Saturday 24 April 2004

BMJ

Nicotine replacement therapy in pregnancy

Is probably safer than smoking

See also *Papers* p 989

Smoking harms unborn children. It increases the risk of growth restriction, preterm birth, miscarriage, and perinatal death,[1 2] but despite this over a quarter of pregnant women in the United Kingdom smoke.[3] Pregnancy motivates a minority to stop for at least part of the pregnancy, but most start again after giving birth.[3] Compared with women who manage to stop, those who continue are younger and less educated; more likely to be single and in manual occupations;[4] and much less likely to perceive smoking as a risk to their baby.[3] Reducing smoking in pregnancy is an obvious health priority, but progress has been slow.[3]

Non-pregnant smokers are most likely to quit if offered a combination of behavioural support and pharmacotherapy with either nicotine replacement therapy[5] or bupropion.[6] The addition of pharmacotherapy increases quit rates obtained with behavioural support by 1.5-fold to 2-fold. Behavioural support is also effective in pregnancy,[7] but is usually provided alone because of concerns that drugs may harm the fetus.[8] This is understandable for bupropion, which is an avoidable drug, but nicotine is different. Nicotine is part of the exposure of smoking, and if nicotine replacement is used instead of cigarettes, exposure to the many other toxins in tobacco smoke is avoided. If nicotine replacement were as effective in pregnant smokers as in non-pregnant smokers, withholding it would be harmful.

To date, however, the efficacy of nicotine replacement therapy in pregnancy is not known. The only completed and published randomised controlled trial of nicotine replacement (delivered by transdermal patches) showed no difference from placebo, but the numbers studied were small, and the trial was underpowered to determine whether nicotine replacement was effective.[9] Nevertheless, babies born to women in the nicotine treatment group had significantly higher birth weights than those in the placebo group (mean difference 186 g (95% confidence interval 35 g to 336 g)), indicating that the intrauterine growth restriction caused by smoking is probably not attributable to nicotine. Little other evidence supports the recommendation of the UK National Institute for Clinical Excellence (NICE), that pregnant women can use nicotine replacement "after discussion with a health professional."[10] This lack of evidence also explains the caution evident in UK and US guidelines for managing smoking cessation, which state, respectively, that "the use of [nicotine replacement therapy] by pregnant smokers may benefit mother and foetus if it leads to smoking cessation"[8] and "special consideration" is needed before using nicotine replacement in pregnancy.[11]

Nicotine is metabolised more quickly in pregnancy.[12] Plasma clearances of nicotine and cotinine (its principal metabolite) are increased by 60% and 140%, respectively, and the half life of cotinine is reduced in pregnant women (9 h *v* 17 h in non-pregnant women). Among continuing smokers this could, in theory, lead to compensatory smoking to maintain desired nicotine concentrations, and hence increase fetal harm. It may also reduce the efficacy of nicotine replacement since conventional doses will provide less nicotine substitution. Higher doses of nicotine replacement might, therefore, be needed in pregnancy, but could these increase the risk of fetal damage?

Nicotine gum and patches cause dose related increases in maternal blood pressure and heart rate and lesser effects on the fetal heart rate, but these changes are less pronounced than those caused by smoking.[13] In rodents chronic nicotine exposure, albeit at much higher plasma concentrations than occur in pregnant smokers or nicotine replacement users, is associated with dose dependent changes in behavioural and cognitive responses, a diminished adrenal response to hypoxia that may predispose to sudden infant death syndrome, and central nervous system toxicity.[13]

The route of nicotine administration may also be important by altering the time profile of exposure. Nasal sprays and chewing gum tend to produce high plasma nicotine concentrations for short periods, and when these are used regularly throughout the day nicotine exposure is similar to that from smoking. Patches produce lower, longer lasting, steadier concentrations, and when these are worn for 24 hours they cause continual exposure of the fetus to nicotine, even throughout the night. It is not clear whether this additional nocturnal exposure matters.

Determining policy about nicotine replacement in pregnancy is difficult. Logically nicotine replacement should be safer than smoking, but there is no direct evidence that this is so. Conventional doses may be less effective in pregnancy, but too much nicotine could damage the fetus, and the time profile of nicotine exposure from longer acting nicotine replacement products may also contribute to fetal harm. The overall ratio of benefits and harms of using nicotine replacement in pregnancy depends on any extra effectiveness of nicotine replacement when used in addition to behavioural support[7] and any additional risk incurred from effective doses of nicotine delivered via different

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delivery modes. Any harm caused by nicotine replacement must be compared with that caused by continued smoking—which is extremely harmful to both the woman and her child. Clear evidence of effectiveness and safety is required. We need definitive randomised, placebo controlled, clinical trials of a range of doses and administration routes for nicotine replacement in pregnancy.

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Competing interests: TC has been paid for speaking by GlaxoSmithKline and for consultancy work by Pharmacia. JB has been reimbursed by Glaxo Wellcome for attending international conferences, has received a speaker honorarium from Glaxo Wellcome, and has been the principal investigator in a clinical trial of nicotine replacement therapy funded by Pharmacia. All companies manufacture nicotine replacement products. All three authors are currently bidding for funds to undertake a trial of nicotine replacement therapy in pregnancy.

1 Royal College of Physicians. *Smoking and the young*. London: RCP, 1992.
2 Charlton A. Children and smoking: the family circle. *Br Med Bull* 1996;52:90-107.
3 Owen L, Penn G. Smoking and pregnancy: a survey of knowledge attitudes and behaviour, 1992-1999. London, Health Development Agency, 1999.
4 Tobacco Advisory Group of the Royal College of Physicians. *Nicotine addiction in Britain*. London: Royal College of Physicians of London, 2000.
5 Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation *Cochrane Database Syst Rev* 2002;(4):CD000146.
6 Britton J, Jarvis MJ. Bupropion: a new treatment for smokers. *BMJ* 2000;321:65-6.
7 Lumley J, Oliver S, Waters E. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2000;(2):CD001055.
8 West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;55:987-99.
9 Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. *Obstet Gynecol* 2000;96:967-71.
10 National Institute for Clinical Excellence. *Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation*. Technology Appraisal Guidance No 39. London, National Institute for Clinical Excellence, 2002.
11 Fiore MC, Hatsukami DK, Baker TB. Effective tobacco dependence treatment. *JAMA* 2002;288:1768-71.
12 Dempsey D, Jacob P, III, Benowitz NL. Accelerated metabolism of nicotine and cotinine in pregnant smokers. *J Pharmacol Exp Ther* 2002;301:594-8.
13 Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Saf* 2001;24:277-322.

Making public health interventions more evidence based

TREND statement for non-randomised designs will make a difference

The movement towards evidence based public health policy has been gaining momentum over the past decade. It takes an important step forward with the recent publication of the TREND statement (transparent reporting of evaluations with non-randomised designs).[1] Its aim is to improve the quality of reporting of non-randomised evaluations so that the conduct and findings of such research are transparent and information that is critical for research synthesis is not missing, and to do for public health evaluations what the CONSORT statement has done for randomised controlled trials.[2]

The publication of the TREND statement reflects the increasing recognition that successful evaluation of public health interventions will necessarily entail the use of research designs other than controlled trials[3–5] and various types of evidence, often in combination.[4 6] The reasons for using such interventions include the following.

Firstly, the intervention is already well established or its delivery is by nature widespread—for example, evaluation of the efficacy of BCG in different settings[3] or of the current advertisement campaign in the United Kingdom to encourage adherence to speed limits in built up areas. No control groups exist; the evaluations need to be based on comparisons before and after the intervention and on comparisons of adopters with non-adopters.

Secondly, the intervention has been shown to be efficacious or effective in small scale studies, conducted under ideal conditions, but its effectiveness needs to be shown when scaled up and carried out under routine conditions.[6]

Thirdly, the intervention is multifaceted and the pathways to impact are complex. Victora et al argue that an impact achieved in randomised controlled trials will not convince policy makers unless it is accompanied by additional evidence showing changes in intermediate process outcomes and differences between adopters and non-adopters of the intervention.[6]

Fourthly, ethical issues in the use of a control group, such as occurs when the intervention has known benefits but its efficacy against an important outcome is not known, or when patient choice needs to be factored in.[7] This issue was overcome in the Gambia hepatitis B vaccine trial of the long term impact on liver cancer, by using a "stepped wedge design," with the vaccine introduced district by district on a staggered basis and the order of introduction chosen at random.[8]

The TREND statement follows the exact format of the revised CONSORT statement, retaining the same 22 items, with revised descriptions relevant to non-randomised designs. Some important enhancements have been made that are also relevant to randomised controlled trials evaluating public health interventions. Item 2 (background) now includes the underlying behavioural or social science theory used to develop the intervention, and item 4 (interventions) encourages a more detailed description of both the content and the delivery of the intervention.

The authors' vision is that adoption of the TREND reporting guidelines will ensure that comparable

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