Published in final edited form as:

Prev Med. 2020 November ; 140: 106227. doi:10.1016/j.ypmed.2020.106227.

Abuse Liability of Cigarettes with Very Low Nicotine Content in Pregnant Cigarette Smokers

Sarah H. Heil, PhD^a, Cecilia L. Bergeria, PhD^{a,1}, Dustin C. Lee, PhD^b, Janice Y. Bunn, PhD^a, Roxanne F. Harfmann, BA^a, John R. Hughes, MD^a, Haley J. Tetreault, BA^a, Stephen T. Higgins, PhD^a

^aVermont Center on Behavior and Health, University of Vermont, UHC MS #482, 1 South Prospect St., Burlington, Vermont 05401

^bDepartment of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, Maryland 21224-6823

Abstract

The U.S. Food and Drug Administration has proposed reducing the nicotine content of cigarettes to a minimally-addictive level. To our knowledge, this study is the first to examine how pregnant smokers respond to very low nicotine content (VLNC) cigarettes.

In Phase 1, participants blindly sampled two VLNC cigarettes (0.4 and 2.4 mg/g of tobacco) and their usual brand (UB) cigarette in separate sessions, then completed a behavioral economic simulation task and measures of subjective effects, craving/withdrawal, and smoking topography. Phase 2 directly compared the relative reinforcing effects of the cigarettes using concurrent choice testing. All possible dose-pair combinations were tested in separate sessions where puffs were earned *ad libitum* by clicking the code associated with their preferred cigarette 10 times. Phase 3 tested the 0.4mg/g-UB dose-pair where UB puffs could be earned with a progressively incremented number of clicks (maximum 8,400).

Corresponding author: Sarah H. Heil, Ph.D., UHC MS #482, 1 South Prospect St., Burlington, Vermont 05401, Sarah.heil@uvm.edu.

¹Dr. Bergeria is now at Johns Hopkins University School of Medicine, Baltimore, Maryland.

Credit author statement

Heil: conceptualization, methodology, writing – original draft, supervision, project administration, funding acquisition

Bergeria: investigation, writing – review and editing, project administration

Lee: writing – review and editing, supervision

Bunn: formal analysis, data curation, writing – review and editing

Harfmann: investigation, writing – review and editing, visualization

Hughes: conceptualization, methodology, writing – review and editing, funding acquisition

Tetreault: investigation, writing – review and editing

Higgins: conceptualization, methodology, writing – review and editing, supervision, project administration, funding acquisition

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of interest: Dr. Hughes has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control. He currently receives consulting fees from Swedish Match and has received fees in the past from Altria and Philip Morris to assist their efforts to develop less-risky tobacco products such as e-cigarettes.

Ten pregnant smokers in Burlington, VT and Baltimore, MD participated in 2017-2018. Regarding abuse liability, participants chose the 0.4-mg/g dose less than UB (22% vs. 78%) during concurrent choice testing and the 0.4-mg/g dose sustained less demand than the 2.4-mg/g and UB doses on the simulation task. Positive subjective effects were also lower for both VLNC cigarettes vs. UB. Each cigarette reduced nicotine craving/withdrawal and no significant changes indicative of compensatory smoking were noted.

Reducing the nicotine content of cigarettes may decrease their abuse liability in pregnant smokers without causing untoward craving/withdrawal or compensatory smoking. Studies of extended exposure to VLNCs in pregnant women are warranted.

Keywords

cigarette smoking; nicotine content; reduced nicotine content cigarettes; tobacco; addiction; reinforcement; pregnant; women; socioeconomic disadvantage

Introduction

Nicotine is the constituent in cigarettes that causes addiction.¹ The U.S. Food and Drug Administration (FDA) has issued an Advanced Notice of Proposed Rule Making to reduce the nicotine content in cigarettes to a minimally-addictive level² and even more recently approved the marketing of two new reduced nicotine content cigarettes in the U.S.³ Research in smokers from the general population⁴ and those in populations particularly vulnerable to nicotine dependence, such as smokers with psychiatric conditions and socioeconomic disadvantage,^{5,6} indicates that reducing nicotine content to low levels also reduces the reinforcing value and abuse liability of smoking without causing untoward craving/withdrawal or compensatory smoking. However, these studies have uniformly excluded pregnant cigarette smokers. It is important to promote smoking cessation during pregnancy given the adverse health consequences of smoking while pregnant, including pregnancy complications, fetal growth restriction, and detrimental birth and neonatal outcomes,⁷⁻¹⁰ but for pregnant women who are unable or unwilling to quit smoking, innovative strategies to lower nicotine dependence like reducing the nicotine content of cigarettes may help reduce harm.

One physiological change that may make it more difficult for women to quit smoking or reduce the number of cigarettes they smoke during pregnancy is a considerable pregnancy-induced increase in nicotine metabolism.^{11,12} Given the tendency for smokers to titrate nicotine levels, this change may also put pregnant women at greater risk for untoward craving/withdrawal or compensatory smoking compared to smokers in the general population or those in other vulnerable populations. Hence, it is crucial to understand the effects of very low nicotine content (VLNC) cigarettes in pregnant women. The potential policy changes and availability of reduced-nicotine products in the U.S. tobacco marketplace make it especially important to ensure that this population can use these products without untoward craving/withdrawal or engaging in compensatory smoking. The current study is the first to examine the use of VLNC cigarettes in pregnant cigarette smokers, including

their impact on reinforcing effects, subjective effects, craving and withdrawal, and smoking topography.

Methods

Participants in this two-site, within-subject study were 10 adult, pregnant (< 25 weeks estimated gestational age) cigarette smokers (80 ng/mL urine cotinine at screening) with no regular use (>9 days) of other tobacco or nicotine products in the past month and no intentions to quit smoking in the next month. Participants reported no serious psychiatric or medical comorbidities and were determined to be in good general health by a licensed medical professional. The institutional review boards at the University of Vermont (Burlington, VT), and Johns Hopkins University School of Medicine (Baltimore, MD), approved the study and the protocol was reviewed by the FDA Center for Tobacco Products. All participants provided informed consent. Results from our similar study in socioeconomically disadvantaged women of childbearing age were used to estimate sample sizes⁵. A sample size of 10 women provides 80% power to detect differences in smoker preference in the concurrent choice task and total puff volume and number, assuming a Type I error of 0.05.

Participants completed nine experimental sessions under acute smoking abstinence (~6-8 hrs) evidenced by at least a 50% reduction in baseline breath carbon monoxide (CO) levels. At the beginning of each session before study procedures, participants took two puffs of their usual brand (UB) cigarette and waited 30 minutes to standardize time since last puff across sessions and participants. Sessions were organized into three phases. Within each phase, research cigarettes were presented in a random order using a Latin Square Design. In Phase 1 (Sessions 1-4, 2 hrs each), participants were oriented to the study procedures (Session 1) and smoked either UB or one of two VLNC research cigarettes (2.4 and 0.4 mg/g of tobacco) with the VLNC cigarettes tested under double-blind conditions (Sessions 2-4). Participants were instructed to smoke the cigarettes *ad libitum* but used a plastic cigarette holder connected to a Clinical Research Support System (CReSS) Desktop smoking topography device (Borgwaldt KC, Richmond, VA). The UB served as the control, whereas the lowest dose represents a dose below the hypothesized 0.7-mg/g threshold dose for addiction¹³. Subjective value of smoking was assessed in Phase 1 immediately after the participant smoked each cigarette *ad libitum* using the Cigarette Purchase Task (CPT) and modified Cigarette Evaluation Questionnaire (mCEQ). Craving and withdrawal were assessed immediately before and in 15-minute increments for one hour after smoking *ad libitum* with the Questionnaire of Smoking Urges–Brief Scale (QSU–brief) and Minnesota Nicotine Withdrawal Scale (MNWS, 15-item version). Prior to smoking during the session, participants were instructed to complete measures of craving and withdrawal based on how they felt since their last scheduled visit. After smoking during the session, participants completed the scales based on how they felt since smoking. Compensatory smoking was assessed with CO measured immediately before and in 15-minute increments for one hour after smoking *ad libitum* and with smoking topography (puff volume, puff duration, maximum flow, and puff number) measured with a CReSS Desktop device.

Phase 2 (Sessions 5-7; 3 hrs each) directly compared the relative reinforcing value of the cigarettes by allowing participants to choose which they preferred to smoke. Each of the three possible cigarette dose-pair combinations was tested once in separate sessions. During each session, the cigarettes available were represented by distinctive letter codes on a computer screen; sets of two standardized puffs (60mL) could be earned *ad libitum* by clicking 10 times on the letter code associated with the preferred cigarette. Cigarette puffs were measured by a CReSS Desktop device. Phase 3 (Sessions 8-9; 4 hrs each) used the same arrangement as Phase 2, but compared only the 0.4 mg/g dose and UB. Puffs from the lower dose were available for 10 clicks, but the number of clicks necessary to earn puffs from the higher dose started at 10 and incremented progressively to 8400 clicks (progressive-ratio schedule).⁵

Statistical Methods

Analyses of Phase 1 results examined differences between the research cigarettes on the CPT, mCEQ, and smoking topography by using repeated-measures analysis of variance, with nicotine dose as the within-participant factor. The MNWS, QSU-Brief, and CO were examined similarly with time as a second within-participant factor. Analyses also included a fixed effect for session and random effects for sequence and study site. Time-by-dose interactions were included to test whether subjective effects or CO before and after smoking differed by dose; when not significant, interaction effects were dropped from the models. MNWS total score was determined using the following items: angry, irritable, frustrated; anxious, nervous; depressed mood, sad; difficulty concentrating; increased appetite, hungry, weight gain; insomnia, sleep problems, awakening at night; restless; and impatient. Desire to smoke was considered as a separate item.

Differences in preference among all possible dose pairs (Phase 2) were similarly examined using repeated-measures analysis of variance, with each pairwise combination as the within-participant factor. Differences among participants in preference for the highest- vs lowest-dose cigarettes (Phase 3) were examined using a repeated-measures analysis of variance with session as the repeating factor.

Missing data were minimal, amounting to 2% or less for all outcomes, with the exception of the CPT, where data were missing for two women in the low nicotine conditions and one woman in the usual brand condition. A maximum likelihood approach was used, which allows the use of all data that is available without imputation. Significance for all tests was $P < .05$. All statistically significant effects were followed with post-hoc testing to examine specific differences among the three dose conditions. All were 2-tailed, with P values subject to Bonferroni correction.

Results

Participants averaged ($\pm$ SD) 30.6 ($\pm$ 5.2) years of age, 15.2 ($\pm$ 5.0) weeks gestation, smoked 11.9 ($\pm$ 5.2) cigarettes/day with an average nicotine content of 19.1 ($\pm$ 0.9) mg/g per cigarette¹⁴, had a Fagerström Test of Nicotine Dependence score of 3.6 ($\pm$ 1.7), and were not currently planning to quit smoking. Most were White (90%), had a high school education or

less (60%), were never married (90%), and were receiving medication for opioid use disorder (80%).

With respect to abuse liability, UB was chosen more often than chance when paired with the 0.4-mg/g dose ($t_{24}=3.10$, $P=.005$) or the 2.4-mg/g dose ($t_{24}=3.86$, $P=.001$) (Figure 1, Panel A) in Phase 2 concurrent-choice testing. This preference for the UB over the 0.4mg/g dose in Phase 2 concurrent testing was reduced to chance levels when the UB dose was put on a progressive-ratio schedule in Phase 3 ($P=.26$; Cohen's $G=0.11$). In Phase 1, CPT demand decreased by dose ($F_{4,54}=5.18$, $P=.001$), with the 0.4-mg/g dose sustaining less demand than the 2.4-mg/g ($F_{2,36}=3.91$, $P=.03$) and UB doses ($F_{2,36}=11.1$, $P<.001$), although the 2.4-mg/g demand curve did not differ from the UB curve ($F_{2,36}=1.71$, $P=.20$) (Figure 1, Panel B). Also in Phase 1, positive subjective effects of smoking on the mCEQ was lower for both VLNC cigarettes compared to UB ($F_{8,24}=3.64$ – 13.57 , $P=.05$) (Figure 1, Panel C), suggesting reduced abuse liability.

Table 1 shows results on the QSU-brief, MNWS, and breath CO. There was a main effect of time for both QSU factors ($F_{4,36}=9.43$, $P<.001$ and $F_{4,36}=8.21$, $P<.001$, respectively), but no main effect of dose nor interaction of time and dose for Factor 1 ($F_{2,16}=2.87$, $P=.09$ and $F_{8,71}=1.54$, $P=.64$, respectively) or Factor 2 ($F_{2,16}=2.87$, $P=.31$ and $F_{8,71}=1.54$, $P=.68$, respectively). There was a main effect of time for both MNWS desire to smoke item and total score ($F_{4,37}=5.00$, $P<.01$ and $F_{4,37}=5.90$, $P<.01$, respectively), but no main effect of dose nor interaction of time and dose for desire to smoke ($F_{2,16}=2.15$, $P=.15$ and $F_{8,71}=2.02$, $P=.06$, respectively) or total score ($F_{2,16}=1.04$, $P=.37$ and $F_{8,71}=0.56$, $P=.80$, respectively). There was a main effect of time for CO ($F_{4,36}=30.1$, $P<.001$), but no main effect of dose nor interaction of time and dose ($F_{2,16}=0.89$, $P=.43$ and $F_{8,72}=0.97$, $P=.97$, respectively).

Puff number was lower when participants smoked VLNC compared to UB cigarettes ($F_{2,16}=6.96$, $P=.007$), which is inconsistent with compensatory smoking, and there were no other dose differences on mean puff volume ($F_{2,16}=0.86$, $P=.44$), mean puff duration ($F_{2,16}=2.45$, $P=.12$), and maximum flow ($F_{2,16}=0.11$, $P=.90$).

Discussion

The aim of the current study was to evaluate acute response to VLNC cigarettes among pregnant smokers under rigorous laboratory conditions. These results demonstrate that VLNC cigarettes decrease the abuse liability (i.e., relative reinforcing effects) of smoking in pregnant women without causing untoward craving/withdrawal or compensatory smoking. These findings provide further support for a national regulatory policy reducing the nicotine content of cigarettes. These effects are consistent with what has been observed in other vulnerable populations^{5,6} and speak to the potential generalizability of the impact for such a regulatory policy.

The 0.4 mg/g dose most consistently demonstrated decreased abuse liability relative to the participant's UB cigarette, although graded effects were not consistently observed across the 0.4 mg/g and 2.4 mg/g dose. Both VLNC cigarettes produced lower positive subjective ratings, supported less demand, and were less preferred than UB cigarettes.

All cigarettes decreased craving and withdrawal to a comparable degree and there was no evidence that VLNCs resulted in women experiencing untoward levels of craving or withdrawal relative to UB cigarettes. Dose-dependent decreases in craving and withdrawal have been observed among other vulnerable populations.^{5,6} We are not aware of any reason why pregnant smokers would not also be sensitive to these dose differences, suggesting that the lack of dose-dependent differences may be due to limited sample size. Likewise, despite increases in nicotine metabolism, we saw no evidence that pregnant smokers engaged in compensatory smoking, consistent with observations in other vulnerable populations.⁵ Smoking topography and CO exposure were similar across UB and VLNC cigarettes with one exception: on average, participants took 2-3 puffs more when smoking their UB cigarette compared to the VLNC cigarettes, an observation that is opposite of compensatory smoking.

This was the first controlled study examining the effects of VLNC cigarettes among pregnant smokers. The sample size is relatively small, predominantly white and receiving medication for opioid use disorder, potentially limiting the generalizability of these findings. Additionally, this study assessed acute exposure, leaving unanswered whether the present results can be generalized to chronic use of VLNC cigarettes among pregnant women. Another limitation of the study is the use of an unblinded high-dose comparator (i.e., the participant's UB cigarette). This design choice was made in an effort to reduce pregnant smokers' exposure to additional investigational tobacco products. Because of this effort to minimize harms and reduce exposure, it is difficult to know what proportion of the observed effects should be attributed to brand loyalty or dose. Despite these limitations, this study experimentally demonstrates that relative to commercially available cigarettes, VLNCs reduce the abuse liability of smoking without increasing risk for untoward craving/withdrawal or compensatory smoking.

Conclusions

Using rigorous laboratory methods, this study provides further support for a U.S. national policy that would reduce the nicotine content in cigarettes to minimally-addictive levels. These data suggest that pregnant smokers, like other vulnerable populations^{5,6} stand to benefit from such a policy. Findings from this acute-exposure study support the initiation of extended exposure studies with VLNC cigarettes among pregnant women.

ACKNOWLEDGMENTS.

Funding: This study was supported by Tobacco Centers of Regulatory Science award U56DA036114 from the National Institute on Drug Abuse and the U.S. Food and Drug Administration and in part by Centers of Biomedical Research Excellence award P20GM103644 from the National Institute of General Medical Sciences. The sponsors had no role in the study design; collection, analysis, and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the U.S. Food and Drug Administration.

REFERENCES

1. U.S. Department of Health and Human Services. (1988). The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and

Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health DHHS Publication No. (CDC) 88-8406.

2. U.S. Food and Drug Administration. (2018, 3 16). FDA Advance Notice of Proposed Rulemaking on Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, 21 CFR 1130. <https://www.federalregister.gov/documents/2018/03/16/2018-05345/tobacco-product-standard-for-nicotine-level-of-combusted-cigarettes>
3. U.S. Food and Drug Administration. (2019, 12 17). FDA permits sale of two new reduced nicotine cigarettes through premarket tobacco product application pathway. <https://www.fda.gov/news-events/press-announcements/fda-permits-sale-two-new-reduced-nicotine-cigarettes-through-premarket-tobacco-product-application>
4. Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al' Absi M, Carmella SG, Cincirpini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClellon FJ, Montoya ID, Murphy SE, Robinson JD, ... & Hatsukami DK. (2015). Randomized trial of reduced-nicotine standards for cigarettes. *New England Journal of Medicine*, 373(14), 1340–1349. [PubMed: 26422724]
5. Higgins ST, Heil SH, Sigmon SC, Tidey JW, Gaalema DE, Hughes JR, Stitzer ML, Durand H, Bunn JY, Priest JS, Arger CA, Miller ME, Bergeria CL, Davis DR, Streck JM, Reed DD, Skelly JM, & Tursi L. (2017). Addiction potential of cigarettes with reduced nicotine content in populations with psychiatric disorders and other vulnerabilities to tobacco addiction. *JAMA Psychiatry*, 74(10), 1056–1064. [PubMed: 28832876]
6. Tidey JW, Colby SM, Denlinger-Apte RL, Goodwin C, Cioe PA, Cassidy RN, Swift RM, Lindgren BR, Rubin N, Murphy SE, Hecht SS, Hatsukami DK, Donny EC (2019). Effects of six-week use of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine & Tobacco Research*. 21(Suppl 1), S38–S45. [PubMed: 31867650]
7. Dietz PM, England LJ, Shapiro-Mendoza CK, Tong VT, Farr SL, & Callaghan WM (2010). Infant morbidity and mortality attributable to prenatal smoking in the US. *American Journal of Preventive Medicine*, 39(1), 45–52. [PubMed: 20547278]
8. Guerrero-Preston R, Goldman LR, Brebi-Mieville P, Ili-Gangas C, LeBron C, Witter FR, Apelberg BJ, Hernandez-Roystacher M, Jaffe A, Halden RU, & Sidransky D (2010). Global DNA hypomethylation is associated with in utero exposure to cotinine and perfluorinated alkyl compounds. *Epigenetics*, 5(6), 539–546. [PubMed: 20523118]
9. Hackshaw A, Rodeck C, Boniface S. (2011) Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Human Reproduction Update*, 17(5), 589–604. [PubMed: 21747128]
10. Rogers JM (2009). Tobacco and pregnancy. *Reproductive Toxicology*, 28(2), 152–160. [PubMed: 19450949]
11. Arger CA, Taghavi T, Heil SH, Skelly J, Tyndale RF, & Higgins ST (2018) Pregnancy-induced increases in the nicotine metabolite ratio: examining changes during antepartum and postpartum. *Nicotine & Tobacco Research*, 21(12), 1706–1710.
12. Bowker K, Lewis S, Coleman T, & Cooper S (2015) Changes in the rate of nicotine metabolism across pregnancy: a longitudinal study. *Addiction*, 110(11), 1827–1832. [PubMed: 26119134]
13. Benowitz NL & Henningfield JE (1994) Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *New England Journal of Medicine*, 331(2): 123–125. [PubMed: 7818638]
14. Lawler TS, Stanfil SB, deCastro BR, Lisko JG, Duncan BW, Richter P, & Watson CH (2017) Surveillance of nicotine and pH in cigarette and cigar filler. *Tobacco Regulatory Science*, 3(Suppl 1), 101–116. [PubMed: 28989950]

- First study of very low nicotine content (VLNC) cigarettes in pregnant smokers
- VLNCs had less abuse liability than usual brand cigarettes
- VLNCs did not cause untoward craving/withdrawal or compensatory smoking
- Studies of extended exposure to VLNCs in pregnant women are warranted

Figure 1.

Measures of the reinforcing effects of very low nicotine content cigarettes and participant usual brand. A. Least squares mean ($\pm$ SEM) proportion of choices allocated to the usual brand (UB) when it was available at the same response effort (fixed-ratio of 10 responses) as the 0.4-mg/g dose (top) and the 2.4-mg/g dose (bottom). Asterisks (*) indicate the UB was chosen significantly more often than chance. B. Overall demand of cigarettes (estimated consumption levels across prices ranging from \$0 to \$40 per cigarette). Data points represent means across participants. C. Least squares mean ($\pm$ SEM) mCEQ subscale scores across the

three cigarettes. Bars not sharing a letter differ significantly after Bonferroni correction. The study took place in Burlington, VT and Baltimore, MD in 2017-2018.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Time-course of effects collapsed across doses on Questionnaire of Smoking Urges-brief (QSU-brief) Factor 1 & 2 scores, Minnesota Nicotine Withdrawal Scale (MNWS) desire to smoke and total scores, and breath carbon monoxide (CO) level.

	QSU-brief Factor 1	QSU-brief Factor 2	MNWS Desire to Smoke	MNWS Total	CO
Presmoking Baseline	5.8 (0.4)	4.3 (0.6)	3.1 (1.0)	1.5 (0.5)	5.4 (1.4)
+15 min	3.8 (0.4) *	2.7 (0.6) *	1.3 (0.4) *	0.8 (0.3) *	9.8 (1.4) *
+30 min	4.2 (0.4) *	3.0 (0.6) *	2.0 (0.6) *	0.8 (0.3) *	9.5 (1.4) *
+45 min	4.7 (0.4) *	3.3 (0.6) *	2.3 (0.7)	1.0 (0.3)	8.5 (1.4) *
+60 min	5.2 (0.4)	3.6 (0.6)	2.6 (0.8)	1.3 (0.4)	8.1 (1.4) *

Note. Values are means (SEM).

For all measures, an asterisk (*) indicates that the mean score at that timepoint differs significantly from presmoking baseline after Bonferroni correction. There was no significant main effect of dose nor interaction of time and dose on any measure. The study took place in Burlington, VT and Baltimore, MD in 2017-2018.