210 CURRENT TOPICS AND OPINIONS Nicotine replacement therapy in pregnancy

Maternal smoking during pregnancy harms unborn children and, as up to 30% of pregnant women smoke, is a significant public health problem. The adverse effects of smoking during pregnancy include an increased risk of miscarriage and stillbirth, accounting for 4,000 deaths annually and of pre-term birth, intrauterine growth restriction (IUGR) and low birthweight leading to increased perinatal morbidity. Children of mothers who smoke whilst pregnant are at an increased risk of neonatal mortality, sudden infant death syndrome and asthma.

Furthermore, maternal smoking in pregnancy is also associated with an increased risk of attention deficit and learning problems in childhood. Currently, only around 25% of pregnant women smoke, is a significant public health problem. The adverse effects of smoking during pregnancy include an increased risk of miscarriage and stillbirth, accounting for 4,000 deaths annually and of pre-term birth, intrauterine growth restriction (IUGR) and low birthweight leading to increased perinatal morbidity. Children of mothers who smoke whilst pregnant are at an increased risk of neonatal mortality, sudden infant death syndrome and asthma.

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Nicotine replacement therapy in pregnancy: use or avoid?

In an effort to help reduce smoking prevalence during pregnancy, all English NHS Stop Smoking services have been given funds which are specifically dedicated towards providing smoking cessation services for pregnant women. Additionally, some smoking cessation services recommend women to use nicotine replacement therapy (NRT), issuing this via patient group directives (PGDs). PGDs are special arrangements which permit non-medical health professionals (e.g. midwives) to prescribe medications according to a strict protocol under the supervision of a local doctor. Furthermore, in 2003, prescribing guidance to UK doctors (contained in the British National Formulary) began to list pregnancy as a ‘caution’ to the use of nicotine replacement therapy rather than a ‘contra-indication’ as it had done previously. The UK National Institute for Clinical Excellence has also stated that pregnant women can use NRT “after discussion with a health professional” though US and UK guidelines for managing smoking cessation are slightly more cautious on this issue. The current climate in the UK is, therefore, such that the use of NRT in pregnancy is promoted and a substantial minority of UK GPs have already prescribed NRT to pregnant women. Given this situation, it is worth reviewing the evidence that nicotine replacement therapy is effective and safe for smoking cessation when used in pregnancy.

To date, evidence of the effectiveness of NRT in pregnancy is limited to a single, small, placebo randomised controlled trial of NRT as transdermal patches. This study provided no clear evidence that NRT was effective, but the numbers studied were small and the trial was underpowered. An alternative explanation for this negative finding is that pregnant women metabolise nicotine and cotinine (the principal metabolite of nicotine) 60% and 140% faster respectively than non-pregnant women. This means that standard doses of NRT may be ineffective for smoking cessation because they do not adequately replace the nicotine that pregnant women would have received by smoking. More positively, trial results were reassuring about the safety of pure nicotine when used in pregnancy instead of smoking, as babies born to mothers who had been randomised to use NRT (rather than placebo) were significantly heavier than those born to mothers who had used placebo [mean birthweight difference = 186g (95% CI 35, 336 g)]. This suggests that nicotine does not cause the IUGR which is attributable to smoking. In summary, there is no evidence that current maximum doses of NRT harm unborn children, but there is very little human-subject research into the effects of nicotine on the developing fetus per se. Higher doses of NRT may be required for smoking cessation in pregnancy, but it is not known whether these might increase the risk of fetal damage.

When administered to pregnant women, nicotine increases maternal blood pressure and heart rate with lesser effects on the fetal heart rate. The impact of smoking is greater than that caused by nicotine gum or patches, however, and these acute changes are thought unlikely to cause significant harm. The principal potential risk that could occur to the fetus as a consequence of nicotine exposure is probably, neuro-teratogenicity: harm to the developing fetal nervous system. This concern has arisen because chronic nicotine exposure in rats is associated with...
dose-dependent changes in their behavioural and cognitive responses.\textsuperscript{15, 16} Rodent studies have involved, in relative terms, much higher levels of nicotine exposure than occur in pregnant women who either smoke or use NRT, so one cannot be sure that the same effects would be observed in humans.

The route and periodicity of nicotine administration may also be a factor in determining any harm that this might cause. Nicotine nasal sprays and chewing gum tend to produce high plasma nicotine concentrations for short periods and if these are used regularly they mimic the exposure pattern caused by smoking. Nicotine transdermal patches, however, produce lower, more durable nicotine concentrations. The use of 24-hour patches has been questioned, though, because the additional fetal nicotine exposure that occurs during maternal sleeping can be avoided by using a 16-hour patch which women remove at night.\textsuperscript{17}

Concerns about the periodicity of nicotine exposure in pregnancy are theoretical, however, and there is no empirical evidence to underpin them. Quite simply, it is not known whether the variations in nicotine concentrations caused by different products’ delivery mechanisms and dosing actually matter.

So how can health professionals advise pregnant women? Women cannot be told that NRT can help them to stop smoking because there is no evidence to support this notion. Nevertheless, there is a small amount of empirical evidence (summarised above) and good theoretical reasons to suppose that NRT is safer for the fetus than continued maternal smoking. Women who continue to smoke in pregnancy expose themselves and the developing fetus to the vast array of toxic chemicals which are contained in tobacco smoke.\textsuperscript{15} Although nicotine is a known fetal toxin, it is preferable to expose the fetus to this toxin alone, without the thousands of other toxins that cigarette smoke contains. Currently, health professionals can truthfully advise women that using NRT in pregnancy is probably safer than smoking, but that there is little evidence from research conducted on humans to support this. To provide fully informed consent about the use of NRT in pregnancy, however, women need to be aware that there is absolutely no evidence that NRT will help them to achieve smoking cessation. Clearly, randomised controlled trials investigating the effectiveness and safety of NRT in pregnancy are urgently required to provide guidance for all health professionals working with women who smoke during pregnancy.

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