Nicotine Patches for Pregnant Smokers: A Randomized Controlled Study

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***Objective*: To assess the effect of nicotine patches on continine-validated smoking cessation in pregnant women and the effect of nicotine on birth weight and preterm delivery.**

***Methods*: Pregnant women who smoked ten or more cigarettes after the first trimester ($N = 250$) were randomly assigned to receive nicotine patches ($n = 124$) or placebo patches ($n = 126$). Women randomized to nicotine were treated with 15-mg patches (16 hours/day) for 8 weeks, and 10-mg patches (16 hours/day) for 3 weeks.**

***Results*: Overall, 26% stopped smoking and 14% were nonsmokers 1 year after delivery. There was no difference between nicotine and placebo groups. At the end of the intervention, the mean value of cotinine in saliva in women assigned to nicotine was 120 ng/mL and placebo 153 ng/mL (mean difference −33; 95% CI −72, 6 ng/mL). Mean birth weight difference was 186 g (95% CI 35, 336 g) higher in the nicotine than placebo group, and there was an insignificantly lower rate of low birth weight (under 2500 g) in the former group. There was no difference in the rate of preterm delivery between the two groups.**

***Conclusion*: Nicotine patches had no influence on smoking cessation during pregnancy, although they might increase birth weight in comparison with placebo. (Obstet Gynecol 2000;96:967–71. © 2000 by The American College of Obstetricians and Gynecologists.)**

Smoking during pregnancy increases the risk of low birth weight and preterm delivery, both of which are associated with increased risk of perinatal morbidity and mortality.[1,2] However, if pregnant smokers stop smoking, the risk of preterm delivery and low birth weight is reduced to a level comparable with that in women who have not smoked during pregnancy.[3–5] Tobacco smoke contains more than 3500 chemical substances, and it is not known which might be responsible for the harmful effects of smoking. Nicotine is the substance on which smokers depend physically and which causes withdrawal symptoms in those who stop smoking. Randomized studies in nonpregnant populations have shown that in smokers who are motivated to stop smoking, nicotine replacement increases the chances of smoking cessation.[6,7] By using nicotine patches instead of smoking during pregnancy, the amount of nicotine absorbed by the pregnant woman and the fetus is reduced during treatment, and all other potentially harmful substances in tobacco smoke are avoided.[8,9] Pregnant smokers who do not stop smoking by themselves or with counseling can benefit from treatment with nicotine patches.

The aim of the present study was to evaluate the effect of nicotine patches on smoking cessation in pregnant women who smoked beyond the first trimester, the effect of nicotine on birth weight and preterm delivery compared with placebo, and smoking cessation during the study period compared with smoking cessation during the year before and the year after the study period.

Materials and Methods

As part of a prospective follow-up study, all women who were to deliver at our department were asked to complete two questionnaires at about 16 weeks' gestation and one questionnaire at 30 weeks.[10] Information from the first questionnaire was used for the women's medical records and for entry to the study. It provided medical and obstetric information, information about age, smoking habits before pregnancy and during the first trimester, and alcohol intake during pregnancy. The second questionnaire provided information on marital status, education, employment status, and caffeine intake during pregnancy.

Healthy pregnant women ($n = 611$) who smoked ten

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or more cigarettes per day and were less than 22 weeks pregnant were invited to participate in the present study from October 1995 to October 1997. They received letters with information about the study, and within a week a midwife telephoned them with further information. Women were informed that the aim of participation was prenatal smoking cessation counseling with a midwife four times during pregnancy and smoking cessation using patches. Those who agreed to participate (n = 250) were randomly assigned, in balanced blocks of six, to nicotine (n = 124) or placebo (n = 126) patches. Pharmacia & Upjohn (Copenhagen, Denmark) generated the randomization list, supplied the patches with randomization numbers, and kept the code between patch number and the specific treatment until data collection was finished. As the women entered the study they were assigned consecutive numbers on the randomization list that corresponded to specific patches. The Danish Health Authorities and the local ethics committee approved the study and all participants provided written informed consent.

Treatment status was not known by the women or the midwife throughout the study. Smoking cessation counseling was done by our midwife (LBJ), and the visits were independent of routine antenatal care visits. At first visits, which lasted 45–60 minutes, participants were interviewed about their smoking habits and previous attempts to stop smoking. Nicotine dependence was measured by the Fagerstrom score.[11] Women were informed about pharmacologic and psychologic aspects of smoking and the consequences of smoking during pregnancy. Methods to stop smoking were carefully explained and the day of stopping was planned. A pamphlet on smoking and pregnancy also was distributed. The pamphlet was designed for the study by two authors (KW and NJS) and contained information about the harmful effects of smoking and gave brief advice on smoking cessation. Treatment with patches was planned for 11 weeks. The women who received nicotine patches were treated with 15-mg patches (16 hours/day) for 8 weeks, and 10-mg patches (16 hours/day) for 3 weeks. Second and third visits were scheduled 8 and 11 weeks after first visit and fourth visits were 4 weeks before the expected delivery date. Those visits lasted 15–20 minutes. Women who did not attend visits were given another appointment within the subsequent 2 weeks. If they did not attend again they were contacted by telephone. At second, third, and fourth visits, 76 (31%), 106 (44%), and 129 women (53%), respectively, were telephoned. Attendance was independent of treatment status and smoking habits. Information about smoking status, compliance, and side effects was collected at each prenatal visit. Information about smoking habits at the second, third, and fourth visits was missing for 23 (9%), 33 (13%), and 33 (13%) women, respectively. Those women were all categorized as smokers.

To further evaluate the effect of nicotine patches during pregnancy, cotinine in saliva was sampled in a cotton dental roll at each prenatal visit. Cotinine is the major metabolite of nicotine. Those who were interviewed by telephone received the cotton dental roll by mail. After collection, samples were centrifuged (3000 rpm for 10 minutes at 10C) and kept at −50C. Cotinine was analyzed by radioimmunoassay with a test kit from Diagnostic Products Corporation (London, England). The limit of detection of the test was 20 ng/mL, and the interserial precision was 5% (n = 56).

The effect of transdermal nicotine on smoking cessation was analyzed using the principle of intention to treat. The primary outcome was self-reported abstinence of at least 7 days at second, third, and fourth prenatal visits. Those who reported abstinence were asked if they had smoked during the past week. If a woman smoked, she was asked for how many weeks she had been abstinent and the number of cigarettes smoked per day. To evaluate the long-term effects of intervention, participants were interviewed by telephone 3 months and 1 year after delivery. Participants were considered continuously abstinent during pregnancy if they were abstinent at the second, third, and fourth prenatal visits and had a salivary cotinine level less than 26 ng/mL at the fourth visit. Women who had spontaneous abortions (n = 7) and one woman who delivered twins were excluded from analyses of the effect of nicotine versus placebo on birth weight. Those analyses included 120 women randomized to nicotine patches and 122 randomized to placebo patches.

To study the effect of the intervention program, smoking cessation among all who were offered participation in the study and who completed questions about smoking habits at 30 weeks' gestation (n = 362) was compared with smoking cessation in a comparable group of smokers who booked for delivery during a period from 1 year before to 1 year after the study period (n = 535). Those who participated in the randomized study (n = 157) received intensive counseling as described and followed the routine antenatal care program. Those who were offered participation in the randomized study but declined participation (n = 205), and smokers in the control group, followed the routine antenatal care program.

Based on the results of a Danish study of nicotine patches in a nonpregnant population, we assumed that 20% of those randomized to nicotine patches and 5% of those randomized to placebo patches would stop smoking.[12] We estimated that 100 women were needed in

each group for the study to have a power of 0.80 to detect such a difference at an alpha level of 0.05.

Age, parity, caffeine and alcohol intake, educational level, occupational status, Fagerstrom score, and the number of previous attempts to stop smoking were analyzed with Student *t* test (continuous variables) or χ^2 test for independence within contingency tables (categorical variables) when the nicotine group was compared with the placebo group. Caffeine intake was calculated from the daily intake of coffee (one cup = 100 mg), tea, hot chocolate (one cup = 50 mg), and cola (one bottle = 50 mg). Caffeine intake was considered low when less than 400 mg/day and high when 400 mg or more/day.

The proportions of women in each group who stopped smoking were compared using χ^2 test for independence within contingency tables. Birth weight was compared using Student *t* test and linear regression, and the risk of low birth weight and preterm birth with χ^2 and multiple logistic regression analyses. Two-sided $P < .05$ was considered statistically significant. Mean values are presented with one standard deviation (SD), and relative risks (RR) with 95% confidence intervals (CI).

Results

Compared with those who agreed to participate, the mean number of cigarettes smoked per day was slightly higher among nonparticipants (12.8 versus 12.1; mean difference 0.7 [95% CI 0.1, 1.4]). With respect to age, parity, marital status, years of schooling, occupational status, and caffeine and alcohol intake, participants and nonparticipants were comparable. The main reason that participation was declined was the desire to stop smoking or to reduce the number of cigarettes without nicotine patches.

At the start of intervention the number of cigarettes smoked per day, nicotine dependence, and a number of sociodemographic and lifestyle factors were distributed equally in the nicotine and placebo groups (Table 1). Compliance with the assigned treatment was low in both groups. The median number of patches used was 14 (range 0–77) in the nicotine group and 7 (range 0–77) in the placebo group. In the nicotine group 17% used all 15-mg patches and 11% used all 10-mg patches. In the placebo group 8% and 7% used all patches. The number of patches used was independent of number of cigarettes smoked at the first visit, number of attempts to stop smoking before and during pregnancy, and nicotine dependence measured by Fagerstrom score. Among women who did not use the patches, only 11 stated that the reason was adverse effects, such as skin irritations and headache. Other adverse effects reported were palpitations ($n = 5$) and nausea ($n = 2$). Among women randomly assigned to nicotine, 44% believed that they were treated with nicotine patches, among women randomly assigned to placebo, 11% believed that they were treated with nicotine patches ($P < .05$).

Overall, 26% reported no smoking at fourth prenatal visits and 14% were nonsmokers 1 year after delivery with no difference between groups (Table 2). The proportion of pregnant women who were continuously abstinent after the start of intervention was 21% in the nicotine group and 19% in the placebo group (RR 1.1, 95% CI 0.7, 1.8). At fourth visits the mean cotinine value in saliva in women randomly assigned to nicotine was

Table 1. Smoking Habits, Nicotine Dependence, Maternal Characteristics, and Lifestyle Factors*

	Nicotine ($n = 124$)	Placebo ($n = 126$)
Cigarettes/day (mean ± SD)	13.4 ± 4.0	14.2 ± 4.4
Cotinine in saliva at first visit (ng/mL) (mean ± SD)	231 ± 125	226 ± 107
Number of previous attempts to stop smoking		
0–2	79 (64%)	93 (74%)
3–15	45 (36%)	33 (26%)
0–4	73 (59%)	68 (54%)
5–8	51 (41%)	58 (46%)
FTND score†		
Maternal age (mean ± SD)	28.2 ± 4.9	28.5 ± 5.2
Parity		
Primiparous	55 (44%)	52 (41%)
Multiparous	69 (56%)	74 (59%)
Marital status		
Married/cohabiting	95 (77%)	96 (76%)
Single	10 (8%)	18 (14%)
Missing	19 (15%)	12 (10%)
Years of schooling		
<10	23 (18%)	23 (18%)
≥10	79 (64%)	88 (70%)
Missing	22 (18%)	15 (12%)
Occupational status		
Working	62 (50%)	65 (52%)
Unemployed	25 (20%)	38 (30%)
Student	12 (10%)	7 (6%)
Missing	25 (20%)	16 (13%)
Caffeine intake (mg/day)		
<400	51 (41%)	46 (37%)
≥400	53 (43%)	66 (52%)
Missing	20 (16%)	14 (11%)
Alcohol intake (drinks/wk)		
0–2	109 (88%)	110 (87%)
≥3	7 (6%)	11 (9%)
Missing	8 (6%)	5 (4%)

SD = standard deviation.

* There was no statistically significant difference in any of the variables in the table between the nicotine group and the placebo group.

† FTND score = Fagerstrom score, which measures nicotine dependence. High scores indicate more severe dependence.

Table 2. Nonsmokers and Mean Number of Cigarettes

	Nonsmokers (%)			Mean number of cigarettes/day		
	Nicotine	Placebo	*P*	Nicotine	Placebo	*P*
First prenatal visit				13.4	14.2	.78
Second prenatal visit	37	29	.15	6.7	7.2	.50
Third prenatal visit	32	26	.29	7.0	6.4	.16
Fourth prenatal visit	28	25	.52	6.7	6.5	.56
3 months postpartum	21	18	.57	7.2	7.0	.59
1 y postpartum	15	14	.92	6.8	7.3	.55

120 ng/mL and to placebo was 153 ng/mL (mean difference −33, 95% CI −72, 6 ng/mL) (Table 3).

Mean birth weight was 3457 g in the nicotine group and 3271 g in the placebo group (mean difference 186 g, 95% CI 35, 336 g), and the proportion of infants with birth weight under 2500 g was 3% and 9%, respectively (RR 0.4, CI 0.1, 1.1). Adjustment for preterm delivery, smoking habits, and other factors associated with birth weight yielded comparable results. Among children born after 37 weeks' gestation the mean birth weight was 3539 g in the nicotine and 3381 g in the placebo group (mean difference 157 g, 95% CI 25, 291 g). The rate of preterm delivery was 8% in the nicotine group versus 10% in the placebo group (RR 0.8, 95% CI 0.4, 1.7).

Self-reported smoking cessation at 30 weeks' gestation among all smokers who were offered participation was 14% (n = 51) compared with 3% (n = 18) in pregnant women 1 year before and 1 year after the study period (RR 4.8, 95% CI 2.8, 8.4).

Discussion

Randomized studies in nonpregnant smokers have shown that when smokers who are motivated to stop smoking use nicotine replacement, the chances of stopping smoking are doubled.[6,7] In our general population of pregnant women, almost four of ten smokers stopped smoking spontaneously at the start of pregnancy.[13] Despite that high proportion, 20% of pregnant women smoked at the end of the first trimester, and half smoked ten or more cigarettes per day. We know from previous studies in our population that few women who smoke at the end of the first trimester stop smoking spontaneously later in pregnancy.[10,14] The present study found no effect of nicotine patches on smoking cessation compared with placebo, but the frequency of smoking cessation was much higher than expected. In a prospective interventional study of smoking cessation during pregnancy in a routine antenatal care setting, we evaluated the effect of an intensive education program directed by midwives.[14] The results showed that specially trained midwives were unsuccessful in helping pregnant women stop smoking by giving advice during routine antenatal care. It seems that pregnant women who still smoked at the end of the first trimester might not be willing to stop or might need more intensive support.

Until now the Danish Health Authorities advised pregnant women against using nicotine replacement. By offering pregnant smokers treatment with nicotine patches, it is possible that the seriousness of smoking during pregnancy was emphasized to an extent that might induce smoking cessation more than actual treatment.

Independent of treatment status, participants were offered four individual prenatal visits with smoking cessation counseling that lasted 2.5 hours. Participants were motivated to stop smoking, and at first visits only eight women (3%) were unsure they would stop smoking. One of those actually stopped. The rate of smoking cessation during the study was high, so our results might indicate that offering intensive smoking counseling to pregnant women who are motivated to stop increases the number of pregnant women who stop smoking.

Table 3. Salivary Cotinine

	Nicotine/placebo	Cotinine (ng/mL)		Mean difference (95% CI)
		Nicotine	Placebo	
First prenatal visit	121/122	231	226	5 (−24, 35)
Second prenatal visit	90/92	153	174	−21 (−58, 16)
Third prenatal visit	83/84	121	153	−32 (−63, −1)
Fourth prenatal visit	75/71	120	153	−33 (−72, 6)

Very few women had adverse effects and no serious adverse effects were reported, but compliance with assigned treatments was low. Women who did not abstain from cigarettes were told to discontinue treatment with patches. Others were reluctant to use patches despite receiving thorough information about them before the study. The fact that pregnant women had been advised not to use nicotine replacement and lack of experience with the effect of nicotine patches during pregnancy might have influenced compliance negatively. It is possible that the rate of smoking cessation would have been higher in the nicotine replacement group if women had used the patches as prescribed. More than twice as many women stopped smoking when they used the patches for more than 2 weeks, compared with those who had used them for less than 2 weeks (data not shown). However, that difference was independent of treatment status, and might be explained by the fact that those who used the patches were most determined to stop smoking.

The higher mean birth weight in children born to women randomly assigned to nicotine patches compared with children whose mothers used placebo patches could not be explained by differences in preterm delivery or smoking habits between groups. We found that mean birth weight was 244 g (95% CI 7, 481 g), 345 g (95% CI 38, 651 g), and 494 (95% CI 107, 882 g) higher for women who used nicotine compared with placebo patches for at least 2, 4, and 9 weeks. Among women who used all 77 patches and were nonsmokers at the second, third, and fourth visits, mean birth weight was 509 g (95% CI −149, 1168 g) higher for women who used nicotine compared with placebo patches. The fact that nicotine inhibits the production of thromboxane, which causes vasoconstriction and stimulates platelet aggregation,[15] is a possible explanation of our findings. However, further studies on the specific effect of transdermal nicotine on birth weight are needed.

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