

ORIGINAL ARTICLE

A Randomized Trial of Nicotine-Replacement Therapy Patches in Pregnancy

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ABSTRACT

BACKGROUND

Nicotine-replacement therapy is effective for smoking cessation outside pregnancy and its use is widely recommended during pregnancy. We investigated the efficacy and safety of nicotine patches during pregnancy.

METHODS

We recruited participants from seven hospitals in England who were 16 to 50 years of age with pregnancies of 12 to 24 weeks' gestation and who smoked five or more cigarettes per day. Participants received behavioral cessation support and were randomly assigned to 8 weeks of treatment with active nicotine patches (15 mg per 16 hours) or matched placebo patches. The primary outcome was abstinence from the date of smoking cessation until delivery, as validated by measurement of exhaled carbon monoxide or salivary cotinine. Safety was assessed by monitoring for adverse pregnancy and birth outcomes.

RESULTS

Of 1050 participants, 521 were randomly assigned to nicotine-replacement therapy and 529 to placebo. There was no significant difference in the rate of abstinence from the quit date until delivery between the nicotine-replacement and placebo groups (9.4% and 7.6%, respectively; unadjusted odds ratio with nicotine-replacement therapy, 1.26; 95% confidence interval, 0.82 to 1.96), although the rate was higher at 1 month in the nicotine-replacement group than in the placebo group (21.3% vs. 11.7%). Compliance was low; only 7.2% of women assigned to nicotine-replacement therapy and 2.8% assigned to placebo used patches for more than 1 month. Rates of adverse pregnancy and birth outcomes were similar in the two groups.

CONCLUSIONS

Adding a nicotine patch (15 mg per 16 hours) to behavioral cessation support for women who smoked during pregnancy did not significantly increase the rate of abstinence from smoking until delivery or the risk of adverse pregnancy or birth outcomes. However, low compliance rates substantially limited the assessment of safety. (Funded by the National Institute for Health Research Health Technology Assessment Programme; Current Controlled Trials number, ISRCTN07249128.)

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SMOKING IN PREGNANCY IS THE LEADING preventable cause of morbidity and death among women and infants. Adverse pregnancy and birth outcomes associated with smoking include placental abruption, miscarriage, prematurity, low birth weight, congenital abnormalities, and neonatal or sudden infant death.^{1,2} The prevalence of smoking during pregnancy is between 13% and 25% in high-income countries³⁻⁵ and is increasing rapidly in low-income and middle-income countries.⁵ Cessation of smoking during pregnancy is important for maternal and fetal health.

A meta-analysis of trials has shown that behavioral support for smoking cessation helps pregnant women to stop smoking, which improves birth outcomes.⁶ There is, however, considerable uncertainty about whether medications that have been shown to improve cessation rates among non-pregnant women are also effective during pregnancy. Concerns regarding potential teratogenicity have prevented clinical trials of varenicline⁷ and bupropion.⁸ Such concerns are less pressing with nicotine-replacement therapy,⁹ because this therapy contains only nicotine, whereas tobacco smoke contains this and many other toxins.¹⁰

There is a general consensus that nicotine-replacement therapy is probably less harmful than smoking,¹⁰ and its use in pregnancy is recommended by several sets of guidelines for smoking cessation in pregnancy.¹¹ Yet good evidence to support these recommendations is lacking. To date, individual clinical trials of nicotine-replacement therapy in pregnancy have been too small to definitively assess whether it is effective or safe in this context,¹² and the pooled risk ratio for cessation in later pregnancy obtained through meta-analysis of these studies is inconclusive (risk ratio, 1.63; 95% confidence interval [CI], 0.85 to 3.14).¹² We performed a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to assess the efficacy and safety of standard-dose nicotine-replacement patches for prolonged abstinence from smoking during pregnancy.

METHODS

STUDY POPULATION

Between May 2007 and February 2010, we recruited pregnant women who agreed to set a quit date, were 16 to 50 years of age, were at 12 to 24 weeks of gestation, smoked 10 or more cigarettes daily before pregnancy, currently smoked 5 or more

cigarettes daily, and had an exhaled carbon monoxide concentration of at least 8 ppm. Participants were recruited at appointments for ultrasonography at seven hospital antenatal clinics in the East Midlands (England) and by means of posters in these clinics and at local smoking-cessation services. Enrollment occurred after discussion with a research midwife. Exclusion criteria were known major fetal abnormalities, inability to provide informed consent, chemical or alcohol dependence, and contraindications to nicotine-replacement therapy (i.e., recent cerebrovascular accident or transient ischemic attack, chronic generalized skin disorders, or sensitivity to a nicotine patch).

STUDY PROTOCOL AND INTERVENTIONS

The study followed a published protocol,¹³ which was approved by the Oxfordshire Research Ethics Committee A and is available with the full text of this article at NEJM.org. The first author vouches for the accuracy and completeness of the reported data and the fidelity of the study to the protocol. Research midwives were trained to provide behavioral support according to national standards,¹⁴ with the use of a manual that included guidance from a British expert trainer of smoking-cessation professionals and behavioral approaches from the Smoking Cessation or Reduction in Pregnancy Treatment trials¹⁵ that were believed to be relevant to British smokers (see the Supplementary Appendix, available at NEJM.org).

At enrollment, research midwives provided behavioral support lasting up to 1 hour, and participants agreed to a quit date within the following 2 weeks; follow-up was timed from the quit date. Subsequently, participants were randomly assigned to receive a 4-week supply of transdermal patches for nicotine-replacement therapy (at a dose of 15 mg per 16 hours) or visually identical placebos, which were started on the quit date (all study treatment was purchased at market rates from United Pharmaceuticals). One month after the quit date, women who were not smoking, as validated by an exhaled carbon monoxide concentration of less than 8 ppm,¹⁶ were issued another 4-week supply of patches.

In addition to behavioral support at enrollment, research midwives provided three sessions of behavioral support by telephone to participants: one session on the quit date, one session 3 days afterward, and one at 4 weeks. The women who collected a second month's supply of nicotine-replace-

ment or placebo patches also received face-to-face support from the research midwife at the time of collection. Women were offered additional support from local National Health Service smoking-cessation services and were encouraged to ask for support from the research midwives or smoking-cessation service staff; support was provided according to the manual.

RANDOMIZATION

Eligibility criteria were entered into a secure online database of the Nottingham Clinical Trials Unit before randomization, which was performed with the use of a computer-generated sequence, in random permuted blocks of randomly varying size and with stratification by recruiting site. Identically packaged study patches were dispensed, and all participants and study personnel were unaware of the study assignments.

DATA COLLECTION

At baseline, saliva samples were collected for cotinine measurements, and the following data were collected: the score on the Heaviness of Smoking Index¹⁷ (which measures nicotine addiction on a scale from 0 to 6, with higher scores indicating more severe addiction), age, number of cigarettes smoked daily before pregnancy, partner's smoking status, weeks of gestation, race or ethnic group, age at leaving full-time education, parity, previous use of nicotine-replacement therapy during the current pregnancy, height, and weight. At 1 month, research midwives asked by telephone about smoking status, about use of the study patches and of any nicotine-replacement therapy obtained outside the trial, and whether additional behavioral support was obtained. Women who reported not smoking were visited to obtain validation by measurement of the exhaled carbon monoxide concentration; women who could not be contacted by telephone were sent a questionnaire by mail.

When women were admitted to the hospital in established labor, or as soon as possible afterward, research midwives ascertained smoking status and asked about the use of study patches (and any non-study nicotine-replacement therapy) and receipt of additional behavioral support. Women who reported abstinence of at least 24 hours were asked for samples of exhaled carbon monoxide and salivary cotinine.

During all in-person and telephone contacts, participants were asked about adverse events.

Medical records were also examined monthly for adverse events and were examined after delivery for maternal and infant outcome data. We included as serious adverse events only maternal, fetal, and infant deaths. We did not classify hospitalizations as serious adverse events because hospitalizations (e.g., for suspected labor) are not uncommon in pregnancy, but we included hospitalizations among other, nonserious adverse events.

OUTCOMES

The primary outcome was self-reported abstinence from smoking between the quit date and childbirth, as validated at delivery on the basis of the exhaled carbon monoxide concentration and estimated salivary cotinine concentration. Temporary, brief smoking lapses of up to five cigarettes in total (on up to five occasions) were permitted.¹⁸ The concentration of either carbon monoxide or salivary cotinine could be used for validation, but, if both were available, both were required to reflect abstinence as defined for the primary outcome: an exhaled carbon monoxide concentration of less than 8 ppm and a salivary cotinine concentration of less than 10 ng per milliliter.¹⁶

Secondary outcomes included self-reported abstinence from smoking for 1 month, self-reported abstinence until delivery, abstinence until delivery with validation both at 1 month and at delivery, and validated abstinence for more than 24 hours before delivery. We also report abstinence for 1 month, as validated by measurement of the exhaled carbon monoxide concentration, although this outcome was not specified in the original protocol. Birth outcomes included miscarriage (fetal death at <24 weeks of gestation) and stillbirth (fetal death at ≥24 weeks of gestation). We also report neonatal death (defined as death between birth and 28 days of age), later neonatal death (defined as death between 29 days and 2 years of age), birth weight (and z score), Apgar score at 5 minutes, cord-blood arterial pH, gestational age at birth, intraventricular hemorrhage, necrotizing enterocolitis, neonatal convulsions, congenital abnormality, maternal death, mode of delivery, and hypertension (i.e., any blood-pressure readings higher than 140/90 mm Hg that were measured twice or more during routine antenatal care, regardless of blood-pressure levels before pregnancy), admission to the neonatal intensive care unit (with or without ventilator use), and termination of pregnancy (with reasons noted).

STATISTICAL ANALYSIS

We calculated that enrollment of 1050 study participants would provide 93% power at a 5% significance level to detect an absolute difference of 9 percentage points in the rate of the primary outcome between the two groups. We anticipated a cessation rate of 16% in the placebo group, on the basis of the observations that 10% of pregnant women who are smokers stop smoking with usual care after their first antenatal visit and that with behavioral support, another 6 to 7% quit.⁶ We sought to detect the same treatment effect that nicotine-replacement patches have outside of pregnancy (odds ratio for cessation, as compared with placebo, 1.74; 95% CI, 1.57 to 1.93),⁹ giving a projected cessation rate of 25% in the nicotine-replacement group.

Analysis was performed on an intention-to-treat basis; participants who, for any reason, had missing outcome data were assumed to be smoking. The proportion of women who reported prolonged abstinence from smoking immediately before childbirth was compared between study groups by logistic regression, with adjustment for recruitment center. Statistical significance was assessed with the use of the likelihood-ratio test. We planned a secondary analysis with adjustment for baseline level of salivary cotinine, maternal educational level, and partner's smoking status as potentially important prognostic factors.¹⁹ Other smoking-cessation outcomes were analyzed similarly.

Fetal and maternal birth outcomes were compared on an intention-to-treat basis. For fetal outcomes, the primary analysis was of singleton births, and we undertook a sensitivity analysis that included multiple births to allow for the clustering of outcomes.

For binary outcomes, odds ratios were obtained with the use of logistic regression with adjustment for recruitment center and also with the use of the likelihood-ratio test (when the numbers of events were small, we used Fisher's exact test and ignored stratification by center). For continuous outcomes, we compared means between groups, with adjustment for recruitment center, with the use of multiple linear regression.

RESULTS

Of 2410 women who expressed interest in the study, 1051 (43.6%) underwent randomization; 521 were assigned to receive nicotine-replacement therapy,

and 530 to receive placebo (Fig. 1). One woman was enrolled twice, owing to sequential pregnancies; her second enrollment (in the placebo group) was removed, giving a final sample size of 1050 (529 in the placebo group). Of 1050 pregnancies, 1038 were singleton, and 12 twin.

Follow-up rates were similar in the two groups. At 1 month, 856 women (81.5%) provided outcome data; of these, 592 (69.2%) responded by telephone or questionnaire and 264 (30.8%) attended face-to-face consultations with research midwives. At delivery, 981 (93.4%) provided outcome data. However, 56 women (5.3%) were lost to follow-up or withdrew consent, and 13 (1.2%) who had fetal loss (including one elective termination) were not asked about smoking outcomes. Most self-reported nonsmokers permitted validation of this status. At delivery, validation rates were 89% (58 of 65 women) in the nicotine-replacement group and 92% (45 of 49) in the placebo group; at 1 month, the rates were 89% (116 of 131) and 85% (63 of 74), respectively. Ascertainment was more complete for birth outcomes than for smoking outcomes (Fig. 1). Participants in the two groups had similar demographic characteristics (Table 1). The women who were enrolled were heavy smokers; approximately one third smoked within 5 minutes after waking, and the median number of cigarettes smoked daily was 14.

Compliance rates were low in both groups. Only 7.2% of women (35 of 485) assigned to receive nicotine-replacement therapy and 2.8% (14 of 496) assigned to receive placebo reported using trial medications for more than 1 month; rates of use of nonstudy nicotine-replacement therapy were very low. Most participants had no additional contact, either face to face or by text message, with smoking-cessation advisors; among those who did, the frequency of contact was similar in the two groups. The numbers of extra telephone contacts were also similar in the two groups (median number in each group, 2).

The rate of prolonged abstinence at delivery with validation was 9.4% in the nicotine-replacement group and 7.6% in the placebo group (odds ratio for abstinence with nicotine-replacement therapy, 1.26; 95% CI, 0.82 to 1.96) (Table 2). For abstinence that was not validated, there was a slightly larger but still nonsignificant difference in rates: 12.5% with nicotine-replacement therapy versus 9.3% with placebo (odds ratio, 1.40; 95% CI, 0.94 to 2.07). At 1 month, the validated absti-

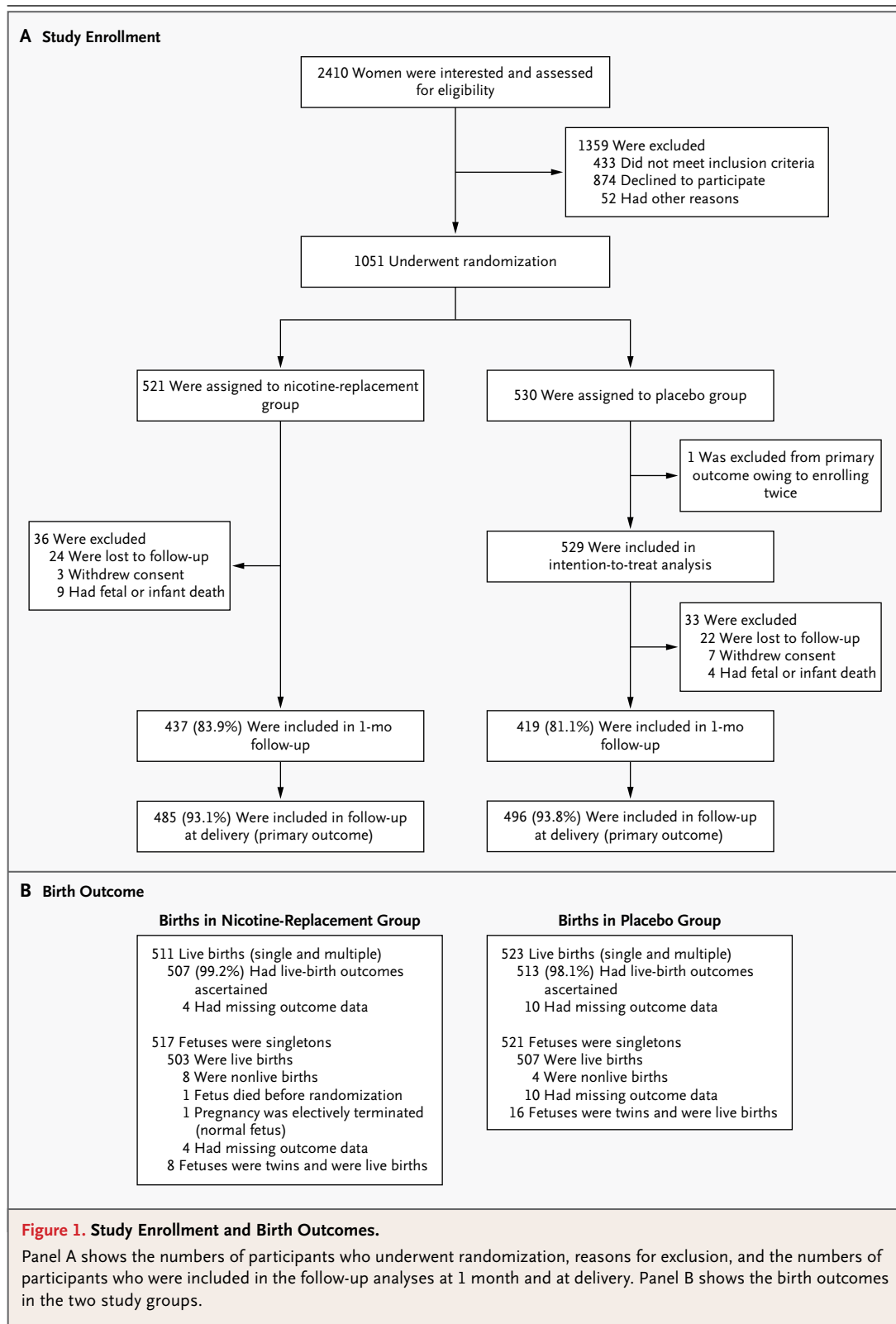


Table 1. Baseline Characteristics, According to Study Group.*

Characteristic	Nicotine Replacement (N = 521)	Placebo (N = 529)
Age — yr	26.4±6.2	26.2±6.1
Cigarettes smoked daily before pregnancy — no.		
Median	20	20
IQR	15–20	15–20
Cigarettes smoked daily at randomization — no.		
Median	13	15
IQR	10–20	10–20
Gestational age — wk	16.2±3.6	16.3±3.5
Race or ethnic group — no. (%)†		
White British	503 (96.5)	515 (97.4)
Other	18 (3.5)	14 (2.6)
Age at leaving full-time education — yr‡	16.2±1.4	16.3±1.7
Parity — no. (%)§		
0–1	356 (68.3)	363 (68.6)
2–3	129 (24.8)	142 (26.8)
≥4	36 (6.9)	24 (4.5)
Cotinine level — ng/ml		
Median	123.1	121.2
IQR	80.1–179.8	77.2–175.9
Time from awakening to first cigarette — no. (%)		
0–15 min	281 (53.9)	285 (53.9)
16–60 min	199 (38.2)	198 (37.4)
>60 min	41 (7.9)	46 (8.7)
Women with partner who smoked — no./total no. (%)¶	356/481 (74.0)	360/482 (74.7)
Height — cm	163.2±6.8	163.0±6.5
Weight — kg**	71.7±18.2	71.6±17.2
Previous preterm birth — no. (%)††	42 (8.1)	50 (9.5)
Length of first behavioral-support session — no. (%)		
<30 min	84 (16.1)	81 (15.3)
31–60 min	428 (82.1)	433 (81.9)
>60 min	9 (1.7)	15 (2.8)
Use of nicotine-replacement therapy earlier in pregnancy — no. (%)‡‡	23 (4.4)	24 (4.5)

* Plus-minus values are means ±SD. All baseline differences between groups were nonsignificant ($P>0.05$). IQR denotes interquartile range.

† Race or ethnic group was self-reported. Race was categorized according to standard U.K. Census categories. Other “white” categories (e.g., white Irish or white other) were reported infrequently and were included as “Other.”

‡ At the time of enrollment, 14 women were still in full-time education.

§ Parity was defined as the number of previous pregnancies that had progressed beyond 24 weeks.

¶ Data exclude 40 women in the nicotine-replacement group and 47 in the placebo group who had no partner.

|| Height was not recorded for 15 participants in the nicotine-replacement group and 23 in the placebo group.

** Weight was not recorded for 12 participants in the nicotine-replacement group and 11 in the placebo group.

†† Previous preterm birth was defined as any previous pregnancy that lasted from 24 to 37 weeks.

‡‡ The median number of days before enrollment that women last used nicotine-replacement therapy among the 47 women who reported current or past use was 31 for the nicotine-replacement group (interquartile range, 15 to 38) and 30 for the placebo group (interquartile range, 14 to 68).

Table 2. Primary and Secondary Abstinence Outcomes.*

Outcome	Nicotine Replacement (N = 521) number (percent)	Placebo (N = 529)	Odds Ratio (95% CI) [†]	Adjusted Odds Ratio (95% CI) [‡]
Primary				
Abstinence from quit date to delivery, with salivary cotinine validation, with or without CO validation§	49 (9.4)	40 (7.6)	1.26 (0.82–1.96)	1.27 (0.82–1.98)
Secondary				
Abstinence from quit date to delivery without validation	65 (12.5)	49 (9.3)	1.40 (0.94–2.07)	1.41 (0.95–2.09)
Abstinence for 1 mo after quit date without validation	131 (25.1)	74 (14.0)	2.07 (1.51–2.85)	2.13 (1.54–2.95)
Abstinence for 1 mo after quit date with CO validation¶	111 (21.3)	62 (11.7)	2.05 (1.46–2.88)	2.10 (1.49–2.97)
Abstinence from quit date to delivery with validation at 1 mo and at delivery	42 (8.1)	32 (6.0)	1.36 (0.84–2.19)	1.37 (0.84–2.22)
Point-prevalence abstinence (cessation for >24 hr) at delivery with CO validation	63 (12.1)	53 (10.0)	1.23 (0.84–1.82)	1.24 (0.84–1.85)
Point-prevalence abstinence (cessation for >24 hr) at delivery without validation	104 (20.0)	89 (16.8)	1.24 (0.90–1.70)	1.25 (0.90–1.72)

* CO denotes carbon monoxide.

[†] Odds ratios were adjusted for recruitment center only (as a stratification factor).

[‡] Odds ratios were adjusted for center, level of salivary cotinine at baseline, partner's smoking status (partner smokes vs. partner does not smoke or no partner), and age at leaving full-time education.

§ The biochemical samples did not validate the report of not smoking (i.e., probable false reporting of cessation) in 9 of 58 women (16%) receiving nicotine-replacement therapy and in 5 of 45 (11%) receiving placebo.

¶ This outcome measure was not included in the original protocol. The biochemical samples did not validate the report of not smoking (i.e., probable false reporting of cessation) in 5 of 116 women (4%) receiving nicotine-replacement therapy and in 1 of 63 (2%) receiving placebo.

nence rate was significantly higher in the nicotine-replacement group than in the placebo group (21.3% vs. 11.7%; odds ratio, 2.05; 95% CI, 1.46 to 2.88). Adjusted analyses yielded similar findings with respect to these outcomes.

For singleton births, mean birth weight and rates of preterm birth, low birth weight, and congenital abnormalities were similar in the two study groups (Table 3). However, there were significantly more deliveries by means of cesarean section in the nicotine-replacement group than in the placebo group (20.7% vs. 15.3%). The results of analyses that included twins were similar. Rates of other adverse events were also similar in the two groups (Table 4).

DISCUSSION

This study shows that supplementing behavioral support with a nicotine patch (15 mg per 16 hours), which is an effective approach for increasing the rate of abstinence from smoking among nonpregnant smokers, was no more effective than placebo in promoting sustained abstinence throughout pregnancy among women at 12 to 24 weeks of ges-

tation, despite higher abstinence rates at 1 month in the nicotine-replacement group than in the placebo group. There was no evidence that nicotine-replacement therapy had either a beneficial or harmful effect on birth outcomes.

In contrast to the findings at delivery, the increased rate of abstinence at 1 month in the nicotine-replacement group was similar to that seen with the use of such therapy in nonpregnant smokers. The absence of a significant longer-term effect of nicotine-replacement therapy may be explained by the low adherence rates. Population surveys show that 54% of users of nicotine-replacement therapy discontinue its use within 1 month, the majority because they are smoking again or believe the therapy is not working.²⁰ Similarly, in trials of nicotine-replacement therapy, adherence is often low because participants usually stop using this therapy when they have a relapse. Two trials involving pregnant women using nicotine patches at a similar dose also showed low adherence; in one trial, the median duration of patch use was 2 weeks,²¹ and in the other, the mean duration of use was 3 weeks.²² In a trial that assessed the efficacy of 2-mg nicotine gum, which had entry cri-

Table 3. Birth Outcomes According to Study Group.*

Outcome	Nicotine Replacement (N=515)	Placebo (N=521)	Odds Ratio (95% CI)†	Mean Difference (95% CI)
Miscarriage — no. (%)‡	3 (0.6)	2 (0.4)	1.52 (0.25 to 9.13)	
Stillbirth — no./total no. (%)‡	5/512 (1.0)	2/519 (0.4)	2.59 (0.50 to 13.4)	
Neonatal death — no./total no. (%)‡	0/507	2/517 (0.4)	NC	
Postneonatal death — no./total no. (%)‡§	1/507 (0.2)	0/517	NC	
Birth weight, unadjusted — kg	3.18±0.61	3.20±0.59		−0.02 (−0.10 to 0.05)
Birth weight — z score	−0.36±0.99	−0.31±1.02		−0.05 (−0.17 to 0.08)
Gestational age — wk	39.5±2.1	39.5±2.1		0.0 (−0.2 to 0.3)
Preterm birth — no./total no. (%)¶	40/507 (7.9)	45/517 (8.7)	0.90 (0.58 to 1.41)	
Low birth weight — no./total no. (%)	56/507 (11.0)	43/517 (8.3)	1.38 (0.90 to 2.09)	
NICU admission — no./total no. (%)	33/507 (6.5)	35/517 (6.8)	0.96 (0.58 to 1.57)	
Apgar score at 5 min <7 — no./total no. (%)	16/507 (3.2)	18/517 (3.5)	0.91 (0.45 to 1.80)	
Cord-blood arterial pH <7 — no./total no. (%)	4/507 (0.8)	7/517 (1.4)	0.57 (0.17 to 1.97)	
Intraventricular hemorrhage — no./total no. (%)	2/507 (0.4)	3/517 (0.6)	0.67 (0.11 to 4.05)	
Neonatal convulsions — no./total no. (%)	5/507 (1.0)	5/517 (1.0)	1.02 (0.29 to 3.54)	
Congenital abnormalities — no./total no. (%)**	9/507 (1.8)	13/517 (2.5)	0.70 (0.30 to 1.66)	
Necrotizing enterocolitis — no./total no. (%)	3/507 (0.6)	6/517 (1.2)	0.50 (0.12 to 2.03)	
Infant on ventilator >24 hr — no./total no. (%)	10/507 (2.0)	11/517 (2.1)	0.93 (0.39 to 2.22)	
Assisted vaginal delivery — no./total no. (%)	38/507 (7.5)	43/517 (8.3)	0.95 (0.59 to 1.50)	
Delivery by cesarean section — no./total no. (%)	105/507 (20.7)	79/517 (15.3)	1.45 (1.05 to 2.01)	

* Plus-minus values are means ±SD. Data include information from singleton births only. Using an intention-to-treat analysis, we calculated a total of 1036 as the number after the exclusion of 12 women with multiple pregnancies and 2 from the nicotine-replacement group (1 with missed abortion [i.e., the retention in the uterus of a dead fetus] before randomization and 1 with elective termination in the presence of a normal fetus). NC denotes not calculated, and NICU neonatal intensive care unit.

† Odds ratios were adjusted for recruitment center (as a stratification factor).

‡ These outcomes were defined a priori as serious adverse events. There were no maternal deaths, and no serious adverse events were judged to be related to nicotine-replacement therapy. The denominator for miscarriage was calculated as the number randomized minus the number of elective terminations. The denominator for stillbirth was calculated as the number randomized minus the number of elective terminations and miscarriages. For all other outcomes, the denominator is the number of singleton live births, including those births for which outcome data were missing (507 in the nicotine-replacement group and 517 in the placebo group).

§ Median age of infant at follow-up was 2.8 years (range, 0.02 to 4.3; interquartile range, 2.2 to 3.4).

¶ Preterm birth was defined as a birth occurring before 37 weeks of gestation.

|| Low birth weight was defined as a weight of less than 2.5 kg.

** The categorization of congenital abnormalities by study group is in the Supplementary Appendix (available at NEJM.org).

teria that were very similar to ours,²³ the gum was used for an average of slightly more than 5 weeks.

Adverse events do not appear to explain the level of discontinuation of treatment. In our trial, adverse events led to the discontinuation of use of the nicotine patch in 8.8% of women; in previous trials, the discontinuation rates were 12% for nicotine gum²³ and 4.4% for nicotine patches or placebo.²² Low adherence rates could be explained by increases in nicotine and cotinine clearance during pregnancy; respective increases of 60% and 140% have been reported to occur by 25 weeks of gestation,²⁴ which would reduce the nicotine levels

generated by nicotine-replacement therapy and could increase withdrawal symptoms. It is possible that for nicotine-replacement therapy to consistently ameliorate nicotine-withdrawal symptoms and be effective throughout pregnancy, a higher dose is required.²⁴ However, this trial did not include assessment of nicotine metabolism and did not assess withdrawal symptoms, and factors other than increases in metabolism may explain low rates of adherence to nicotine-replacement therapy in our study and other, similar trials.¹²

We used a particularly robust outcome measure: abstinence from smoking between a quit date and

Table 4. Adverse Events, According to Study Group.*

Event	Nicotine Replacement (N=521)	Placebo (N=529)
Serious adverse events — no. (%)		
Maternal death	0	0
Other events†	9 (1.7)	6 (1.1)
Maternal adverse events potentially related to treatment — no. (%)		
Patch stopped permanently, owing to adverse event‡	46 (8.8)	32 (6.0)
Skin reactions at patch site (but no discontinuation of treatment)§	97 (18.6)	28 (5.3)
Maternal adverse events as probable complications of pregnancy — no. (%)		
Blood pressure >140/90 mm Hg on at least 2 occasions	24 (4.6)	25 (4.7)
Nausea or vomiting	16 (3.1)	19 (3.6)
Headache	25 (4.8)	16 (3.0)
Abdominal pain	54 (10.4)	50 (9.5)
Vaginal bleeding or hemorrhage	35 (6.7)	38 (7.2)
Premature rupture of membranes¶	6 (1.2)	10 (1.9)
Uterine contractions during pregnancy¶	24 (4.6)	30 (5.7)
Gestational diabetes	3 (0.6)	3 (0.6)
Preeclampsia or eclampsia	3 (0.6)	5 (0.9)
Hospital admission for other pregnancy complication	44 (8.4)	41 (7.8)
Other, less frequent events**	63 (12.1)	73 (13.8)
Fetal adverse events as probable complications of pregnancy — no. (%)		
Decreased fetal movement¶	58 (11.1)	46 (8.7)
Other events**	5 (1.0)	5 (0.9)
Neonatal adverse events — no. (%)**	32 (6.1)	29 (5.5)
Total adverse events — no.††	535	450

* Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.1. For each study group, percentages were calculated as the number of women who had at least one adverse event, divided by the number of women who underwent randomization. Participants may have had adverse events in more than one category.

† Other serious adverse events included miscarriage, stillbirth, and neonatal and postneonatal deaths reported as pre-specified trial outcomes.

‡ The reasons for discontinuation of use of the nicotine patch are summarized in the Supplementary Appendix.

§ Adverse events included pruritus, swelling, erythema, rash, blistering or vesicles, pain, and other local reactions.

¶ Symptoms required hospital admission or assessment.

|| Less than 3% of the participants required overnight admission to the hospital for less-frequent events. The full breakdown of the data is available in the Supplementary Appendix.

** Events occurred in less than 3% of women or infants. The full breakdown of the data is available in the Supplementary Appendix.

†† The total numbers of women or their infants who had at least one adverse event or serious adverse event were 316 (60.6%) in the nicotine-replacement group and 269 (50.8%) in the placebo group.

delivery, with validation at delivery.¹⁸ Previous trials have tended to use the point prevalence of abstinence at up to 7 days after cessation as a primary outcome measure,²⁵ but smoking behavior in pregnancy can be variable, and some women quit and return to smoking repeatedly.²⁶⁻²⁸ Consequently, point-prevalence measures generally indicate higher quit rates but are less likely than measures of prolonged abstinence to accurately reflect ma-

ternal and fetal exposures to tobacco-smoke toxins throughout pregnancy. The more stable measure used in our trial is therefore more likely to be closely related to clinical outcomes. Also, because we validated some reports of cessation when women had returned home after childbirth, some participants who had stopped smoking during pregnancy may have restarted by that time, lowering the overall quit rates. Since the ascertainment

of outcome was conducted similarly in the two study groups, however, this is unlikely to have affected the findings.

Use of nonstudy nicotine-replacement therapy in the placebo group is unlikely to explain the absence of a prolonged effect of the nicotine patches used in the study, because only 2.2% of the women in the placebo group (and 2.5% of those who received nicotine-replacement therapy) reported using nonstudy nicotine-replacement therapy for more than 20 days. Moreover, follow-up rates were equally high in the two groups and the rates of use of additional behavioral support were similar, so neither bias in outcome ascertainment nor differences in the extent of support received are likely to explain the findings. The level of behavioral support provided in our study was similar to that used in trials of nicotine patches with low-intensity support that have been conducted among nonpregnant subjects, in which nicotine-replacement therapy has been found to be effective (risk ratio, 1.78; 95% CI, 1.49 to 2.12).⁹

The rates of adverse outcomes were similar in our two study groups, with the exception of the higher rate of delivery by means of cesarean section in the nicotine-replacement group, a finding that was not expected and that seems likely to be a chance occurrence. However, caution is warranted in interpreting the absence of apparent harm with nicotine-replacement therapy as an indication of its safety, given the low adherence rates for nicotine-replacement therapy and the fact that a much larger sample would be required to comprehensively assess the effect of this therapy on

infrequent adverse birth outcomes. Still, the absence of any apparent harm, coupled with the lack of efficacy of this dose of nicotine-replacement therapy in pregnant women (despite its demonstrated efficacy outside of pregnancy), provides support for the initiation of a randomized trial of a higher dose of nicotine-replacement therapy in pregnant women.

This trial was four times as large as the largest, previous similar study.²² As in the previous, smaller trials, which also tested the standard dose of nicotine-replacement therapy after 12 weeks of gestation,¹² our study showed no significant increase in rates of abstinence from smoking throughout pregnancy after the addition of a nicotine-replacement patch, at a dose of 15 mg per 16 hours, to behavioral support for smoking cessation. Together with the prior results¹² and pending data that show the efficacy of a higher dose of nicotine-replacement therapy in pregnant women, the present findings suggest that guidelines for smoking cessation in pregnancy should be revised to encourage the use of only those interventions that have a secure evidence base — specifically, behavioral support.

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