Addiction
REVIEW
doi:10.1111/j.1360-0443.2010.03179.x

Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis

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ABSTRACT

Aims To determine the efficacy and safety of nicotine replacement therapy (NRT) with or without behavioural support when used to support smoking cessation in pregnancy. **Design, Setting and Participants** A systematic review of randomized controlled trials (RCTs) in which NRT was used with or without behavioural support to promote smoking cessation; trials providing unequal behavioural support to different trial groups were excluded. **Measurements** Efficacy: self-reported smoking cessation in later pregnancy, validated where possible by biochemical measures with appropriate cut-points; infants' safety: mean and low birth weights (LBW), preterm birth, fetal demise and neonatal intensive care unit (NICU) admissions. **Findings** Five trials, enrolling 695 pregnant, regular smokers were included in the review. The pooled risk ratio (RR) and 95% confidence Interval (CI) for smoking cessation in later pregnancy after using NRT was 1.63 (0.85, 3.14). Subgroup analysis comparing studies at lower risk of bias (placebo-RCTs) with those at higher risk of bias (non-placebo-RCTs) found that efficacy estimates varied with trial design [RR (95% CI) for cessation in placebo-RCTs 1.17 (0.83, 1.65) versus 7.81 (1.51, 40.35) for non-placebo-RCTs]. Five of the seven safety outcomes were more positive among infants born to women who had used NRT, but none of the observed differences between trial groups reached statistical significance. **Conclusions** There is currently insufficient evidence to determine whether or not nicotine replacement therapy is effective or safe when used in pregnancy for smoking cessation; further research and, in particular, placebo-randomized controlled trials are required.

Keywords Clinical trials, meta-analysis, nicotine replacement therapy, pregnancy, smoking cessation, systematic review.

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Submitted 12 August 2010; initial review completed 19 August 2010; final version accepted 23 August 2010

INTRODUCTION

Maternal tobacco smoking during pregnancy is the most significant preventable cause of poor health outcomes for women and their babies, with morbidity resulting from placental abruption, miscarriage, stillbirth, prematurity, low birth weight, neonatal or sudden infant death and asthma [1,2]. Despite declining prevalence, smoking in pregnancy remains a major public health problem in high-income countries; in the United States 13% [3] of pregnant women smoke; and in the United Kingdom, Europe and Australia the prevalences of smoking in pregnancy are 17% [4], 25% [5] and 17.4% [6,7], respectively. The burden of disease from smoking is shifting from high-income countries to more populous, low–middle-income countries, where the increasing prevalence of women's smoking is cited as the most ominous development of the global tobacco epidemic [7]. Due to the huge impact of low birth weight and preterm births, the economic cost of smoking in pregnancy is also substantial [8,9], causing up to 40% of socio-economic inequalities in stillbirths and infant deaths [10]. Consequently, reducing the prevalence of smoking in pregnancy is an international public health priority.

In many high-income countries clinicians use nicotine replacement therapy (NRT) in attempts to help pregnant smokers to stop; for example, NRT use in pregnancy is 'cautioned' rather than 'contraindicated' in the United

Kingdom [11]. Also, in the United States [12], Australia [13], New Zealand [14] and the United Kingdom [15,16] guidelines have recommended that, with some qualifications, NRT can be used by pregnant women. However, although NRT is an effective smoking cessation treatment for non-pregnant smokers [17], its efficacy and safety in pregnancy have not been demonstrated adequately. Nicotine is metabolized much more quickly in pregnancy [18], so standard doses of NRT may not be effective when used by pregnant women. NRT may be safer than continued smoking in pregnancy because, unlike cigarette smoke, nicotine from NRT is not accompanied by toxic products of combustion [19]; some experts sanction its use in pregnancy on this basis [20], although there is currently insufficient evidence to support this belief. A previous review has investigated the efficacy of NRT for smoking cessation in pregnancy [21]; however, this analysed trials with multi-modal intervention strategies grouped by their primary intervention strategy. This analysis strategy may have resulted in pooling of data from trials which did not test the independent effects of NRT for smoking cessation in pregnancy with those that did and, hence, a potentially inaccurate estimate for the effect of NRT may have been derived. To inform clinical practice, therefore, we have conducted a systematic review and meta-analysis including only randomized controlled trials with designs from which the independent efficacy and safety of NRT can be determined accurately.

METHODS

Criteria for including studies

We included randomized controlled trials (RCTs) with designs which permitted independent effects of any type of NRT (e.g. patch, gum, etc.) for smoking cessation to be isolated. Included trials needed to provide similar levels of behavioural support or cognitive behavioural therapy to participants provided NRT and those in comparator arms; the following RCT designs were acceptable:

- Placebo-RCTs: any form of NRT with behavioural support/cognitive behavioural therapy or brief advice compared with placebo NRT and behavioural support/cognitive behavioural therapy or brief advice of similar intensity.
- Non-placebo-RCTs: any form of NRT plus behavioural support/cognitive behavioural therapy or brief advice compared with behavioural support/cognitive behavioural therapy or brief advice of similar intensity alone.

Trials were excluded if the level of behavioural support differed substantially between trial arms, because this kind of support is an effective smoking cessation intervention for pregnant women which also has a positive impact on birth outcomes (e.g. birth weight) [21]. Therefore, imbalances in support provided would be expected to have an impact on cessation and birth outcomes, potentially rendering findings difficult to interpret.

Outcome measures

Effectiveness

The primary effectiveness outcome was abstinence from smoking in later pregnancy or at delivery; we included trials in which smoking cessation was ascertained from 20 weeks gestation onwards. Where available, prolonged continuous abstinence measures, set from a defined quit date in early pregnancy, were used with point prevalence abstinence substituted for these as required [22]. We used cut-points for biochemical validation of smoking status which have been agreed by expert consensus [23]: exhaled carbon monoxide (CO), 8 parts per million (p.p.m.) and saliva cotinine, 10 ng/ml.

Safety

Mean unadjusted birth weight, low birth weight (<2500 g), preterm birth (<37 weeks gestation), neonatal intensive care unit (NICU) admissions and fetal demise were extracted to investigate safety. The following categories of fetal demise were used: spontaneous abortions (fetal death < 24 completed weeks gestation), elective abortions, stillbirths (non-live birth at >24 weeks) and neonatal deaths (live birth at >24 weeks, followed by fetal death within 28 days). No study recorded post-neonatal deaths.

Adherence and side effects

Any measures of adherence with NRT or placebo medications and non-serious side effects (serious adverse event data contributed to 'safety' outcomes, above).

Search strategy

Comprehensive searches had been conducted until April 2008 for a Cochrane review of the effectiveness of smoking cessation interventions in pregnancy [21], so trials published prior to 2008 were identified from those categorized within this review as having an intervention strategy involving NRT. To locate papers describing RCTs published after April 2008 (until August 2009), we used an 'auto alert' for the databases CINAHL, EMBASE, MEDLINE and PsychLit which flagged any publications citing 'smoking or tobacco and pregnancy' in the title or abstract. We obtained all papers which described trials of NRT in pregnancy and also the papers from titles which were unclear. We also re-searched the Cochrane Pregnancy and Childbirth Group Trial Register via the Trials Search Co-ordinator; methods for maintaining this

register are published elsewhere [21]. All abstracts and titles describing studies were inspected independently by C.C. and T.C. and papers were sought for any which described potentially relevant trials.

For all trials identified, data were extracted independently by two authors who resolved discrepancies by discussion; effectiveness and birth outcome data (T.C. and J.L.B.); adherence with treatment regimen data (T.C. and C.C.). Where necessary, trial authors were contacted to clarify methodological quality (e.g. methods of randomization sequence generation); outcome (e.g. biochemical validation cut-points) and safety data (e.g. reasons for elective terminations, whether these were performed for fetal morbidity (morbidities) judged incompatible with life and distribution of spontaneous abortion by trial arm), and agreed data were entered into Review Manager 5 [24] by one author (T.C.).

Quality assessment

We adapted the Cochrane Collaboration tool for assessing risk of bias in trials [25] and judged methodological quality according to adequacy of sequence generation; allocation concealment and blinding; using an intention-to-treat analysis and being free of selective outcome reporting. We also considered that inclusion of biochemical validation of smoking status was important and that this should use accepted cut-points to distinguish smokers and non-smokers [23]. As a drug intervention was being assessed, allocation concealment and blinding were particularly important for differentiating placebo effects from those of NRT. Two authors (T.C. and S.C.) rated the methodological quality of studies independently and resolved uncertainties via discussion.

Statistical analysis

Meta-analyses were performed to calculate a weighted intervention effect across all trials using a random-effects (DerSimonian & Laird) model; results are expressed as pooled risk ratios (RR) with 95% confidence intervals (CI). Statistical heterogeneity was assessed using I^2 [26], with meta-analysis not permitted and the studies' findings being summarized separately when I^2>80%. We present meta-analyses of effectiveness outcomes for all included trials versus control conditions and for placebo and non-placebo-RCTs separately, as these latter trials were considered potentially at risk of bias.

Where heterogeneity permitted, we performed meta-analyses for mean birth weight, low birth weight and preterm birth. We present two outcomes for fetal demise: (i) perinatal deaths (i.e. stillbirths plus neonatal deaths) and (ii) post-randomization fetal deaths (i.e. miscarriages, stillbirths, neonatal deaths plus elective terminations performed for fetal morbidity judged to be incompatible with life); miscarriages are presented separately to enable comparison with other work but are a subset of post-randomization fetal deaths. To prevent 'double counting' of adverse outcomes such as fetal demise, the following denominators were used for different outcomes:

(i) low birth weight and preterm births: number of participants randomised minus (elective terminations plus miscarriages);
(ii) post-randomization fetal deaths: number of participants randomized minus [miscarriages in which fetal death was documented to have occurred prior to randomization (i.e. 'missed abortions') plus elective terminations not performed for fetal morbidity judged incompatible with life];
(iii) miscarriages: as for post-randomization fetal deaths (NB: miscarriages are a subset of post-randomization fetal deaths);
(iv) perinatal deaths: number of participants randomized minus [elective terminations plus miscarriages]; and
(v) NICU admissions: number of participants randomized minus (elective terminations + miscarriages + stillbirths).

For mean birth weight the denominator was the number of infants for whom this was recorded and, for dichotomous birth outcomes where data were missing, infants were assumed not to have had the adverse outcome of interest. Sensitivity analyses to investigate the impact of: (i) including all biochemically validated outcomes, irrespective of cut-points (see later) and (ii) excluding any trials which reported substantially lower adherence were planned. Also, for some adverse safety outcomes, we could not ascertain all treatment allocations and, for these events, we conducted sensitivity analyses to investigate how findings might be affected if these had all occurred in the NRT and control groups, respectively. We anticipated that adherence data might need to be presented descriptively if we found that there was substantial variation across studies in how these data were recorded.

FINDINGS

Description of trials

No studies for inclusion were identified from the trials register search, but abstracts and titles describing 54 potential studies for inclusion were identified from bibliographic database searches. After title and abstract inspection, 53 studies clearly did not describe potentially relevant RCTs. One paper was obtained and met inclusion criteria [27] and, from the Cochrane Review, we identified five trials, four of which also met inclusion criteria [28–31], giving a total of five included trials which enrolled a total of 695 pregnant smokers [27–31];

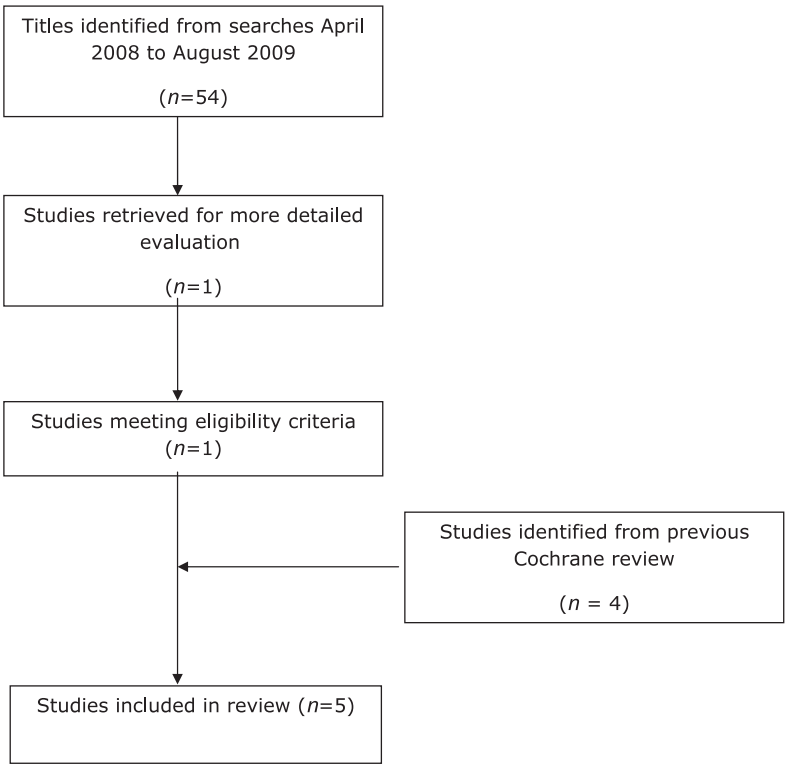

Figure 1 Process of study retrieval

selection process details are in Fig. 1. The one trial included in the Cochrane Review but excluded from analyses here was quasi-randomized—its intervention group was formed by inviting women with non-even birth dates for antenatal care on days when the intervention was delivered. NRT was also offered to intervention group participants as part of a multi-modal intervention strategy [32] and it was not judged possible to identify the independent effect of NRT from this study. Three included studies were placebo-RCTs and two compared NRT plus behavioural support with behavioural support alone. Studies were conducted in the United States ($n = 2$), Australia ($n = 1$), Canada ($n = 1$) and Denmark ($n = 1$). The risk of bias was generally low across trials, with virtually all domains of the bias risk assessment tool being satisfied for the majority of studies and an absence of blinding being the principal difference between trials. One study used a cut-point for saliva cotinine which was higher than the currently accepted level (see below) [28] and another collected information on unreported secondary outcomes, data for which were obtained from authors [29].

In one small trial ($n = 40$) smoking cessation was ascertained between 20 and 28 weeks gestation [31], but in all others this was ascertained at or after 32 weeks. In all studies, biological samples were obtained from participants (Table 1), and after any necessary clarification with authors we determined that all used such samples to validate reported cessation at the primary end-point [27–31]; two studies used exhaled CO [27,29], two saliva cotinine [28,30] and one used both but reported only thiocyanate levels [31]. For two studies, cut-points were obtained from authors [18,30] and we obtained further data on biochemical validation from authors of the trial which used a higher than standard cut-point for saliva cotinine (26 ng/ml) [28]. This revealed that the cotinine assay used had a lower limit of 20 ng/ml, which was also above the currently accepted cut-point of 10 ng/ml, so some smokers may have been been categorized wrongly as abstinent in this study. Consequently, from this trial we used self-report data in principal analyses and biochemically validated data in a sensitivity analysis.

Infant and fetal safety outcomes were reported in three studies [27,28,30]; all reported data on the incidences of mean and low birth weights (defined as <2500 g), preterm infants (born before 37 weeks gestation) and fetal demise, and two trials also reported infants' special care admission rates and neonatal deaths [19,22].

Efficacy

Figure 2 shows meta-analyses relating to efficacy, including subgroup analyses of trials at lower and higher risk of bias and provides no evidence for NRT being effective in pregnancy. For all studies combined, the pooled RR (95% CI) for smoking cessation after using NRT was 1.63 (0.85, 3.14), $I^2 = 45\%$, but using biochemically validated rather than self-reported data from the high cut-point study

Table 1 Characteristics of included studies.

Study	*Setting and design*	*Participants*	*Interventions*	*Primary outcome measure and other follow-up times*	*Verification*
Wisborg *et al.* 2000[28]	Denmark Double-blind placebo-RCT	450 healthy women < 22 weeks pregnant and smoking ≥ 10 cigarettes daily	11-week course of NRT or identical placebo patches: 15 mg/16 hour for 8 weeks then 10 mg/16-hour for 3 weeks plus behavioural counselling and information pamphlet Intervention = active patch, control = placebo	Self-reported abstinence of ≥7 days at 2nd, 3rd and 4th prenatal visits (4 weeks prior to delivery) Follow-ups at times above and also by telephone at 3 months and 1 year after delivery	Saliva cotinine level <26 ng/ml at the fourth visit (4 weeks prior to expected delivery date). The test used could not detect lower than 20 ng/ml
Kapur *et al.* 2001[31]	Canada Double-blind placebo-RCT	30 healthy women between 12 and 24 weeks pregnant and smoking ≥ 15 cigarettes daily who want to quit smoking and could not do so in 1st trimester	12-week course of NRT or identical placebo patches: 15 mg/18-hour patch for 8 weeks, then 10 mg/18-hour for 2 weeks and finally 5 mg/18-hour for 2 weeks. Behavioural counselling at baseline and all follow-up points. Counselling at baseline including a video explaining how to use patch; also counselling at all follow-ups. Weekly telephone contact with women Intervention = active patch, control = placebo	Smoking cessation (unclear if point prevalence or continuous cessation measured) 8 weeks into programme (20–32 weeks into pregnancy). Follow-up also at weeks 1 and 4 into programme with saliva and serum cotinine measured at all time-points	Primary outcome validated at 8 weeks into programme. Cotinine cut-point not stated but paper states that 'in no case was smoking cessation associated with thiocyanate levels of >1 µg/ml/hour
Hotham *et al.* 2006[29]	Australia Non-placebo-RCT	40 healthy women between 12 and 28 weeks pregnant and smoking ≥ 15 cigarettes daily with an exhaled breath CO reading of >8 p.p.m.	Control group: 5 minutes counselling at baseline and further brief counselling (<2 minutes duration) at follow-up visits Intervention: counselling as above plus an element concerning correct use of NRT plus 15 mg/16-hour patches for a maximum of 12 weeks	Smoking cessation (point prevalence) at final antenatal visit Women seen 'at least monthly during gestation'; also seen within 48 hours of delivery when exhaled CO and saliva sample (for cotinine) taken and by telephone at 6 weeks and 3 months	Exhaled CO readings used to validate point prevalence cessation at final antenatal visit Cut-point = 8 p.p.m. CO. Author clarification used
Pollak *et al.* 2007[30]	USA Non-placebo-RCT	181 healthy, English-speaking women between 13 and 25 weeks pregnant, smoking ≥ 5 cigarettes daily and aged ≥ 18 years. Must have smoked > 100 cigarettes in life-time	Control group: five face-to-face and one telephone behavioural counselling sessions with booklet and support materials Intervention group: counselling as above but with additional focus on use of NRT. Women permitted choice of NRT from patch, gum or lozenge. Patch dose depended on CPD: <10 CPD, 7 mg/16-hour, 10–14 CPD 14 mg/16-hour and ≥15 CPD 21 mg/16-hour gum/lozenge—use one 2-mg piece for each cigarette smoked daily Maximum of 6 weeks NRT provided and no NRT provided when women return to smoking Choices of NRT: 72 of 122, patch = 59%, 32 of 122 gum = 26.2% and 12 of 122 lozenge = 9.8%. 19 women chose another formulation as they could not quit with initial selection (changes not recorded)	Self-reported 7-day point prevalence abstinence at 38 weeks Also follow-up at 7 weeks after randomization and 3 months post-partum	Saliva samples for cotinine validation were collected at the intervention session that coincided with each telephone survey from all women regardless of smoking status Cut-point for primary outcome ≤10 ng/ml
Oncken *et al.* 2008[27]	USA Double-blind placebo-RCT	194 healthy, English/Spanish-speaking women ≤ 26 weeks pregnant, smoking ≥ 1 cigarette daily and aged ≥ 16 years	12 weeks treatment with either 2 mg NRT gum or identical placebo—6 weeks full treatment followed by 6 weeks tapering of treatment Instructed not to chew > 20 pieces daily and to use one piece of gum for each substituted cigarette. Additionally, all participants received individual counselling at baseline and all eight follow-ups—two 35-minute counselling sessions at baseline and within 1 week of quit date and shorter sessions at other follow-ups Intervention = active gum, control = placebo	Self-reported 7-day point prevalence abstinence at 32–35 weeks	Exhaled CO of less than 8 p.p.m. at primary outcome point

CO: carbon monoxide; CPD: cigarettes per day; NRT: nicotine replacement therapy; p.p.m.: parts per million; RCT: randomized controlled trial.

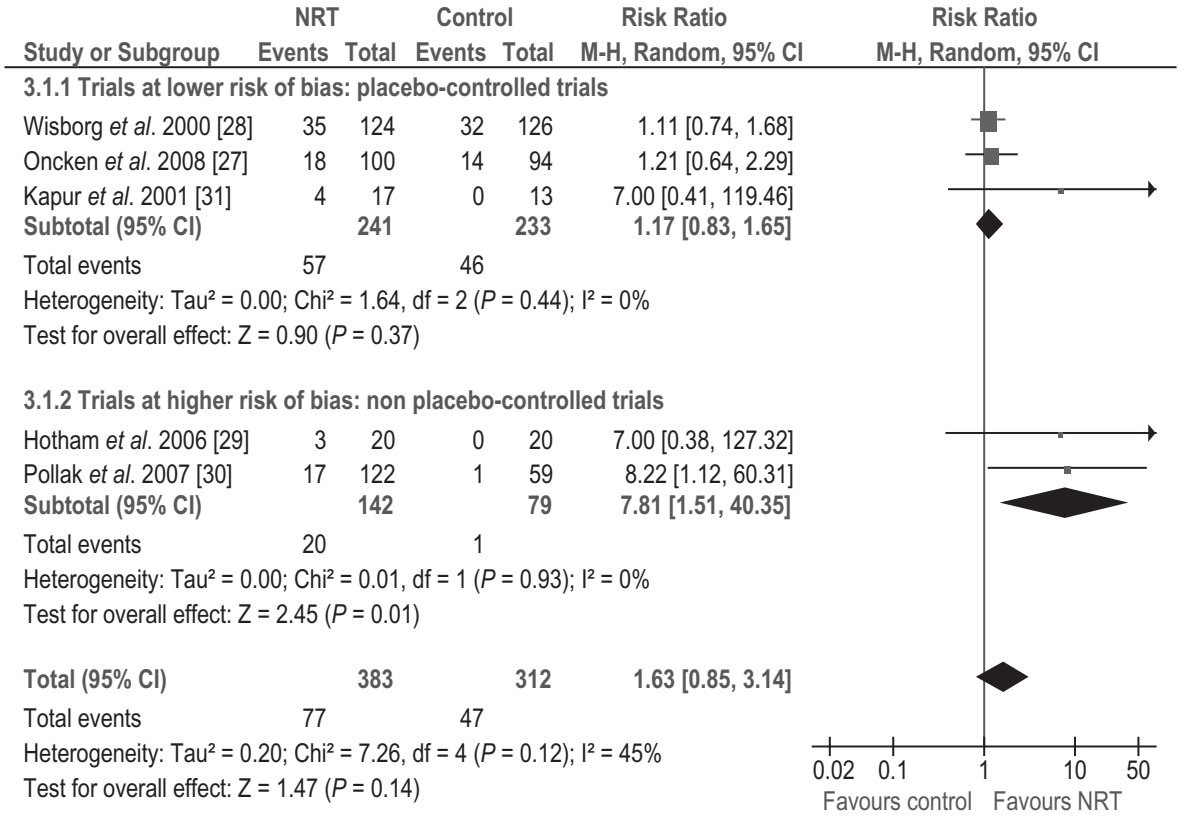

Figure 2 Effectiveness of nicotine replacement therapy (NRT) with subgroup analyses for trials at lower and higher risk of bias. CI: confidence interval

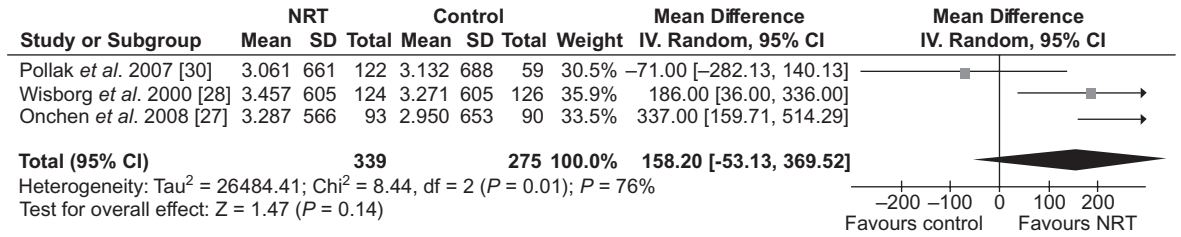

Figure 3 Safety analyses: mean birth weight. CI: confidence interval; IV: intravenous; NRT: nicotine replacement therapy; SD: standard deviation

[28], this became 1.76 (0.92, 3.36), $I^2 = 36\%$ (not shown in figure). Heterogeneity between studies was reduced substantially when placebo and non-placebo-controlled studies were analysed separately (i.e. studies at lower and higher risk of bias); for placebo-controlled studies the effect of NRT in pregnancy appeared lower [RR (95% CI) 1.17 (0.83, 1.65), $I^2 = 0\%$], whereas non-placebo-controlled studies provided a very different estimate for efficacy 7.81 (1.51, 40.35), $I^2 = 0\%$. Including biochemically validated data rather than self-reported data from the 'high cut-point' study made little difference to the placebo-controlled studies' meta-analysis result [RR (95% CI) for cessation, 1.32 (0.86, 2.01), $I^2 = 0\%$] (not shown in figure).

Safety

Pooled estimates for mean birth weight were non-significantly higher among infants born to women in NRT groups of trials (Fig. 3): mean difference (95% CI) 158.20 g (−53.13 g, 369.52 g) with high levels of heterogeneity ($I^2 = 76\%$). The two placebo-controlled trials [27,28] reported higher mean birth weight for infants in NRT groups with less heterogeneity; mean difference (95% CI) 253.80 g (107.59 g, 401.00 g) ($I^2 = 38\%$), but the reverse was seen in the non-placebo-controlled trial [30]; mean difference (95% CI) −71.00 g (−282.13 g, 140.13 g). Figure 4 summarizes findings from other safety analyses showing that preterm births [RR (95%

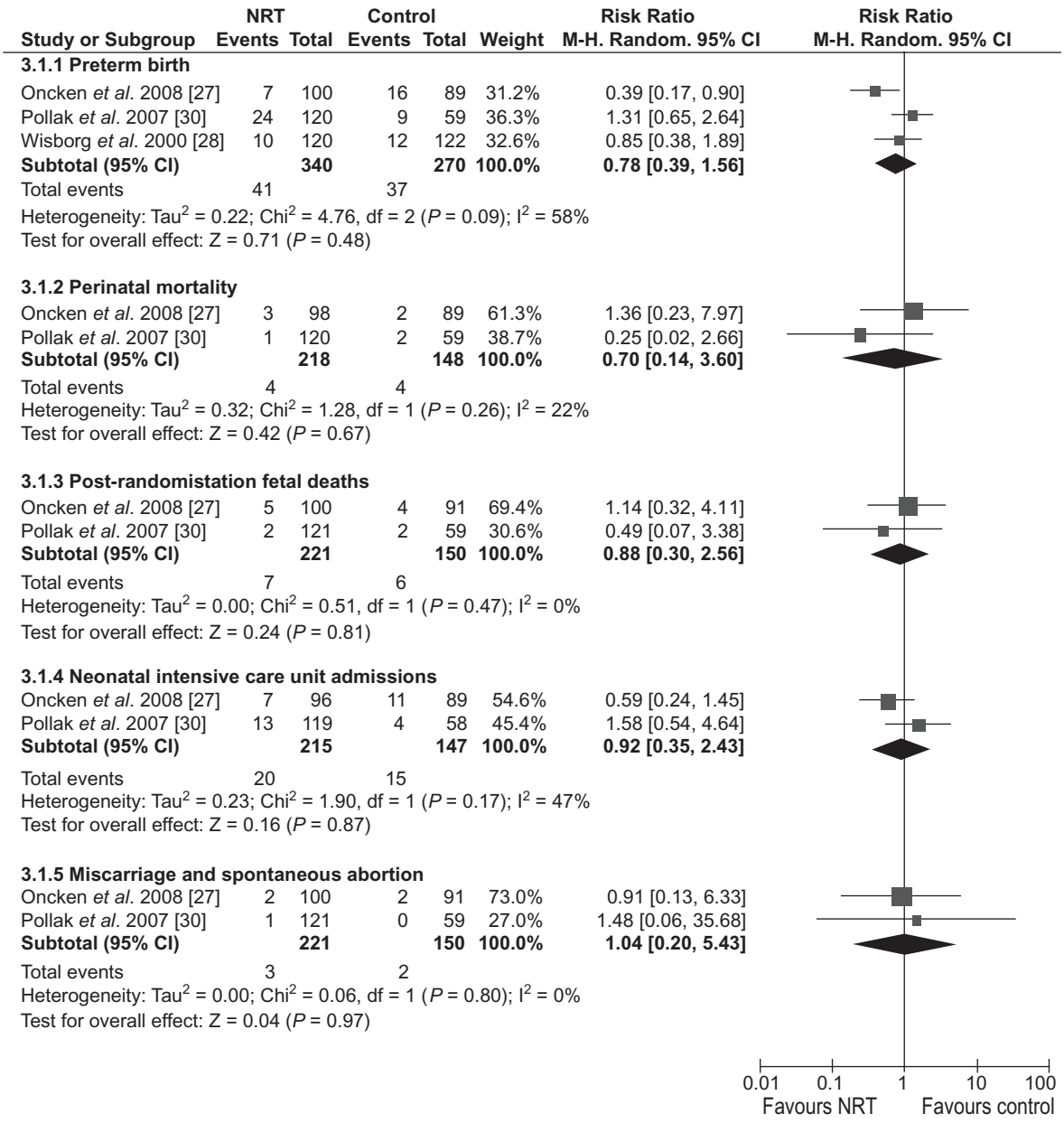

Figure 4 Safety analyses: preterm birth, perinatal mortality, post-randomization fetal deaths (one study reported seven spontaneous abortions/miscarriages, but the treatment allocation of these could not be determined), neonatal intensive care unit admissions and miscarriage/spontaneous abortions. CI: confidence interval; NRT: nicotine replacement therapy

CI), 0.78 (0.39, 1.56), $I^2 = 58\%$, two studies], perinatal mortality [0.70 (0.14, 3.60), $I^2 = 22\%$, two studies], post-randomization fetal deaths [0.88 (0.30, 2.56), $I^2 = 0\%$, two studies] and NICU admissions [0.92 (0.35, 2.43), $I^2 = 47\%$, two studies] were all less frequent in NRT groups, but differences between NRT and control groups did not reach statistical significance. Data relating to low birth weight (LBW) could not be pooled due to high levels of heterogeneity ($I^2 = 81\%$), however, in the two placebo-controlled trials [27,28], LBW births were less frequent in NRT groups [RR (95% CI) for LBW birth 0.22 (0.07, 0.72), $I^2 = 42\%$, two trials], with the opposite pattern noted in the non-placebo-controlled trial [RR (95% CI) for LBW birth 1.67 (0.65, 4.31)] [30]. The risk of miscarriage/spontaneous abortion was similar in both groups [1.04 (0.20, 5.43), $I^2 = 0\%$]; however, despite contacting study authors, for one study [28] we could not determine the treatment allocation for seven miscarriages. Assuming that all miscarriages occurred in the NRT and control groups, respectively, resulted in the following RR (95% CIs) for miscarriage in NRT versus non-NRT groups [2.31 (0.37, 14.38) and 0.48 (0.08, 3.06)]. A similar sensitivity analyses for post-randomization fetal deaths (of which miscarriages are a subset) gave the

following findings: assuming all miscarriages in NRT group, RR (95% CI) for post-randomization fetal death was 1.49 (0.29, 7.78), $I^2 = 54\%$ and assuming all in the control group, 0.48 (0.11, 2.20), $I^2 = 46\%$.

Adherence and side effects

Where adherence was reported this was generally low, as the majority of participants in all studies did not use complete courses of NRT offered; Table 2 summarizes adherence in different trials. As no studies had substantially better or worse adherence than others, no sensitivity analysis relating to this was undertaken. Three trials reported non-serious side effects [27–29]; one reported their frequency within women using NRT, noting that five (25%) participants in the NRT group experienced minor symptoms and two women stopped using patches after unpleasant effects [29]. However, this trial did not monitor non-serious symptoms in the control group, so this figure is difficult to interpret. Oncken *et al.* [27] reported that at least 10% of participants experienced headache, dizziness, fatigue, heartburn, nausea or vomiting, with 14 (15%) in the NRT and 12 (12%) in the control groups discontinuing treatment due to adverse effects. Wisborg *et al.* [28] noted that 11 participants stated that adverse effects (e.g. skin irritations and headache) made them discontinue patches but did not report treatment allocations; five participants in this trial also reported palpitations and two reported nausea.

DISCUSSION

We found that there is currently insufficient evidence to demonstrate that NRT, used by pregnant women for smoking cessation, is either effective or safe. Although birth outcomes were generally better among those infants born to women who had used NRT, none of these observed differences reached statistical significance. By ensuring that the only difference between the arms of included trials was the provision of NRT to all participants, we have isolated the independent effects of NRT which are of most importance to clinicians.

As it has been mandatory for clinical trials to be recorded on a trials register since July 2005, we are confident that our method of searching for those which reported after the previous Cochrane searches were conducted will have identified all relevant research reports. We took particular care to clarify procedures used for biochemical validation of participants' reported smoking cessation, and any differences between outcome figures used here and in previous reviews have arisen from these

Table 2 Adherence with nicotine replacement therapy regimens.

Study	*Adherence with offered regimen as a percentage of complete course*	*Adherence with offered regimen in terms of period of use*
Wisborg *et al.* 2000[28]	Complete adherence with 11-week course: nicotine group = 11%, placebo = 7%. Partial adherence (up to 8 weeks use): nicotine group = 17%, placebo = 8%	Median number patches (ranges): nicotine group = 14 (0–77)—median = approx. 2 weeks, placebo = 7 (0–77)—median approx. 1 week
Kapur *et al.* 2001[31]	In the nicotine group, four of 17 (23.5%) completed the 14-week programme. In the placebo group no participants completed the programme	In the nicotine group, four of 17 (23.5%) completed the 14-week programme, three of 17 (17.6%)—used patch for at least 3 weeks and 10 of 17 (58.8%)—used patch for less than 1 week In the placebo group no participants completed the programme, three of 13 (23%) used patch for between 4 and 5 weeks and 10 of 13 (76.9%) used patch for <1 week
Hotham *et al.* 2006[29]	25% (five) participants complied fully with protocol 'continuous patch use till 12 weeks or confident that abstinence achieved or AR experienced'	50% (10) of participants used NRT for 6 or less weeks
Pollak *et al.* 2007[30]	Difficult to ascertain from this manuscript. A secondary publication reported that 29% of participants used NRT as directed for intended 6-week programme [33]	Means of reported periods of use: Patch = 23.4 patches = 3.3 weeks Gum = 8 days Lozenge = 4 days
Oncken *et al.* 2008[27]	Not clearly reported	The nicotine group used gum for a mean (SD) of 37.8 (3.8) days (i.e. just >5 weeks). The placebo group reported using gum for a mean (SD) of 29.9 (3.4) days (i.e. just >4 weeks)

NRT: nicotine replacement therapy; SD: standard deviation.

clarifications. Findings reported in this paper are based on currently accepted, evidence-based cut-points for determining abstinence from smoking [23], rather than ones which might have been acceptable in the past, enhancing the validity of findings. Although we excluded a strongly positive study [32] which contributed to previous reviews, this was not a RCT and NRT group participants also received intensive behavioural support delivered by specially trained staff who were present in study hospitals only on 'intervention' days [32]. As behavioural support is an established, effective cessation intervention for pregnant women [21], this trial tells us about the combined effect of offering NRT with intensive behavioural support, rather than about its independent effect [32]. Consequently, we believe that our findings provide an accurate estimate for the efficacy of NRT when used in pregnancy for smoking cessation.

Clinical guidelines from a number of countries [12–15] assume that when pregnant women are heavily dependent upon nicotine, using NRT will be less harmful to them and their babies than continued smoking; however, our findings have not produced evidence for this assumption. The general trend of our safety analyses was for birth outcomes to be more favourable in infants born to women who had been allocated NRT; this trend was found for five of seven outcomes and only miscarriages were more prevalent among women given NRT. However, none of these findings were statistically significant; substantial heterogeneity prevented meta-analysis for one and the treatment allocation of a number of miscarriages could not be ascertained. We found that NRT used in pregnancy may be ineffective for smoking cessation, or it may have a smaller effect than can be detected by pooling the findings of current trials. If the latter is true, then the best estimate for the likely efficacy of NRT (in patch or gum formulations) would be from placebo-RCTs included in this review; an RR (95% CI) of 1.17 (0.83, 1.65), in favour of cessation after using NRT. This is lower than the RR (95% CI) for the effectiveness of the NRT patch or gum outside of pregnancy [patch, 1.66 (1.53–1.81) and gum 1.43 (1.33–1.53)] [17] and would be consistent with reduced efficacy of NRT in pregnancy due to increased metabolism of cotinine [18]. Alternatively, NRT could be effective in pregnancy and our negative findings may be due to trial participants' generally poor adherence and failure to use sufficiently long courses of NRT. However, if this were the case, it remains unclear how women could be encouraged to use longer courses of NRT to test this hypothesis; non-serious side effects were not reported comprehensively in all studies, but the levels reported appear too low to have had a substantial effect on women's adherence with NRT use.

Clearly, further research is required and, given the apparent tendency for the non-placebo-RCTs included in this review to overestimate the effectiveness of NRT, future trials should incorporate placebo-controlled designs. These will enable non-biased estimates for the effectiveness of NRT to be derived and to address safety issues which are particularly importantly in pregnancy. In the absence of evidence for either the effectiveness or safety of NRT use in pregnancy, perhaps guidelines should emphasize the importance of using proven, behavioural strategies to promote smoking cessation in pregnancy; this may be particularly important in poorer countries struggling with the increasing problem of maternal smoking in pregnancy.

Declarations of interest

Within the last 5 years, Tim Coleman has been paid for consultancy work by Johnson and Johnson and Pierre Fabre Laboratories (manufacturers of nicotine replacement therapy). No remaining authors have any connections with pharmaceutical companies; no authors have links with the tobacco or gaming industries; and no third parties have exerted any influence on the submission of this manuscript. Tim Coleman is Chief Investigator and Sue Cooper Trial Manager for a placebo randomized controlled trial of NRT in pregnancy. Catherine Chamberlain is an author of the Cochrane Review, which included a subgroup analysis of trials involving provision of NRT as part their intervention strategies. This work was not funded directly, but Tim Coleman and Jo Leonardi-Bee receive funding from the UK Centre for Tobacco Control Studies and Tim also is supported by the NIHR National School for Primary Care Research.

Acknowledgements

Tim Coleman and Jo Leonardi-Bee are members of the UK Centre for Tobacco Control, a UKCRC Public Health Research: Centre of Excellence. Funding from the British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council and the Department of Health, under the auspices of the UK Clinical Research Collaboration is gratefully acknowledged. The authors are also grateful to Clare Randall for help with preparing this manuscript and to Dr Mary-Ann Davey for advice on birth outcome reporting.

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