The SNAP trial: a randomised placebo-controlled trial of nicotine replacement therapy in pregnancy – clinical effectiveness and safety until 2 years after delivery, with economic evaluation

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Scientific summary

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Background

Maternal smoking in pregnancy causes substantial morbidity and mortality and remains a public health problem internationally. Although in many developed countries the rates of smoking in pregnancy are falling, increases in populous middle- and low-income jurisdictions are expected to transfer a rising health burden to these nations in future years. In addition to improving women's health, stopping smoking in pregnancy improves fetal and infant health outcomes; cessation has, for example, been shown to reduce the incidence of low-birthweight (LBW) infants. Unfortunately, there is a limited evidence base to guide the delivery of cessation support in pregnancy. Only behavioural support from a health professional and 'self-help' support, are of proven efficacy.

Pregnant women generally avoid medications and the only drug treatment for cessation that is widely used during gestation is nicotine replacement therapy (NRT). The consensus view is that NRT should be safer than smoking because it contains medicinal nicotine alone, whereas inhaled tobacco smoke contains nicotine and many additional toxins. However, there are strong, biological reasons to suspect that standard doses of NRT, which have only been demonstrated to work in non-pregnant smokers, may be less effective for smoking cessation in pregnancy. Nicotine metabolism is much quicker in pregnancy, therefore, nicotine substitution will be less complete when pregnant women use this and successful amelioration of nicotine withdrawal symptoms is less likely. Prior to this trial, only 695 women had been enrolled in studies investigating the efficacy and safety of NRT in pregnancy and, together, these provided insufficient evidence to say whether or not NRT could be effective or safe when used for smoking cessation in pregnancy. The **S**moking, **N**icotine **A**nd **P**regnancy (SNAP) trial was designed to provide much needed evidence for both issues.

Objectives

The overall aim of the study was to investigate whether NRT is more effective than placebo in achieving smoking cessation for women between 12 and 24 weeks pregnant, who currently smoke five or more cigarettes per day and who smoked at least 10 cigarettes per day before pregnancy.

The specific study objectives were to compare:

i. the clinical effectiveness and cost-effectiveness for achieving biochemically validated smoking cessation of 15 mg per 16 hours transdermal nicotine patches with placebo patches in women at delivery
ii. the effects of maternal NRT patch use with placebo patch use during pregnancy on (1) disability, behaviour and development and (2) respiratory symptoms in infants at 2 years of age.

Methods

The SNAP trial was a double-blind, randomised, placebo-controlled trial with an accompanying health economic evaluation. Potentially interested pregnant smokers with the above characteristics (see *Objectives*) were identified as they attended ultrasonography appointments at seven hospital antenatal clinics in the Midlands and north-west England. Research midwives (RMs), who worked in each centre, discussed the study with potential participants and enrolled them and gained consent, as appropriate. Participants set quit dates and RMs provided behavioural support lasting up to 1 hour before randomising women to receiving either a 4-week supply of 15 mg per 16 hours transdermal nicotine patches or visually

identical placebos. One month later, women who remained abstinent were issued another 4-week patch supply. RMs provided three more telephone behavioural support sessions on participants' quit dates, 3 days afterwards and at 1 month. Those women who collected a second month's supply of NRT also received face-to-face support at 1 month. Women were offered further support from the RM and from local NHS Stop Smoking Services (SSS), and delivery of behavioural support was guided by a shared manual.

Research midwives followed up participants at 1 month after their quit dates and when women were admitted to hospital in established labour, or as soon as possible afterwards. Following delivery, RMs retrieved birth outcome data from medical records. After childbirth, follow-up was conducted from a central trial office and postal questionnaires were sent to women at 6, 12 and 24 months after childbirth with a variety of methods used to maintain contact with participants and maximise response rates. If responses were not received at 24 months, follow-up questionnaires enquiring about infants' health was sent to participants' general practitioners (GPs).

The primary outcome was self-reported prolonged abstinence from smoking between the quit date and childbirth, validated at delivery by exhaled carbon monoxide (CO) and/or salivary cotinine (COT) estimation. Temporary, brief smoking lapses of up to five cigarettes in total (on up to five occasions) were permitted. Further outcomes were collected 2 years after birth and the primary outcome at this time point was infant survival 'without impairment', defined as no disability or problems with behaviour and development having been detected using standard parental or health professional questionnaires (HPQs).

Smoking status and smoking behaviour were ascertained at all follow-up points. The following outcomes were also ascertained: at delivery, maternal and fetal birth outcomes and pregnancy morbidity; at 6 months, health status [using the European Quality of Life-5 Dimensions (EQ-5D) scale] and health service use; at 1 year, respiratory symptoms and, at 2 years, child development outcomes, including 'survival without impairment' and respiratory symptoms.

We aimed to recruit 1050 participants providing 93% power at a 5% significance level to detect a 9% absolute difference between groups. We anticipated a 16% cessation rate in the placebo group, based on the observations that 10% of smokers stop with usual care after their first antenatal visit and behavioural support results in cessation by another 6–7%. We sought to detect the same treatment effect that NRT patches have outside of pregnancy [odds ratio (OR) 1.74, 95% confidence interval (CI) 1.57 to 1.93], giving a projected 25% NRT group cessation rate.

At delivery, participants who, for any reason, had missing smoking outcome data were assumed to be smoking. For fetal outcomes, the primary analysis was of singleton births and for all outcomes, analysis was on an intention-to-treat (ITT) basis and logistic regression, adjusted for centre, was used to compare treatment groups. At 2 years, impairment of infants (i.e. disability or behaviour and development problems) was assessed using parent-completed items from the Ages and Stages Questionnaire®, third edition (ASQ-3™) (Squires J and Bricker D. *Ages and Stages Questionnaire: A Parent-Completed Child-Monitoring System*. 3rd edn. Baltimore, MD: Paul H Brookes Publishing Co.; 2009) and questionnaires returned by health professionals. The proportions of singleton infants without impairments were compared and multiple imputation methods investigated the impact of missing data. Singleton 'complete case' analyses using data from both questionnaires and an analysis including twin births with allowance for clustering were also conducted.

Economic analyses aimed to determine costs of delivering the intervention, to conduct a cost-effectiveness analysis using 'cost-per quitter' as an outcome and, also, to undertake a cost–utility analysis using EQ-5D data collected at 6 months after delivery, combined with modelling of the impacts of any variation in birth outcomes.

Results

A total of 1050 women were enrolled in the trial (521 NRT, 529 placebo). From 1050 pregnancies, there were 1034 live births (1010 singletons, 24 twins), five miscarriages, seven stillbirths, one elective termination, one missed abortion (documented as having occurred before randomisation) and 14 for which birth outcomes were unknown. Completeness of follow-up rates were similar in both groups at all time-points and ascertainment rates based on participants' responses were at 1 month, 82%; at delivery, 93%; at 6 months, 66%; at 1 year, 58% and at 2 years, 90%. Ascertainment rates for birth outcomes were even higher. Rates of biochemical validation of smoking status at delivery were 89% in NRT and 92% in placebo groups, respectively, and, at one month, corresponding rates were 89% and 85%. Adverse event (AE) rates were similar in both groups. All 1034 (1010 singleton) infants were included in the follow-up and, of singletons, among whom principal analyses were conducted, information on 88.2% (891; 445 NRT and 446 placebo group) was returned at 2 years.

Smoking outcomes: at delivery, the validated, prolonged smoking cessation rate was 9.4% in the NRT and 7.6% in the placebo group (OR for cessation with NRT 1.26, 95% CI 0.82 to 1.96). At 1 month, the validated cessation rate was significantly higher in the NRT group (21.3% vs. 11.7%, OR for cessation with NRT 2.05, 95% CI 1.46 to 2.88). After delivery, there were no statistically significant differences in cessation. Self-reported prolonged abstinence since the quit date was: at 6 months, 5.4% in the NRT group and 3.2% in the placebo group; at 1 year, 3.7% and 2.1%; and, at 2 years, 2.9% and 1.7%, respectively.

Adherence: relatively few participants reported using a full 8-week course of NRT. Of the 981 participants followed up at delivery, only 7.2% (35/485) of women randomised to NRT and 2.8% (14/496) randomised to placebo reported using trial medications for over 1 month. Additionally, of the 205 women who reported abstinence at 1 month (173 had validated abstinence), only 101 accepted the offer of a further 4-week supply of patches.

Birth outcomes: these were generally similar between treatment groups. The only significant difference was that more caesarean births occurred in the NRT group than in the placebo group (20.7% vs. 15.3%).

Infant outcomes at 2 years: 72.6% (323/445) of NRT group infants survived with 'no impairment', compared with 65.5% (290/443) born to participants in the placebo group (OR 1.40, 95% CI 1.05 to 1.86). Sensitivity analyses including twins or using only questionnaires returned by parents gave similar findings. There was no significant difference between groups in infants' reported respiratory problems; these occurred in 132 out of 444 (29.7%) of NRT and 111 out of 444 (25%) of placebo group infants, respectively (OR for symptoms in NRT vs. placebo 1.30, 95% CI 0.97 to 1.74).

Economic analyses: total mean costs (costs of delivering the intervention and resource-use costs) were approximately £91 higher in the NRT group and the incremental cost-effectiveness ratio (ICER) associated with NRT use was £4926 per additional quitter (bootstrapped 95% CI –£114,128 to £126,747), or £4156 (bootstrapped 95% CI –£65,994 to £82,059) in analyses restricted to singleton infants; however, CIs show there was substantial uncertainty around these estimates. It was not possible to model cost–utility of NRT owing to very similar adverse birth outcomes rates and EQ-5D scores in both trial groups and the likely amplification in uncertainty of estimates that such analyses would have caused.

Conclusions

The SNAP trial demonstrates that at 12–24 weeks' gestation, supplementing behavioural support with a 15 mg per 16 hours nicotine patch was no more effective than placebo in promoting sustained smoking cessation throughout pregnancy. Despite significantly higher cessation rates occurring at 1 month in the NRT group, this effect did not persist until delivery. The quit rate was slightly, but not statistically

significantly, higher in the NRT group at delivery and this (still non-significant) difference remained at 6, 12 and 24 months. We do not know why NRT had a large, clinically and statistically significant effect early in pregnancy, which disappeared as gestation progressed. There was no evidence for NRT having either a beneficial or a harmful effect on birth outcomes, apart from slightly higher caesarean rates in the NRT group. However, as adherence was poor, birth outcome findings are difficult to interpret and could have been different had greater adherence with trial treatments occurred.

At 2 years, infants born to participants randomised to NRT were more likely to have survived without any impairment, but there were no significant differences in infants' respiratory problems. The most likely reason for better NRT group infant outcomes are the lower, albeit largely non-significant, smoking rates in NRT group mothers.

Total mean costs were approximately £91 higher in the NRT group, representing a small (3%) difference in costs between trial groups and these higher costs were mainly attributable to the cost of the NRT patches (mean = £46). According to the incremental cost-effectiveness estimates, NRT would be the preferred option if decision-makers are willing to pay more than £4926 for an additional quitter. However, there was substantial uncertainty around the estimates and there is no accepted threshold for funding health-care interventions based on this kind of outcome.

Recommendations for research (in priority order)

1. Randomised controlled trials (RCTs) investigating the efficacy and safety of NRT when used for smoking cessation in pregnancy should test a higher than standard dose NRT such as (1) patches delivering more than 15 mg nicotine in 16 hours (21 mg in 24 hours), (2) 4-mg gum used as required or, (3) NRT patch combined with any 'on demand' short acting NRT (e.g. gum or nasal spray).
2. To investigate whether or not apparent differences in infants' outcomes persist into childhood. RCTs investigating NRT for smoking cessation in pregnancy should assess infants' clinical and economic outcomes after 2 years of age.
3. Randomised controlled trials investigating the efficacy of NRT or other interventions for smoking cessation used in pregnancy should include an assessment of impacts on infants using outcomes similar to those employed in SNAP.
4. Reasons for pregnant women's low levels of adherence with NRT should be investigated; findings could be used in future trials to enhance participants' adherence with NRT.
5. Increases in nicotine metabolism, occurring as pregnancy progresses could explain the reduced efficacy that NRT has in later pregnancy. Further research should investigate this hypothesis.

Implications for health care

In the UK and some other health-care systems, NRT has become an established component of cessation support for pregnant women. Although the SNAP trial found no evidence that standard dose NRT is effective for smoking cessation, there was also no evidence that this is less safe than smoking; indeed, the study suggests that NRT use in pregnancy is safe in terms of infant outcomes assessed at 2 years and may have a protective effect on infant development. Although this is the first time that a smoking cessation intervention has been observed to have a beneficial effect on pregnant smokers' offspring, this finding provides support for interventions involving NRT in pregnancy. Overall, our findings provide no evidence that NRT should not be used in pregnancy, rather that NRT might be beneficial in this setting.

Effects of NRT on infant development are likely to be mediated through the small, observed changes in maternal smoking. There are good reasons to believe that NRT used at higher doses might affect both maternal smoking and infant development more substantially and trials of higher-dose NRT are indicated. Other cessation interventions delivered in pregnancy might have similar impacts on infants, but this

requires confirmation. Choosing between interventions for use with pregnant smokers is, therefore, difficult; both 'self-help' and behavioural smoking cessation support promote maternal smoking cessation and improve birth outcomes. However, while there is no evidence that NRT has these effects, NRT does appear to have a potentially important protective effect on infant development. Therefore, this study supports the offering of NRT to pregnant women who smoke; however, any such offer should take account of the rather stronger research evidence from other studies indicating that behavioural and 'self-help' support both have beneficial effects on smoking behaviour in pregnancy.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN07249128.

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