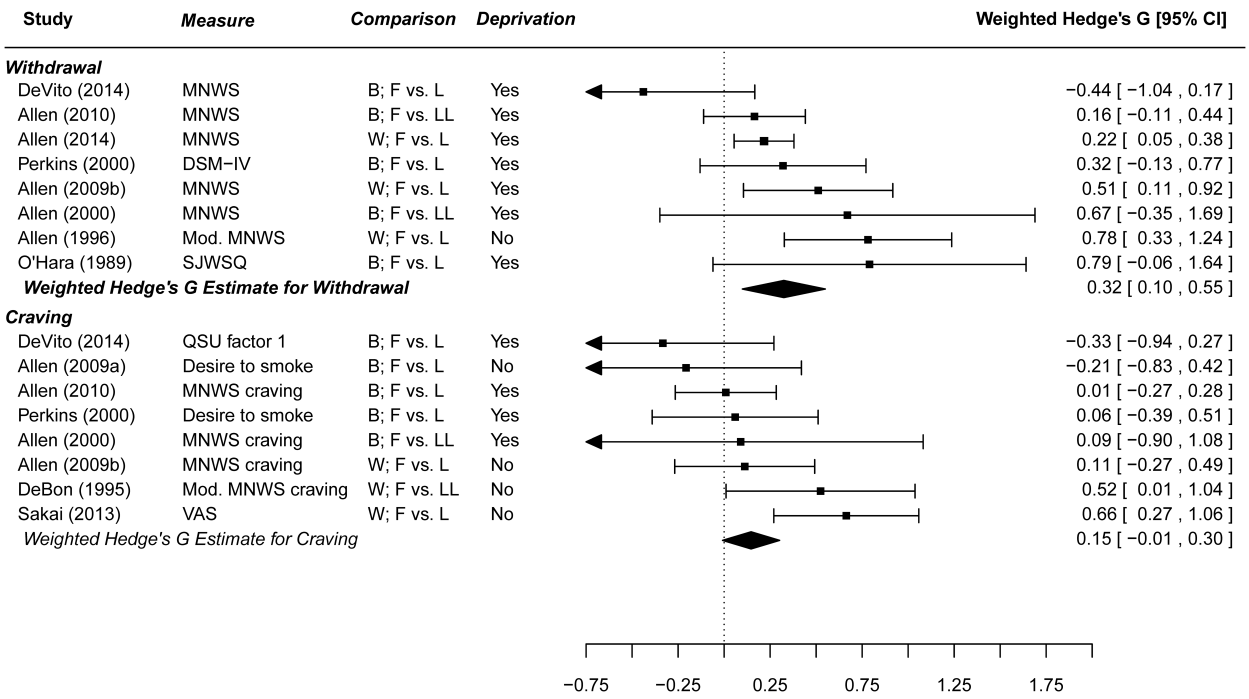

Figure 1. Meta-analytic findings for withdrawal and tonic cravings by menstrual phase. MNWS = Minnesota Nicotine Withdrawal Scale; QSU = questionnaire of smoking urges; SJWSQ = Shiffman-Jarvik Withdrawal Symptom Questionnaire; VAS = visual analog scale; B = between subject comparison; F = follicular; L = luteal; LL = late luteal; W = within subject comparison. When deprivation = yes, estimates were calculated during a nicotine deprivation condition of the study. Weighted Hedge's G for withdrawal calculated using a random-effects model (significant heterogeneity); for craving calculated using a fixed-effects only model (non-significant heterogeneity). Allen et al., 2009a is reference Allen, Allen, Widenmeir, et al.[48] and Allen et al., 2009b is reference Allen, Allen, Pomerleau[49].

and there were not sufficient data available to compare important sub-phases that may show different associations with smoking behavior due to changes in hormone levels within the phase (e.g., mid-luteal when progesterone is highest vs. late luteal when progesterone decreases to lower levels; early follicular during menses vs. mid- or late-follicular when estrogen levels rise to a peak). There is a need for more studies that use precision in measuring hormone levels during difference sub-phases of the menstrual cycle. For example, Schiller and colleagues[41] found that women smoked more intensely when there were larger drops in progesterone and estrogen, which occur during the latter part of the luteal phase. There is also a need for studies to consider not just changes in estrogen and progesterone but how the two hormones interact with each other over the course of the menstrual cycle. Schiller et al.[41] also found that higher levels of estrogen relative to progesterone, which occurs in the follicular phase, were associated with more intense smoking consistent with preclinical data suggesting that the estrogen may promote use of an addictive substance like nicotine[18] and highlighting the importance of examining levels of estrogen and progesterone relative to each other by calculating the ratio of progesterone to estrogen. Studies that capture dynamic changes in ovarian hormone levels across the cycle can provide novel information about the best timing for women to attempt to quit smoking and best type of treatment to match the timing of the quit attempt. For example, Saladin and colleagues[75] found that increases in progesterone levels (consistent with the early luteal phase) were associated with greater success at smoking cessation and, importantly, that these benefits were found in women using TNP but not women taking varenicline.

Linked to the need to determine ways to use information about the menstrual cycle to improve cessation outcomes, research is also needed that includes assessment of menstrual cycle phase at relapse. The majority of women and men relapse to smoking within a few days of the quit attempt[76] and, for women, relapse more often occurs in the same phase of the menstrual cycle as the quit attempt.[46,51] In addition, women appear to relapse to smoking at higher rates than men over longer periods of time[77] highlighting the need for continued efforts to reduce relapse both in the short- and the long-term. Continued research on all aspects of smoking by menstrual cycle phase or ovarian hormones is needed to allow for additional and more finely-grained statistical analyses.

Future research may also benefit from taking a more comprehensive look at the progesterone and estrogen system (e.g., the impact of metabolites of the ovarian hormones). Allopregnanolone is a metabolite of progesterone that also is found in higher levels in the luteal phase compared to the follicular phase[69,78] and a study of female adult smokers found that allopregnanolone levels during smoking abstinence, relative to ad lib smoking, increased in the luteal phase and decreased in the follicular phase.[69] Additional research can help clarify the relationship between progesterone and allopregnanolone level changes and smoking cessation including the effects of natural increases in progesterone versus administrated progesterone on smoking behavior and whether progesterone or its metabolites have benefits as a treatment for nicotine dependent smokers[18] as preclinical research has demonstrated reduced nicotine withdrawal symptoms in response to allopregnanolone pretreatment.[79]

Premenstrual symptoms, which demonstrate overlap with withdrawal symptoms,[32] are greatest during the late luteal phase[40,44,58,60]

and higher premenstrual symptomatology is associated with greater cigarette consumption, withdrawal, and relapse in some studies (e.g., Allen, Allen, and Pomerleau[49]; O'Hara et al.[66]; Perkins et al.[37]; Sakai and Ohaski[40]; although some results differ, see also Marks et al.[62]; Mello[68]; Pomerleau et al.[64]). The available data did not allow us to account for premenstrual symptoms in the association of withdrawal and menstrual cycle phase. It will be important for future work to clarify the role of premenstrual symptoms in the association between withdrawal and menstrual cycle phase. In addition, future studies should also examine the impact of successful treatment of premenstrual symptoms on cessation outcomes.

An estimated 11 million women in the United States take oral contraceptives making it the most commonly used method of contraception by women of reproductive age.[80] Oral contraceptives which contain estrogen are related to faster nicotine metabolism[23,81] which is itself related to worse smoking cessation outcomes.[27] Only three studies in the review[35–37] reported that they included women using oral contraceptives (see Results) and these data should be considered preliminary as the number of oral contraceptive users in each study was small (*n*s = 10–15). No research was identified that examined the association of an injectable contraception such as medroxyprogesterone acetate (Depo-provera), a progestin-only shot, to smoking behavior. Female smokers taking estrogen and progesterone-based contraceptives are a large yet understudied group in the smoking literature and it is not known how hormone-based contraceptive use impacts cessation outcomes. It can be hypothesized that contraceptives that deliver estrogen may hinder quit attempts while contraception that delivers progesterone may aid quit attempts, but very little is known at this time about the impact of hormone-based contraceptive use on smoking-related behaviors including differences for women receiving contraceptives that deliver estrogen and progesterone versus progesterone alone.

While menstrual cycle phases have an impact on smoking behavior, smoking behavior conversely effects the menstrual cycle. Smoking in women is associated with dysmenorrhea and menstrual irregularity[9,82] and altered ovarian cycle and hormone levels.[83,84] Compared to female nonsmokers, female smokers demonstrate changes in estrogen metabolism and lower circulating estrogen,[85,86] a shorter reproductive lifespan,[9,87,88] lower ovarian reserve,[89,90] and quicker entry into all stages of the menopausal transition.[91,92] Pregnancy-related smoking consequences include infertility, spontaneous abortion, preterm delivery, and perinatal mortality.[9,89] These data again highlight the importance of measuring hormone levels when conducting smoking research in women. Using information about the association of the menstrual cycle to smoking to improve cessation outcomes for women may also have important consequences on improving menstrual cycle health.

Conclusions

The impact of menstrual cycle phase on smoking behavior and cessation outcomes is complicated and continued research is needed to elucidate the relationships. Specifically, there is a need for studies to collect ovarian hormone levels to more precisely quantify the impact of hormone levels, changes in hormone levels, and the interactions of estrogen and progesterone on smoking behavior. It will be critical for future research to consider ovarian hormones as a system that continually undergoes dynamic changes. Clarifying the relationship between ovarian hormones and smoking, including cessation outcomes and interactions with medication response, would guide information on the best types and timings of interventions to help women achieve successful long-term cessation.

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Declaration of Interests

None declared.

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