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

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CRD summary
The authors concluded that there was insufficient evidence to determine whether or not nicotine replacement therapy was effective and safe when used in pregnancy for smoking cessation. The conclusions reflect the evidence presented and are likely to be reliable, but should be viewed with caution given the potential for publication bias.

Authors' objectives
To determine the efficacy and safety of nicotine replacement therapy with or without behavioural support when used to support smoking cessation in pregnancy.

Searching
CINAHL, EMBASE, MEDLINE and PsycLIT were searched for papers published between April 2008 and August 2009. Search terms were reported. Cochrane Pregnancy and Childbirth Group Trial Register was searched. A previous Cochrane review of the effectiveness of smoking cessation interventions in pregnancy was searched for relevant studies.

Study selection
Randomised controlled trials (RCTs) where nicotine replacement therapy was used with or without behavioural support to promote smoking cessation were eligible for inclusion. Trials that provided unequal behavioural support to different trial groups were excluded. Outcome measures were: effectiveness (self-reported smoking cessation in later pregnancy or at delivery; validated where possible by biochemical measures with appropriate cut-points); safety (mean unadjusted birth weight, low birth weight of <2,500g, preterm birth <37 weeks gestation), foetal demise (spontaneous abortions, elective abortions, stillbirths and neonatal deaths) and neonatal intensive care unit admissions; measures of adherence with nicotine replacement therapy and non-serious side effects.

All studies were conducted in high-income countries (USA, Australia, Canada and Denmark). All trials except one enrolled pregnant women who smoked at least 10 cigarettes daily. Smoking cessation was ascertained at or after 32 weeks in all trials except one. Durations and schedules of nicotine replacement therapy interventions were varied. Non-placebo control groups received counselling (face to face or telephone). Methods used to validate reported smoking cessation included biological samples (all trials), exhaled carbon monoxide (two trials), saliva nicotine (two trials), both saliva and exhaled carbon monoxide (one trial).

Two reviewers independently screened studies to determine eligibility for inclusion.

Assessment of study quality
Study quality was assessed using the Cochrane Collaboration tool for assessing risk of bias. Key criteria assessed were adequacy of sequence generation, allocation concealment and blinding, use of intention-to-treat analysis and protection from selective outcome reporting. Inclusion of biochemical validation of smoking status was assessed. Study authors were contacted to clarify data where necessary.

Two reviewers independently assessed study quality; disagreements were resolved by discussion.

Data extraction
Two reviewers independently extracted effectiveness, birth outcome and adherence data to permit the calculation of risk ratios (RRs) and 95% confidence intervals (CIs). Discrepancies were resolved by discussion. Authors were contacted to clarify outcome data where necessary.
Methods of synthesis
Pooled risk ratios and their corresponding 95% CIs were calculated using a random-effects (DerSimonian and Laird) model. Statistical heterogeneity was assessed using $I^2$. Subgroup analysis examined potential differential effects of birth weight and foetal demise. Sensitivity analyses assessed the effects of including all biochemically validated outcomes irrespective of cut-points and excluding trials that reported substantially lower adherence.

Results of the review
Five RCTs (n=695 participants, range 30 to 450) were included: three double-blind placebo RCTs and two non-placebo RCTs. Risk of bias was stated to be low as most trials satisfied most quality criteria; details were not reported.

No effect of nicotine replacement therapy on smoking cessation in later pregnancy was found (pooled RR 1.63, 95% CI 0.85 to 3.14, $I^2=45$%; five RCTs).

Five of the seven safety outcomes (mean birth weight, preterm births, perinatal mortality, post-randomisation foetal deaths, neonatal intensive care admissions) were more positive among infants born to women who had used nicotine replacement therapy, but none of the differences reached statistical significance.

No differences were found between groups in the risk of miscarriage. No differences were found between groups in rates of adherence and three RCTs that reported details of non-serious side effects found no significant differences between groups.

Efficacy estimates were significantly higher in studies that were at higher risk of bias (non-placebo RCTs RR 7.81, 95% CI 1.51 to 40.35; $I^2=0$%) compared with those at lower risk of bias (placebo RCTs RR 1.17, 95% CI 0.83 to 1.65; $I^2=0$%).

Authors’ conclusions
There was insufficient evidence to determine whether or not nicotine replacement therapy was effective and safe when used in pregnancy for smoking cessation.

CRD commentary
The review question was clearly stated. Four relevant databases were searched. No attempts were made to search for unpublished papers and so relevant studies may have been missed. Review processes were conducted in duplicate, which reduced risks of error and bias. Study quality was assessed with appropriate criteria, but no details of the assessment were reported. Statistical methods used to combine data appeared appropriate.

The conclusions reflect the evidence presented and are likely to be reliable, but should be viewed with caution given the potential for publication bias.

Implications of the review for practice and research
Practice: The authors stated that given a lack of evidence for the effectiveness and safety of nicotine replacement therapy use in pregnancy, guidelines should emphasize the importance of using proven behavioural strategies to promote smoking cessation in pregnancy, particularly in low-income countries.

Research: The authors stated that future trials on the effectiveness and safety of nicotine replacement therapy use in pregnancy should incorporate placebo-controlled designs.

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