SMOKING Cessation ROUNDS

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Pragmatic Strategies to Help Pregnant Smokers Quit

By Peter Selby MBBS, CCFP, and Rosa Dragonetti, MSc.

Maternal smoking is the leading cause of poor pregnancy outcomes, including neonatal morbidity and mortality. However, the behavioural effects on the baby often manifest later in life. The damage begins with DNA adducts in paternal sperm due to the incorporation of tobacco smoke into the zygote. The damage continues if the mother smokes while pregnant. The nicotine, cadmium, thiocyanates, and carbon monoxide present in smoke mediate the harm. Although the true prevalence of smoking in pregnancy is unknown, at least 11% of Canadian women admit to smoking during their most recent pregnancy. While pregnancy is a time of change, most pregnant smokers do not quit. Of those who do, most stop during the first trimester and, at best, 30% will respond to a behavioural intervention. The use of pharmacotherapy is controversial, but should be added if behavioural interventions are not working by themselves. Breastfeeding is recommended even if a woman continues to smoke or uses nicotine replacement therapy (NRT). However, although bupropion may be used during pregnancy, it should not be used while breastfeeding. There is insufficient evidence on the safety of varenicline during pregnancy and, therefore, it should be avoided at this time. The role of healthcare providers in treating pregnant patients who smoke is crucial and they should prescribe pharmacotherapy when necessary to help them stop for good.

Cigarettes contain approximately 4000 chemicals, including 50 to 60 known carcinogens.[1] Between one-third to one-half of smokers will die from smoking-related diseases, and 50% of these deaths will be premature deaths.[2] The use of tobacco products in women of child-bearing age is a particular concern, not only because of the effects on their own health, (see *Smoking Cessation Rounds*, July 2007), but also on their reproductive health. Although many heathcare providers focus on the effects of smoking while a woman is pregnant, it is important to note that there is a dose-response relationship between the number of cigarettes smoked and effects on the developing fetus. Therefore, eliminating exposure, even before a woman becomes pregnant, is ideal. Since most pregnancies are unplanned, however, many female smokers find themselves pregnant and then attempt to stop.

According to the Canadian Tobacco Use Monitoring Survey (CTUMS), the prevalence of smoking in women aged 20 to 44 is 9.8%.[3] In 2003, women aged 20 to 44 years were asked about smoking during any pregnancy during the previous 5 years.[4] Approximately 11% admitted to smoking and at least 12% stated that their spouses smoked regularly at home when they were pregnant. These figures certainly underestimate the true prevalence of smoking due to the demand characteristics of survey questions.

In the United States, smoking costs $250 million in direct medical costs each year. The largest smoking-attributable costs are due to low birth-weight and lower respiratory tract infections.[5] The additional costs during the first year after birth range from $1142 to $1358 per smoking pregnant woman. An annual percentage point decrease in smoking prevalence among pregnant women could prevent the delivery of 1300 low birth-weight infants, thereby, saving about $21 million in direct medical costs during the first year alone.

Natural history of smoking in pregnancy

It is estimated that between 25% and 40% of women who become pregnant will try to stop smoking once they learn that they are pregnant. One study in Nova Scotia revealed

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that approximately 70% of women who were smokers prior to becoming pregnant were also smoking at the time of delivery.[5] Only 8.5% of women who were smokers at their first prenatal visit were nonsmokers at the time of delivery, while 13.1% maintained their smoke-free status throughout their pregnancy. Furthermore, 20% of those who had quit at the time of their first prenatal visit had relapsed by the time they delivered. For those who continued to smoke, there appeared to be a reduction in the total number of cigarettes smoked daily (by 2 cigarettes) over the course of the pregnancy. However, given the ability of smokers to compensate by smoking intensely to achieve the same level of nicotine, this is not a clinically-significant reduction.

Women who continue to smoke while pregnant generally are younger and single (odds ratio [OR] = 4.8, 95% confidence interval [CI], 3.8-6.0), or have a low level of education, a socioeconomic disadvantage, concurrent mental health problems, and/or other addictions, low self-esteem, and/or are living with a partner who smokes (OR 2.3, 95% CI, 1.9-2.7).[6,7] Nevertheless, 50% of pregnant women report cutting down when planning to become pregnant or once they find out that they are pregnant.[8,9] An additional 2%-22% may quit later in their pregnancy.[10]

Pregnant women who cut down their smoking and those who quit "cold turkey" experience withdrawal symptoms.[11] The only difference is that smokers have mild withdrawal because of continued smoking, while those who quit report significant irritability and difficulty concentrating. Moreover, relapse in the postpartum period is substantial. Between 50% and 60% of women who quit during their pregnancy relapse to smoking within 6 months postpartum. In a pilot study examining the timing and predictors of postpartum relapse, 50% of women relapsed within days of their delivery. Mothers who had lower levels of education, were poor, living in households where others smoked, and who were not breastfeeding were more likely to relapse. Further, women indicated that the primary reasons for relapse were stress and exposure to another person smoking.[12] Lemola also found evidence that the smoking status of the woman's mother and mother-in-law had an effect on her ability to quit. Hence, the focus of an intervention to stop smoking needs to be broadened to include not only the pregnant woman, but also her partner and other family members[13] to ensure quit success and reduce the risk of relapse.

It appears that although pregnancy motivates many women to stop smoking,[14] most will continue to smoke, and those who stop, tend to relapse during the pregnancy or within the postpartum period. These findings suggest that women are stopping primarily for their fetus, rather than for themselves.

The effects of tobacco smoke

The effects of smoke on sperm: Tobacco smoke is toxic and nicotine leads to the fragmentation of DNA in sperm.[15] Zenzes et al demonstrated that smoking causes benzo(a)pyrene diol epoxide DNA (BPDE-DNA) adduct formation in human sperm.[16,17] The source of benzopyrene is from inhaled tobacco smoke. Therefore, paternal smoking, through gametic transmission of modified DNA, results in BPDE-DNA adducts in the embryo. There are similar proportions of BPDE-DNA adducts in embryos where both parents smoke, compared to those where only the father smokes, suggesting that DNA adducts come mainly from sperm. Moreover, male smokers have other abnormalities in sperm motility and morphology that can result in infertility. It is imperative, therefore, that potential fathers quit smoking for ≥3 months before attempting to get their partners pregnant. This should be standard advice in any medical work-up for couples entering infertility treatment.[18]

The effects of tobacco smoke on oocytes: Smokers enter menopause approximately 1 to 4 years earlier than nonsmokers, primarily due to the anti-estrogen effects of tobacco smoke.[19,20] The damage to a woman's ovaries from tobacco smoke occurs in those exposed to tobacco smoke as a fetus *in utero*. Advancing the age of menopause by 2 years requires the destruction of 25% of oocytes at birth.[21] Moreover, smokers attending infertility treatment have an increased proportion of diploid oocytes, ie, the percentage of abnormal oocytes in smokers is 20% versus <5% in nonsmokers, while ex-smokers and light smokers have about 12% abnormal oocytes.[22] Therefore, women should quit smoking before they get pregnant. It is unknown if the effects are completely reversible.

Effects of tobacco smoke on pregnancy: There have been several reviews on the effects of smoking during pregnancy.[23,24] Although women who smoke are less likely to experience preeclampsia in pregnancy, the overall effects of smoking are detrimental to both the mother and the fetus.[25] Early pregnancy complications include ectopic pregnancy with a relative risk (RR) = 2.2; 95% CI, 1.3-3.6, compared to nonsmokers, and spontaneous abortion with a RR=1.8; 95% CI, 1.3-2.5).[26] Other pregnancy complications include an increased incidence of placenta previa (RR = 2.6; 95% CI, 1.3-5.5), prematurity, abruptio placenta,[27,28] and preterm rupture of membranes.

Effects of tobacco smoke on the fetus and the infant: The immediate effects on the fetus are observable, with inhibition of fetal breathing and, occasionally, fetal movement during, or immediately after, a woman smokes a cigarette.[29,30] There is also decreased fetal heart rate variability.[31] Moreover, there are detectable withdrawal symptoms in infants born to smoking mothers.[32,33] Selby reported a case of intrauterine fetal withdrawal when a mother tried to quit cold turkey in the second trimester.[34]

The most important reason for intrauterine growth retardation (IUGR) and subsequent low birth weight in developed nations is maternal smoking. The IUGR tends to be symmetrical and can be observed at 22 weeks gestation, with the relative risk ranging from 2.41 to 4.0, depending on the population studied.[35,36] Given that most fetal weight gain occurs during the third trimester, smoking during this trimester has the most severe effects on birth weight, resulting in IUGR and infant prematurity.[26] The decrease in birth weight is inversely related to the number of cigarettes smoked and exposed infants may weigh between 150-300 gms less than unexposed infants. Mothers exposed to environmental tobacco smoke or second-hand smoke have infants who weigh about 107 gms less than unexposed infants. Furthermore,

there is a 20% observed increase in perinatal mortality in mothers who smoke >20 cigarettes/day.

One of the most dramatic postnatal effects of maternal smoking is sudden infant death syndrome (SIDS), which usually occurs within the first 9 months of life. It is estimated that the RR=6.2 (95% CI, 2.8-14.1) in infants of women who smoke >20 cigarettes/day.[37,38] Even after controlling for social disadvantage, tobacco smoke is independently associated with SIDS. Recent evidence also implicates that continued exposure to smoke in the postpartum period also contributes to SIDS.

Effects of tobacco smoke on breastfeeding: Women who smoke during the postpartum period continue to transmit nicotine and other constituents of smoke to the developing infant. Tobacco smoke itself reduces milk production by 30%. However, continuing to breastfeed delays relapse to smoking and, overall, breastfeeding is beneficial to the infant, even if the mother continues to smoke, especially in women experiencing socioeconomic disadvantages.

Effects of tobacco smoke on mental and behavioural development: Due to the effect of nicotine on the developing brain – especially the cholinergic, dopaminergic, and adrenergic neurotransmitter systems – the effects of prenatal smoke exposure are associated with a range of persistent behavioural problems such as attention deficit disorder (ADD),[39,40] externalizing behaviour,[41,42] and early substance and alcohol abuse, including earlier onset of smoking.[43,44] Further, some cohort studies that followed children up to age 33 have reported a dose-dependent association between maternal smoking and antisocial behaviours in male offspring.[45-48]

What causes the harm to the developing fetus?

Although it is not certain which constituent is responsible for the adverse effects associated with cigarette smoking during pregnancy, hydrogen cyanide, carbon monoxide,[49,50] and nicotine are the major suspects.

The evidence for hydrogen cyanide: Inhaled hydrogen cyanide is rapidly absorbed and converted to thiocyanate in the liver. At higher doses, cyanide and thiocyanate are toxic and can inhibit cytochromes and reduce intracellular oxygen utilization, interfere with vitamin B_{12} metabolism, act as hypotensive agents, cause degenerative neurological disease, and alter thyroid function.[51,52] These effects are observed in the fetus and may have long-term effects.

The evidence for carbon monoxide: Growth retardation observed in the fetuses of smoking mothers is a potential manifestation of fetal ischemia and hypoxemia, possibly induced by the combination of both carbon monoxide and nicotine. The developing fetus is normally in a low oxygen environment.[53,54] Smoking 2 packs of cigarettes per day leads to a 10% blood carboxyhemoglobin level that is equivalent to a 60% reduction in fetal blood flow rate. There is no fetal compensatory mechanism for reduced blood flow since fetal cardiac output is at, or near, maximum levels. This leads to fetal polycythemia and a relative anoxic state of fetal development.

The evidence for nicotine: Nicotine inhaled with tobacco smoke is rapidly absorbed into the arterial circulation and binds stereo-selectively to presynaptic junctions of nicotinic cholinergic receptors located in the peripheral and central nervous system. The pharmacodynamic effects of nicotine include increases in heart rate, blood pressure, and cardiac output, changes in endocrine and metabolic function, cutaneous and systemic vasoconstriction, and a decrease in muscular tone. The action of nicotine on the adrenal medulla is critical in pregnancy. Nicotine intensifies the secretion of noradrenaline, adrenaline, and acetylcholine. The increased level of circulating catecholamines causes uterine vasoconstriction and reduced uteroplacental perfusion, thereby, decreasing the amount of oxygen and nutrients reaching the fetus.[55,56] Furthermore, nicotine crosses the placenta and leads to increases in fetal blood pressure and heart rate.

However, transdermal nicotine has less effect on cathecolamine release than does smoking.[57] Studies on the effects of nicotine in pregnant rats reveal that continuous nicotine infusion leads to more neuroteratogenic effects in offspring than pulsed nicotine doses.[58] However, the doses used were much higher than those observed in heavy human smokers or in those using NRT.[59] Regardless, based on the above findings, Slotkin theorizes that continuous nicotine exposure, as in transdermal NRT, might be more harmful to light smokers and those who have periods of abstinence during the day.[58] He recommends the use of NRT in the first trimester, with discontinuation in the second and third trimester due to the absence of nicotinic receptor expression in early pregnancy; however, he acknowledges that heavy smokers who maintain a steady level of plasma nicotine throughout the day are also exposed to other noxious substances in cigarette smoke. Therefore, any effective NRT regimen has to provide a lower dose of nicotine and allow for a nicotine-free period that allows DNA synthesis to occur, thus minimizing the detrimental effects of nicotine on the developing brain. This intervention will also prevent the hypoxic effects associated with smoking and protect the fetus from exposure to carbon monoxide and hydrogen cyanide.

Smoking cessation in pregnant smokers

Comorbid psychiatric conditions and smoking: Anxiety and depressive disorders are very common in smokers.[60,61] In addition, negative mood states post-cessation predict early relapse, and the use of alcohol and other drugs of abuse increase the odds that a woman will not stop smoking. Hence, it is important to also screen for these problems in all pregnant smokers.

Interventions with pregnant women: To decrease the prevalence of smoking during pregnancy, both a population and clinical approach should be adopted. Policies and interventions that aim to prevent women and men who are considering having a child from smoking are necessary. In clinical settings, it is important to screen all patients, including pregnant women, for smoking and to intervene aggressively to help them stop, not just during the pregnancy, but also for their entire life. Furthermore, it is recommended to use behavioural and psychosocial interventions that have been adapted for pregnant women in the first trimester. If they are unable to quit or "stay

Figure 1. Benefits of Quitting Smoking

Benefits of quitting for the woman

- Decreased risk of developing cancers, heart disease, stroke, and circulatory problems
- Decreased risk of respiratory diseases (asthma, emphysema, chronic bronchitis, flu, colds, pneumonia)
- Decreased risk of developing peptic ulcers, tooth loss, gum disease, osteoporosis, thyroid disease, and menstrual problems

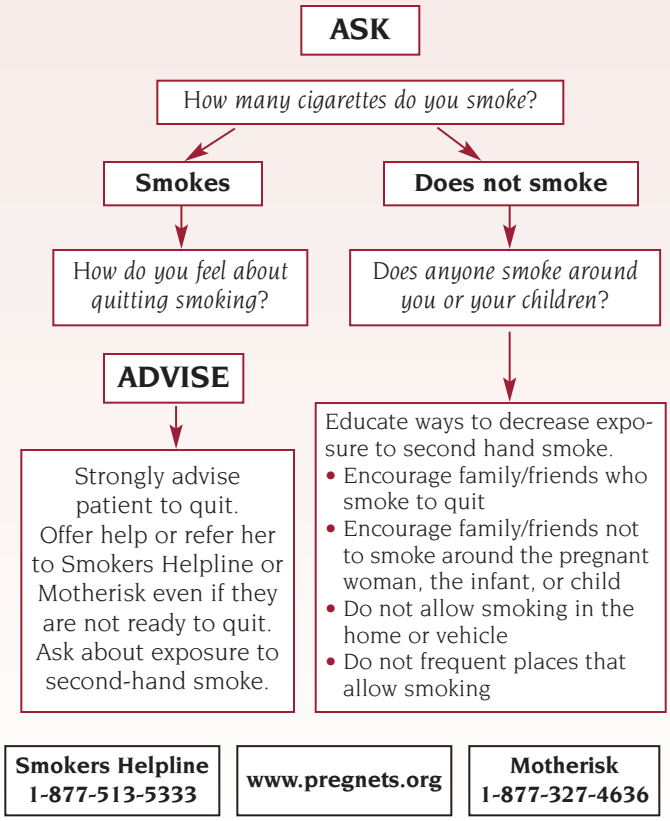
Benefits of quitting for the pregnancy

- Decreased risk of spontaneous abortion and perinatal mortality
- Decreased risk of vaginal bleeding, premature delivery, developing abruptio placenta and placenta previa
- Decreased effect on quality and quantity of breast milk

Benefits of eliminating exposure to second hand smoke exposure by infants and children

- Decreased risk of Sudden Infant Death Syndrome
- Decreased risk of children developing asthma and allergies
- Reduced risk of middle ear infections
- Less chance of cranky and colicky babies

"RISK" is defined as the chance of experiencing the negative consequences, but it does not mean that it will definitely occur.



quit," pharmacotherapy may be added under the supervision of a trained healthcare provider. It is imperative to address smoking within the family, particularly that of her partner or other members in her household.

Psychosocial interventions: Due to the benefits of quitting smoking for both the mother and the fetus, all pregnant smokers should be offered counselling proven to be efficacious in pregnant smokers.[62-64] Although validated primarily in the United States, the modified Smoking Cessation or Reduction in Pregnancy Treatment (SCRIPT) Model was derived from 2 meta-evaluations and 2 meta-analyses.[64-66] It includes the use of motivational strategies that incorporate pregnancy-specific counselling strategies, a patient education video, *Commit to Quit Smoking – During and After Pregnancy*, and the use of a validated self-help manual, *Pregnant Woman's Self-Help Guide to Quit Smoking*.[67] A recent study of 948 pregnant smokers has also demonstrated the efficacy of proactive telephone counselling in pregnant smokers with a self-reported cessation rate of 20%.[68]

The desk reference in Figure 1 provides an outline of the benefits of quitting smoking and the steps to screening and referring pregnant women for cessation counselling.

Pharmacological interventions: The safety of NRT in pregnancy is a concern for practitioners; therefore, most avoid recommending its use in smokers. There have been at least 2 negative trials of NRT in pregnancy. In both randomized trials, the NRT patch was applied for approximately 16 hours and removed at night.Wisborg enrolled pregnant smokers (n=250) who smoked >10 cigarettes per day in their second trimester. Women were randomized to NRT or placebo patches for 11 weeks. There were no differences in results between the NRT and placebo group; however, these findings were due to inadequate doses of NRT and high drop-out rates.[69,70]

Interestingly, pregnant women demonstrate increased nicotine metabolism in the late second and third trimester.[71] In some studies, minimal-effective doses of nicotine in immediate-release formats (eg, gum) are thought to allow for nicotine-free periods.[72-74] However, if a woman continues to smoke ≥1 cigarette every waking hour, then long-acting preparations such as the NRT patch may be more suitable. Furthermore, breastfeeding while using NRT provides the same level – or less – of nicotine to the infant, without the other chemicals in smoke.[75,76]

Bupropion is considered less dangerous than NRT during pregnancy, with the advantage of providing antidepressant effects[77,78] But, the risk of seizures makes it the second choice for many clinicians treating pregnant smokers. Bupropion is not recommended while a woman is breastfeeding due to the risk of seizures in the infant.[79-81] There have been no studies on the safety and efficacy of varenicline in

pregnant smokers. It should be avoided until more data become available.

Preventing smoking relapse: Given the high rate of relapse postpartum, it is strongly recommended that women be counselled and supported in maintaining their smoke-free status antepartum and immediately postpartum. Strategies to enhance and prolong breastfeeding and frequent follow-up will help delay, if not prevent, relapse to smoking. It is important to discuss the need to stay smoke-free with the patient, not only for her own reproductive health, but also if she is planning another pregnancy in the future. If a decision is being made about the use of oral contraception, then the importance of staying smoke-free should be stressed, since smoking while using oral contraception is associated with its own set of risks.

Dealing with relapse: If a woman experiences a relapse at any point during the process, she should be encouraged to report it immediately to her healthcare practitioner or counsellor. Counselling and optimization of pharmacotherapy may be necessary to prevent a full-blown return to smoking.

Conclusion

Healthcare practitioners have a role in providing education and intervention to couples who are contemplating pregnancy, as well as intervening when a woman is pregnant. A woman-centred approach that addresses the social and other determinants of her smoking will help her and her offspring have the best odds of a healthy outcome and break the cycle of the negative effects of tobacco use.

For a list of resources on smoking cessation with pregnant and post-partum women, visit www.pregnets.org.

Rosa Dragonetti *is the Manager of the Nicotine Dependence Service at the CAMH that includes projects such as the STOP Study, the TEACH project, and PREGNETS (www.pregnets.org). Rosa also contributed to the development and implementation of CAMH's Smoke-Free Policy, the Rainbow Tobacco Intervention Project, Tobacco Control Area Network Steering Committee, and the Provincial Cessation Task Group.*

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Upcoming Meeting

27 February – 1 March 2008
Society for Research on Nicotine and Tobacco (SRNT)
14th Annual Meeting
Hilton Portland and Executive Tower
Portland, Oregon, USA
Contact: www.srnt.org

10-13 April 2008
American Society of Addiction Medicine (ASAM)
Toronto, Ontario
Contact: www.asam.org

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