

# Smoking cessation therapy during pregnancy

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## Abstract

**Question** Despite being highly motivated to quit, many of my patients struggle with smoking cessation during pregnancy. Can you comment on the current treatment options and discuss their safety and efficacy during pregnancy?

**Answer** Given the considerable and well-documented adverse effects of antenatal smoking on mother and fetus, pharmacotherapy for smoking cessation should be considered. Available medications include nicotine replacement therapy, sustained-release bupropion, and varenicline. Nicotine replacement therapy and bupropion do not appear to increase the risk of major malformations; however, there is currently limited evidence on the use of varenicline during pregnancy. Given that these agents are only marginally successful in smoking cessation, their use should always be accompanied by behavioural counseling and education to maximize quit rates.

## Thérapie pour l'abandon du tabagisme durant la grossesse

### Résumé

**Question** Même si elles sont très motivées à arrêter de fumer, beaucoup de mes patientes enceintes éprouvent de la difficulté à y arriver. Pouvez-vous nous dire ce que vous pensez des choix de traitements actuels, et traiter de leur sécurité et de leur efficacité durant la grossesse?

**Réponse** Étant donné les effets indésirables considérables et bien documentés du tabagisme pendant la grossesse sur la mère et le fœtus, il y a lieu d'envisager une pharmacothérapie pour arrêter de fumer. Les médicaments disponibles incluent les thérapies de substitution de la nicotine, le bupropion à libération prolongée et la varénicline. Les thérapies de substitution de la nicotine et le bupropion ne semblent pas augmenter le risque de malformations majeures; par ailleurs, les données scientifiques sont limitées sur l'utilisation de la varénicline durant la grossesse. Étant donné que ces agents n'ont qu'un taux de réussite marginal pour arrêter de fumer, leur utilisation devrait toujours être accompagnée par un counseling comportemental et de la formation pour améliorer les taux d'abandon.

The risks of smoking during pregnancy are well known.<sup>1</sup> Cigarette smoke contains thousands of compounds, many of which are well-documented reproductive toxins and carcinogens. Since the last Motherisk update on nicotine replacement therapy (NRT),<sup>2</sup> new medications have been released that show improved efficacy in smoking cessation among nonpregnant populations compared with standard NRT or placebo.

### Nicotine replacement

Nicotine is a highly toxic and addictive substance. It is most frequently encountered as a component of cigarette smoke; however, it can be readily derived from other "smokeless" tobacco products. The benefits of NRT during pregnancy are potentially 2-fold: it delivers nicotine without delivering the additional reproductive toxins present in tobacco smoke and it can reduce withdrawal symptoms, including cravings, which can aid in smoking cessation.

A retrospective study using the Danish National Birth Cohort (1996 to 2002) did not demonstrate a significant association between birth weight and duration of NRT use (difference in birth weight of 0.25 g for each week of NRT use; 95% CI, 2.31 to 2.81) or type of NRT product (patch, gum, inhaler).<sup>3</sup> Another study using the Danish National Birth Cohort (1997 to 2003) reported no increased risk of major malformations (relative risk [RR]=1.13; 95% CI, 0.62 to 2.07).<sup>4</sup>

A systematic review and meta-analysis of the safety and efficacy of NRT for smoking cessation during pregnancy concluded that information on the efficacy of NRT during pregnancy is lacking. With regard to NRT safety during pregnancy, low birth weight, preterm birth, perinatal mortality, and neonatal intensive care admissions were all less frequent among mothers taking NRT than among mothers who continued to smoke or who received placebo (N= 695 pregnancies); however, none of the differences in these outcomes was statistically significant.<sup>5</sup>

In 2 reviews of NRT use during pregnancy, authors concluded that pregnant women smoking fewer than 5 cigarettes per day should use behavioural support and not NRT, but that those with moderate to high levels of addiction could use NRT under medical supervision.<sup>6,7</sup>

According to the 2011 guidelines from the Society of Obstetricians and Gynaecologists of Canada, controlled trials have shown that NRT might reduce the number of cigarettes smoked but they have not demonstrated that NRT increases rates of smoking cessation during pregnancy.<sup>8</sup> Adding NRT to cognitive behavioural therapy results in higher quit rates during pregnancy, and the Society of Obstetricians and Gynaecologists of Canada suggests offering NRT if counseling alone fails and after an informed discussion of the benefits and risks of therapy. The lowest effective dose of NRT should be used. If a patch is used, the patient should consider removing it at night. Nicotine replacement should be discontinued if the woman continues to smoke at the same rate.<sup>8</sup>

### Bupropion

Bupropion is an aminoketone antidepressant. It is commonly used in a sustained-release formulation as a smoking cessation aid. Evaluation of bupropion efficacy as a smoking cessation aid in pregnancy is limited; however, in a prospective, controlled observational study, pregnant smokers receiving bupropion had a higher quit rate (45%) compared with controls (14%) who did not receive any medications.<sup>9</sup>

Motherisk reported on 136 outcomes of pregnancies exposed to bupropion (either for smoking cessation [n=37] or depression) during the first trimester of pregnancy. There were no major malformations reported. The rate of spontaneous abortion in the bupropion group was higher than in the group of women taking nonteratogenic medications (14.7% vs 4.5%,  $P=.009$ ), but not different from the rate among women taking other antidepressants (12.3%).<sup>10</sup>

A study of 1213 infants born to mothers exposed to bupropion in the first trimester of pregnancy showed no increased prevalence of malformations compared with babies exposed to other antidepressants in the first trimester (adjusted odds ratio 0.95; 95% CI, 0.62 to 1.45).<sup>11</sup> Further, analysis of data from the manufacturer's pregnancy registry, which reported on prospectively enrolled pregnancies with 1005 outcomes, observed no increased rate of major malformations compared with the general population.<sup>12</sup>

Bupropion use during pregnancy does not appear to be associated with increased risk of major congenital malformations. Small increases in risk of spontaneous abortion in women taking antidepressants have been observed, but the contribution of potentially mismanaged underlying depression cannot be ruled out. There is no evidence suggesting that bupropion is associated with a higher risk of spontaneous abortion than other


antidepressants are. There are no adequate studies on rates of spontaneous abortion among pregnant women taking bupropion for smoking cessation.

### Varenicline

Varenicline is a partial agonist of the  $\alpha_4\beta_2$  nicotinic acetylcholine receptor, the receptor believed to be responsible for the dependence-producing properties of nicotine.<sup>13</sup> As a partial agonist, varenicline offers the therapeutic benefit of relieving negative symptoms of nicotine withdrawal and cigarette craving, while simultaneously blocking the reinforcing effects of continued nicotine use.<sup>14</sup> In a recent meta-analysis of all randomized clinical trials of varenicline in nonpregnant populations, varenicline was shown to significantly increase abstinence rates at 6 months or longer compared with bupropion (RR=1.52; 95% CI, 1.22 to 1.88), NRT (RR=1.13; 95% CI, 0.94 to 1.35), and placebo (RR=2.31; 95% CI, 2.01 to 2.66).<sup>15</sup>

Despite an effective smoking-cessation profile in nonpregnant populations, limited data are available regarding the use of varenicline during pregnancy. Preclinical animal studies have reported no increased risk of congenital anomalies at maternal doses greater than 36 times the human dose.<sup>16</sup> To address the lack of human data, an observational phase 4 clinical trial is currently under way to assess the safety of varenicline during pregnancy and to determine the risks of major malformations and other undesirable pregnancy outcomes.<sup>17</sup> Until these results are released, it is only advisable to use this product as a smoking cessation aid during pregnancy when the benefits of treatment substantially outweigh any undue risk (eg, in heavy smokers with failed quit attempts or who have not responded to other smoking cessation aids).

### Conclusion

Behavioural therapy and patient education should be recommended as first-line therapy for smoking cessation. In the event that patients fail to stop smoking or do not respond to behavioural therapy, NRT or bupropion can be offered after an informed discussion of the benefits and risks of therapy. 

#### Competing interests

None declared

#### References

- Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. *Semin Neonatol* 2000;5(3):231-41.
- Koren G. Nicotine replacement therapy during pregnancy. *Can Fam Physician* 2001;47:1971-2.
- Lassen TH, Madsen M, Skovgaard LT, Strandberg-Larsen K, Olsen J, Andersen AM. Maternal use of nicotine replacement therapy during pregnancy and offspring birthweight: a study within the Danish National Birth Cohort. *Paediatr Perinat Epidemiol* 2010;24(3):272-81.
- Morales-Suárez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use, and congenital malformations. *Obstet Gynecol* 2006;107(1):51-7.
- Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. *Addiction* 2011;106(1):52-61. Epub 2010 Nov 4.
- Forinash AB, Pitlick JM, Clark K, Alstat V. Nicotine replacement therapy effect on pregnancy outcomes. *Ann Pharmacother* 2010;44(11):1817-21. Epub 2010 Oct 23.
- Osadchy A, Kazmin A, Koren G. Nicotine replacement therapy during pregnancy: recommended or not recommended? *J Obstet Gynaecol Can* 2009;31(8):744-7.

8. Wong S, Ordean A, Kahan M; Society of Obstetricians and Gynecologists of Canada. Substance use in pregnancy: no. 256, April 2011. *Int J Gynaecol Obstet* 2011;114(2):190-202.
9. Chan B, Einarson A, Koren G. Effectiveness of bupropion for smoking cessation during pregnancy. *J Addict Dis* 2005;24(2):19-23.
10. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: a prospective comparative study. *Am J Obstet Gynecol* 2005;192(3):932-6.
11. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 2007;16(5):474-84.
12. GlaxoSmithKline. *The Bupropion Pregnancy Registry. Final report. 1 September 1997 through 31 March 2008*. Wilmington, NC: Kandle International Inc; 2008. Available from: [http://pregnancyregistry.gsk.com/documents/bup\\_report\\_final\\_2008.pdf](http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf). Accessed 2011 Nov 24.
13. Tapper AR, McKinney SL, Nashmi R, Schwarz J, Deshpande P, Labarca C, et al. Nicotine activation of alpha4\* receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004;306(5698):1029-32.
14. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296(1):56-63.
15. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2011;(2):CD006103.
16. *Chantix* [package insert]. New York, NY: Pfizer Inc; 2008. Available from: [www.accessdata.fda.gov/drugsatfda\\_docs/label/2008/021928s008bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021928s008bl.pdf). Accessed 2011 Nov 1.
17. Pfizer Inc; University of Aarhus, Karolinska Institutet. *Varenicline pregnancy cohort study*. Bethesda, MD: National Library of Medicine; 2000. Available from: <http://clinicaltrials.gov/ct2/show/NCT01290445>. Accessed 2011 Nov 1.

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