BRIEF REPORT

Comparison of Cotinine Levels in Pregnant Women Whilst Smoking and When Using Nicotine Replacement Therapy

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ABSTRACT

Background: Nicotine replacement therapy (NRT) helps smokers quit smoking, but trials indicate that there is no evidence that it is effective in pregnancy. As metabolism increases during pregnancy, NRT may deliver insufficient nicotine to alleviate withdrawal symptoms. There is mixed evidence as to what levels of cotinine are reached from nicotine exposure in pregnancy while using NRT, compared with smoking.

Methods: We analyzed data on 33 pregnant participants from the NRT arm of a randomized control trial who had stopped smoking and were still using 15 mg/16 hr nicotine patches 1 month after quitting. Salivary cotinine levels when smoking at baseline were compared with levels on NRT at 1 month using the Wilcoxon test.

Results: Cotinine levels were a median of 98.5 ng/ml while smoking and 62.8 ng/ml while using NRT and remaining abstinent (p = .045). Participants with the highest cotinine measurements when smoking also tended to have the steepest reduction in cotinine levels while using NRT. This was most noticeable among participants with baseline cotinine levels more than 150 ng/ml (n = 9) who had a greater reduction in median cotinine levels (median difference −134.8 ng /ml [95% CI = −144.5 to −125.9]) than those with a baseline cotinine level under 150 ng/ml (n = 24; median difference −27.9 ng/ml [95% CI = −49.35 to −1.75]).

Conclusions: In a pragmatic trial that replicated clinical practice, cotinine levels generated using NRT in pregnancy were lower than levels achieved from smoking. Although the sample size of this study was small, our findings are significant and are consistent with the hypothesis that NRT patches deliver an inadequate dose of nicotine to aid smoking cessation in pregnancy.

INTRODUCTION

Smoking in pregnancy is strongly associated with adverse pregnancy and birth outcomes (Cnattingius, 2004; Dechanet et al., 2011; Jaddoe et al., 2008; Li & Daling, 1991). In the United Kingdom, 26% of women smoke at some point during pregnancy and 12% of women continue to smoke throughout (The NHS Information Centre, 2011). Nicotine replacement therapy (NRT) in combination with behavioral support is often used to help pregnant smokers quit smoking (National Institute for Clinical Excellence, 2010). NRT is thought to be safer than smoking, as it does not contain all of the toxins present in tobacco smoke, and delivers only nicotine in doses aimed at relieving withdrawal symptoms (Benowitz et al., 2000).

NRT is effective in nonpregnant smokers (Stead, Bergson, & Lancaster, 2008), but its efficacy is unproven in pregnancy (Coleman, Chamberlain, Davey, Cooper, & Leonardi-Bee, 2012). Cotinine is the major metabolite of nicotine and is a specific marker for assessing nicotine exposure (Benowitz, Hukkanen, & Jacob, 2009). Nicotine is metabolized more rapidly in pregnancy, with a reported 60% increase in nicotine clearance and 140% increase in cotinine clearance, obtained by both plasma and urinary measurement (Dempsey, Jacob, & Benowitz, 2002). This faster metabolism could mean the nicotine supplied from a standard NRT patch is insufficient to alleviate smoking withdrawal symptoms in pregnancy.

This study has used data from a trial of NRT in pregnancy, which attempted to replicate routine clinical practice, to compare the cotinine levels in women generated by smoking with those from using NRT transdermal patches while abstinent.

METHODS

Data for this secondary analysis are from a double-blind, randomized placebo-controlled study: the Smoking, Nicotine, and Pregnancy (SNAP) trial. The trial recruited 1050 women

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from antenatal clinics within U.K. hospitals and investigated NRT 15 mg/16 hr transdermal patch use in pregnant smokers (n = 521) compared with placebo patches (n = 529; Coleman et al., 2012). The trial had a pragmatic design and intended, as far as possible, to mimic routine clinical practice; a description is available elsewhere (Coleman, Cooper, et al., 2012).

Participants were included in SNAP if they smoked ≥5 cigarettes/day and ≥10 prior to pregnancy, were 12–24-weeks pregnant, were aged 16–45 years, and had an exhaled carbon monoxide reading (CO) of ≥8 p.p.m. After enrolment, data on sociodemographics and smoking behavior were asked, and saliva cotinine was measured. Women were initially given a 4-week NRT supply to start on their quit date, followed by another 4-weeks' supply if they were abstinent, confirmed by an exhaled CO reading of <8 p.p.m. Women were instructed to remove patches at night and discontinue them if they restarted smoking.

At 1 month, women who reported not smoking (≤5 cigarettes smoked since quit date) had their abstinence validated by exhaled CO readings; those with validated abstinence, and who were also still using patches, were asked for a saliva sample to measure cotinine levels. Adherence with NRT trial patches between quit date and follow up was calculated as the total number of days the participant reported using the trial patches as a percentage of the length of time between the participant's quit date and their follow-up appointment.

We wanted to perform analyses on participants who were allocated to NRT and who were reasonably adherent. Consequently, we included in analyses, women from the NRT group with validated abstinence, who reported at least 80% adherence with NRT (defined previously). This final criterion was used to ensure that participants were pregnant women using NRT on a regular basis.

Salivary cotinine levels were not normally distributed and were analyzed using nonparametric statistics; within-subject changes in cotinine levels between baseline and 1 month were analyzed using the Wilcoxon rank sum test.

RESULTS

Of the 521 women in the NRT arm of the trial, 131 self-reported smoking abstinence at 1 month and 111 permitted a research midwife to visit them to validate their abstinence using an exhaled CO reading. A total of 55 women were excluded due to low self-reported adherence to taking NRT (<80% adherence) and 23 women did not have a before and after cotinine measurement to compare and subsequently were excluded. This left a sample size of 33 women.

Participant characteristics are presented using the median and interquartile ranges (IQRs) for the eligible 33 participants (Table 1). The participants were White British women, with the exception of one participant who was from an Asian/other background. They were on average 26 years old at recruitment. Most (67%) smoked 5–10 cigarettes/day prior to beginning the trial. All participants were in the second trimester of pregnancy at recruitment with the median gestational age being 14.4 weeks. We looked at how many of our sample stopped smoking in the SNAP trial, and nine participants (27%) were validated as abstinent from smoking at delivery.

The median cotinine level for participants while smoking at baseline was 98.5 ng/ml (IQR 71.3–177.8) and while abstinent and using NRT at 1 month was 62.8 ng/ml (IQR 33.3–82.7). There was a significant reduction in cotinine levels between baseline when smoking and 1 month while using NRT (median difference −54.2 ng/ml, [95% CI = −70.5 to −25.5 ng/ml], p = .045). The majority of participants had cotinine levels at 1 month, which were lower than their levels at baseline (n = 27); six participants had cotinine levels at 1 month, which were higher than baseline.

Of the 33 participants, 17 participants reported no smoking at all between their quit date and 1-month follow up, and the remaining 16 participants reported smoking five times or less. Six of the 16 participants reported smoking a cigarette in the 24 hr before their 1-month visit. We performed sensitivity analysis on the 27 women who had not smoked in the previous 24 hr before the 1-month visit; the median difference in cotinine levels in this group was similar to that of the whole group −46.6 ng/ml (95% CI = −125 to −24.1 ng/ml).

We found a significant, positive correlation between baseline and 1-month cotinine levels, Spearman correlation coefficient ρ 0.35 (p = .04). Although the association was weak, it suggests that participants with the highest baseline levels in the study also tended to have higher 1 month levels. However, the scatter plot (Figure 1) shows that for the majority of participants (n = 27), cotinine levels at 1 month were lower than at baseline. The scatter plot also demonstrates that participants in the highest range of baseline cotinine levels appear to have the greatest reduction in 1-month cotinine levels. This is most noticeable among participants with baseline cotinine levels more than 150 ng/ml (n = 9); these participants had a greater reduction in median cotinine levels (median difference −134.8 ng/ml [95% CI = −144.5 to −125.9]) compared with

Table 1. Participant Characteristics

Characteristics	Women included in study (n = 33), median (interquartile range or %)
Age (median, 25% and 75%)	26.12 (22.29–32.35)
Ethnicity	
White British	31 (98%)
Asian background	1 (2%)
Body mass index	25.6 (22.7–29.3)
Age left full time education (years)	16 (16–17)
Gestational age at baseline (weeks)	14.4 (13.3–17.8)
Current cigarettes smoking per day	
5–10	22 (67%)
11–15	8 (24%)
16–20	–
>20	3 (9%)
Heaviness of Smoking Index	3 (2–3)
Partner smoking status	
Partner smokes	23 (70%)
Partner non smoking	6 (18%)
No partner	4 (12 %)
Nicotine metabolite ratio	0.4 (0.3–0.5)
Adherence with NRT trial patch[a]	
80%–99%	12 (37%)
100%	20 (63%)
Cotinine level baseline (ng/ml)	98.5 (71.3–177.8)
Cotinine level 1 month (ng/ml)	62.8 (33.3–82.7)
Validated smoking abstinent at delivery	9 (27%)

Note. NRT = nicotine replacement therapy. [a]% of days used trial patch from baseline to 1-month follow up.

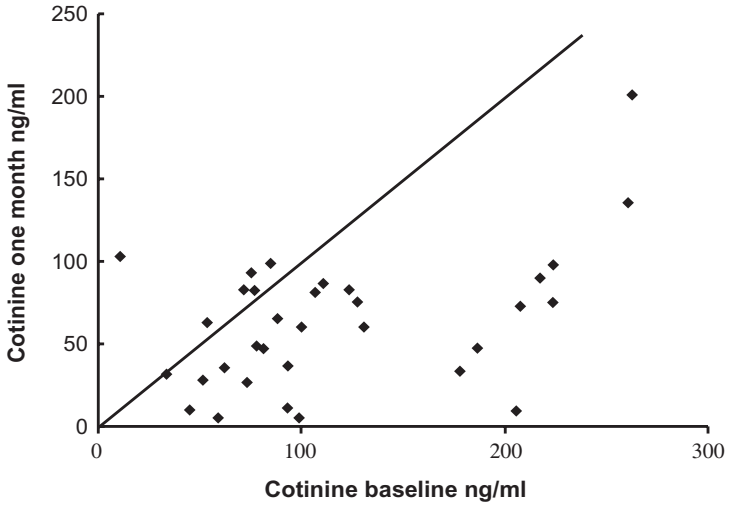

Figure 1. Cotinine levels at baseline while smoking and at 1 month while abstinent and using nicotine replacement therapy.

those with a baseline cotinine level under 150 ng/ml (n = 24; median difference −27.9 ng/ml [95% CI = −49.35 to−1.75]).

DISCUSSION

Main Findings

Our findings have shown that cotinine levels generated using NRT transdermal patches in pregnancy are lower than cotinine levels generated while smoking. Although these findings arise from a clinical trial, this had a relatively pragmatic design and was intended to replicate how NRT is used in routine clinical practice. We found a correlation between baseline and 1-month cotinine levels and observed that participants in the highest range of cotinine measurements at baseline (>150 ng/ml) tended to have the steepest reduction in cotinine levels while using NRT.

A strength of our study design was that it accounted for within-person differences and, therefore, change in cotinine levels will not have been influenced by inter-participant variation (e.g., in nicotine metabolic rate). We were also able to observe cotinine levels generated in a setting, which is similar to routine clinical practice, while also only including abstinent women who adhered to patches, so cotinine levels are very likely based on regular and continuous NRT use.

For unknown reasons, as in other randomized controlled trials, compliance with NRT in SNAP was low (Pollak et al., 2007; Wisborg, Henriksen, Jespersen, & Secher, 2000) and, as our analyses included only women who used patches regularly, cotinine levels measured are unlikely to reflect those generated in women using NRT intermittently. Additionally, it could be speculated that women who were excluded from the analysis might have lower cotinine levels than those included. In order for NRT to effective, it is expected that cotinine levels achieved from using NRT would need to be similar to those achieved by smoking (Benowitz, Zevin, & Jacob, 1997). Such lower cotinine levels could have caused these women to suffer from more withdrawal symptoms, making them more likely to re-start smoking and stop using patches, resulting in their exclusion. A final weakness of our study is that cotinine measurements on NRT and when smoking were taken 1 month apart; if, as research suggests, nicotine metabolism increases during pregnancy (Dempsey et al., 2002), then this may partially explain lower cotinine levels seen when using NRT at the 1-month follow up. It could be speculated that NRT may have become increasingly insufficient as gestation increased, which is why only nine of the 33 women had validated smoking abstinence at delivery.

Smaller laboratory-based studies have been able to report on the paired difference while using NRT. In one study, researchers administered 15 mg/16 hr patch over 5 days and found cotinine levels were 48% less than those achieved when smoking (p = .029) (Oncken, Campbell, Chan, Hatsukami, & Kranzler, 2009); our findings are consistent with this. However, another study that used patches over 5 days (Oncken et al., 1997) and a study that applied patches over an 8-hr period (Ogburn et al., 1999) did not. It is possible that, in pregnancy, use of NRT for longer than 8 hr is required before stable cotinine levels are generated. Although informative, these studies were laboratory based and may not accurately represent cotinine levels achieved from using NRT in routine clinical practice.

Trials exploring the effects of NRT have reported lower cotinine levels in pregnant women randomized to NRT than those randomized to placebo; they have also reported lower levels after randomization to NRT than prior to study enrolment (Oncken et al., 2008; Wisborg et al., 2000). However, these studies have not restricted comparisons to those women who achieved abstinence from smoking; consequently, these comparisons may reflect cotinine levels generated by smoking, NRT use, or both.

CONCLUSIONS

In summary, in pregnancy, cotinine levels generated by 15 mg/16 hr nicotine patches are lower than those generated by smoking. Although the sample size of this study was small, our results are significant. They do indicate that an apparently low level of nicotine substitution may be insufficient for NRT to have efficacy in pregnancy and may, at least partially, explain why standard dose NRT used by pregnant women has not been shown to be effective.

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DECLARATION OF INTERESTS

On two occasions since 2008, TC has been paid to attend and present at symposia arranged by Pierre Fabre Laboratories (PFL); PFL are a manufacturer of NRT.

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