Pharmacotherapy for smoking cessation during pregnancy

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Introduction: The risk-vs.-benefit question

As noted elsewhere in this issue, many pregnant women continue to smoke during pregnancy despite advice from health care providers that they should quit and/or because they have failed behavioral therapy. Continuing to smoke in the face of compelling reasons not to do so is an indication of addiction—that is, loss of control of drug use. Nicotine is responsible for addiction to cigarette smoking (Benowitz, 1999). The more severe the addiction, the harder it is to quit smoking. More highly addicted smokers obtain greater relative benefit from pharmacotherapy (vs. placebo) compared with less highly addicted smokers (Sutherland et al., 1992). Evidence also indicates that more highly addicted smokers are more likely to quit if they receive higher doses of nicotine medications, whereas less dependent smokers do as well with lower doses of nicotine (Tonnesen et al., 1988). Given that women who continue to smoke during pregnancy are likely to be highly dependent, it makes sense that pregnant smokers would benefit from pharmacotherapy to aid cessation, and that the doses of medications may need to be relatively high compared with those used in less dependent smokers.

Data are scarce on the efficacy of medications to aid smoking cessation in pregnant smokers, largely because health care providers have been hesitant to expose pregnant women to medications for fear that the medications may have a negative effect on the pregnancy or the fetus. Thus, the safety of pharmacotherapy is the key question that needs to be resolved before we progress in enhancing smoking cessation during pregnancy.

With respect to drug therapy, safety is not an absolute measure. Rather, safety reflects the conclusion that a drug’s benefits outweigh its risks. Because the benefits of pharmacotherapy to enhance cessation in pregnant smokers are unknown, this article focuses primarily on the question of risk, specifically, on the risks associated with cigarette smoking vs. the risks associated with medications that might result in a woman quitting.

Risks associated with cigarette smoking during pregnancy

Cigarette smoking is the largest modifiable risk factor for pregnancy-related morbidity and mortality in the United States and other developed countries. Table 1 summarizes the adverse effects of cigarette smoking.

Reproductive toxins in cigarette smoke

In considering the risks vs. the benefits of the medications used for smoking cessation, particularly nicotine, it is useful to consider the variety of reproductive toxins present in cigarette smoke and the suspected mechanisms of toxicity. Cigarette smoke contains thousands of chemicals (Table 2). Many
of these chemicals may contribute to reproductive toxicity. Of particular concern are carbon monoxide, nicotine, and oxidizing chemicals. The pharmacology and toxicology of nicotine in pregnancy are reviewed in a later section. For a more complete review of chemicals and mechanisms of smoking-related reproductive toxicity, see Dempsey & Benowitz (2001).

Carbon monoxide

Carbon monoxide is the most biologically significant reproductive toxin in cigarette smoke. Accidental exposure of a pregnant woman to carbon monoxide may result in stillbirth or persistent neurological damage to the fetus, even if the mother recovers fully (Koren et al., 1991). Hemoglobin is responsible for binding and transporting oxygen in the body. Carbon monoxide binds with a high affinity (more than 200 times that of oxygen) to maternal and fetal hemoglobin and has a half-life of 4–5 hours. Thus, the smoker is exposed to excessive levels of carbon monoxide 24 hours per day. Carbon monoxide both displaces oxygen and impairs the release of oxygen from hemoglobin. This action adversely affects the transfer of oxygen from maternal hemoglobin, across the placenta, to fetal hemoglobin. The result is a reduction in oxygen available for the fetus. Fetal hemoglobin binds carbon monoxide more avidly than does maternal hemoglobin (Longo, 1977). At steady state, fetal carboxyhemoglobin levels exceed maternal levels with an average ratio of 1.8. The binding of carbon monoxide to fetal hemoglobin impairs the transfer of oxygen to fetal tissues, resulting in fetal hypoxia (Longo, 1976). Hypoxia is a likely mechanism for fetal growth retardation. In animals, even mild, low-level carbon monoxide exposure, with carboxyhemoglobin levels of 4%–9% (similar to those found in human smokers), results in fetal growth retardation (Lynch & Bruce, 1989).

In animals, chronic carbon monoxide exposure results in detrimental effects to fetal brain development, including reduced fetal brain weight, altered brain neurotransmitter levels, and postnatal behavioral and cognitive impairments (Penney, 1996). Chronic carbon monoxide exposure in pregnant rats produces cardiac hypertrophy in the fetus and persistent tachycardia in the adult rat exposed to carbon monoxide in utero (Clubb, Penney, Baylerian, & Bishop, 1986).

The functional anemia produced by chronic carbon monoxide exposure stimulates erythrocyte production, resulting in elevated hematocrit and increased blood viscosity in pregnant smokers and their fetuses (Buchan, 1983). High blood viscosity is a risk factor for stroke in the newborn, as well as for thrombosis in the placenta.

Thus, carbon monoxide is unequivocally a potent reproductive toxin. Any intervention that can eliminate or reduce carbon monoxide exposure in the pregnant smoker is likely to benefit the pregnancy.

Oxidizing chemicals

The toxicity of oxidizing chemicals has been of considerable research interest with respect to smoking and the pathogenesis of cardiovascular disease. Cigarette

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### Table 1. Cigarette smoking–related outcomes of pregnancy.

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<tr>
<th>Pregnancy wastage</th>
<th>Fetal demise</th>
<th>Stillbirths</th>
<th>Premature rupture of membranes</th>
<th>Premature labor and delivery</th>
<th>Placental abruption</th>
<th>Placental previa</th>
<th>Fetal toxicity</th>
<th>Growth retardation</th>
<th>Neurotoxicity</th>
<th>Pulmonary effects</th>
<th>Postnatal outcomes</th>
<th>Sudden infant death syndrome</th>
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<td>Medical conditions associated with passive smoking in childhood</td>
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<td>Pneumonia and other respiratory illnesses</td>
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<td>Otitis media</td>
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<td>Burn and fire deaths</td>
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*Increased prevalence of childhood passive smoking among children born to mothers who smoke (modified from Dempsey & Benowitz, 2001).*

### Table 2. Selected chemicals in cigarettes.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Dose per cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide</td>
<td>10–23 mg</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1–3 mg</td>
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<tr>
<td>Hydrogen cyanide</td>
<td>400–500 mg</td>
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<tr>
<td>Aniline</td>
<td>360–655 mg</td>
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<tr>
<td>Catechol</td>
<td>200–400 mg</td>
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<tr>
<td>Nitrogen oxide</td>
<td>100–600 mg</td>
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<tr>
<td>Methanol</td>
<td>100–250 mg</td>
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<tr>
<td>Phenol</td>
<td>80–160 mg</td>
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<tr>
<td>Acrolein</td>
<td>60–140 mg</td>
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<tr>
<td>Pyridine</td>
<td>16–40 mg</td>
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<tr>
<td>Ammonia</td>
<td>10–130 mg</td>
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<tr>
<td>Hydrogen sulfide</td>
<td>10–90 mg</td>
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<tr>
<td>Arsenic</td>
<td>40–120 mg</td>
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<tr>
<td>Hexavalent chromium</td>
<td>4–70 ng</td>
</tr>
<tr>
<td>Cadmium</td>
<td>4–70 ng</td>
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<tr>
<td>Nickel</td>
<td>0–600 ng</td>
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<tr>
<td>Lead</td>
<td>34–85 ng</td>
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<tr>
<td>Polynuclear aromatic hydrocarbons</td>
<td>60–190 ng</td>
</tr>
<tr>
<td>Heterocyclic compounds</td>
<td>3–14 ng</td>
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<tr>
<td>N-nitroamines</td>
<td>200–4,900 ng</td>
</tr>
<tr>
<td>Aromatic amines</td>
<td>30–670 ng</td>
</tr>
<tr>
<td>N/heterocyclic amines</td>
<td>40–300 ng</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>570–1,500 ng</td>
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<tr>
<td>Volatile hydrocarbons</td>
<td>500–1,150 ng</td>
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</table>

*Source.* Hoffmann, Hoffmann, & Wynder (1998)
smoke in both tar and gas phases is an abundant source of oxidizing chemicals, including oxides of nitrogen and a variety of free radicals. Oxidizing chemicals degrade nitric oxide and/or impair nitric oxide synthase, resulting in diminished endothelial vasodilation (Celermajer et al., 1993). Maternal cigarette smoking is associated with decreased placental nitric oxide synthase activity and decreased production of nitric oxide in umbilical arteries (Sooranna, Morris, & Steer, 1995; Ulm, Plockinger, Pirich, Gryglewski, & Sinzinger, 1995). Nitric oxide also is a potent myometrial relaxant. By inhibiting nitric oxide release, smoking could contribute to maternal and placental vasoconstriction as well as to preterm labor.

Oxidizing gases also may activate platelets. Cigarette smoking is associated with placental thrombosis and infarction, which are associated with adverse pregnancy outcomes (Naeye, 1978).

Oxidizing gas exposure results in consumption of endogenous antioxidants, for example, resulting in lower levels of vitamin C. Ascorbic acid (vitamin C) is required for the biosynthesis of collagen. Low ascorbic acid levels are associated with a higher risk of premature rupture of membranes (Wideman, Baird, & Bolding, 1964). Ascorbic acid levels have been shown to be reduced by 50% in the amniotic fluid of cigarette smokers, compared with that of nonsmokers (Barrett, Gunter, Jenkins, & Wang, 1991). Thus, reduced ascorbic acid levels resulting in impaired collagen synthesis may be a mechanism by which cigarette smoking contributes to premature rupture of membranes.

Other reproductive toxins

A great many additional biochemical, cellular, and physiological effects of smoking or chemicals found in cigarette smoke have been described, and a number of mechanisms of reproductive toxicity from smoking have been proposed (see Dempsey & Benowitz, 2001, particularly Appendix 4, for more detailed review). No single agent in cigarette smoke is responsible for the varied adverse pregnancy outcomes seen in smokers. Rather, many chemical agents acting by different mechanisms appear to work additively or synergistically to cause reproductive injury.

Gene-environment interactions

A recent area of research interest that provides insight into how smoking causes reproductive injury is that of gene-environment interactions. The ability to metabolize and eliminate drugs and toxins is highly variable in the population. Much of the variability is due to genetic polymorphisms of metabolizing enzymes. Some of the differences between phenotype and genotype are due to the inducibility of many drug-metabolizing enzymes. Phenotypic variability and genetic polymorphisms have been associated with the risk of reproductive toxicity from exposure to particular drugs or chemicals (Buehler, Delimont, van Waes, & Finnell, 1990; Wang et al., 2000).

Gene interactions with maternal cigarette smoking have been reported (Hong et al., 2001; van Rooy et al., 2001). Among the most important cigarette smoke carcinogens are polycyclic aromatic hydrocarbons, arylamines, and N-nitrosamines. Polycyclic aromatic hydrocarbons are lipophilic and undergo detoxification by a two-step process. The first step involves the enzyme aryl hydrocarbon hydroxylase (CYP1A1), which metabolizes polycyclic aromatic hydrocarbons to reactive electrophilic intermediates. These reactive intermediates are then metabolized to nontoxic polar metabolites by a second step involving conjugation with glutathione, after which they are excreted from the body. One of the enzymes responsible for glutathione conjugation is glutathione S-transferase (GSTT1). Both the CYP1A1 and GSTT1 genes are polymorphic in the population. In the research described below, the CYP1A1 MspI polymorphism was studied, which includes the AA (homozygous wild type), Aa (heterozygous variant), and aa (homozygous variant) genotypes. For GSTT1, the presence of a deletion polymorphism (no activity) was assessed.

A case-control study included 207 preterm delivery and/or low birth weight infants and 534 full-term, non-low-birth-weight infants (Wang et al., 2002). All infants were singletons without malformations. Among babies born to mothers who were nonsmokers, the genotypes for the CYP1A1 and GSTT1 enzymes were not associated with decreased birth weight. Overall, maternal smoking was associated with a mean decrease in birth weight of 377 grams. When babies born to smokers were examined by genotype, the CYP1A1 (AA) genotype was associated with a mean decrease of 252 grams, whereas the Aa or aa genotypes were associated with a 520-gram decrease. For the GSTT1 genotype, the presence of GSTT1 was associated with a 285-gram decrease, whereas the GSTT1 deletion (absence of the enzyme) was associated with a 642-gram decrease. Eleven babies were born to mothers who smoked and had the CYP1A1 (Aa or aa) genotype and GSTT1 deletion genotype, and their average birth weight reduction was 1,285 grams.

Drug metabolism is complex, and the effects of pregnancy on drug metabolism are not easily predicted. Genotypes for drug-metabolizing enzymes may indicate potential metabolic pathways, but they do not necessarily predict the dominant pathways or the metabolite profile (phenotype). At present we can only speculate as to why a particular genotype is associated with growth retardation and premature delivery among smokers. Future studies are needed.
to clarify the nature of this association and elucidate mechanisms of smoking-related reproductive toxicity. Because the enzymes CYP1A1 and GSTT1 metabolize polycyclic aromatic hydrocarbons (as well as other carcinogenic chemicals) but not nicotine, these data indicate that nicotine may not be a major cause of impaired fetal growth or premature delivery among smokers.

In summary, cigarette smoking exposes the pregnant woman to numerous chemicals that are clearly detrimental to pregnancy or to fetal development. A reduction in exposure to these chemicals would likely result in improved reproductive outcomes. Even if nicotine per se contributes to the adverse effects of smoking during pregnancy, if a woman were to take in the same level of nicotine from a medication as she would from smoking, but could eliminate exposure to the other reproductive toxins found in cigarette smoke, an overall benefit would result for the woman and the fetus.

**Pharmacokinetics and pharmacodynamics of nicotine in the mother and fetus**

Before reviewing the adverse effects of nicotine in pregnancy, it is important to consider pharmacokinetic and pharmacodynamic factors. The adverse effects of nicotine in pregnancy are likely to be influenced by the route, rate, and dose of nicotine administered. The faster the administration of nicotine, the higher the resulting peak arterial blood concentrations, and the higher the concentrations in various body tissues of the mother. Also, the more rapid the administration, the less time there is for the development of acute tolerance, which occurs for many effects of nicotine. For any given dose, higher peak levels result in more intense cardiovascular and subjective effects of nicotine. Thus, the most intense effects are seen with cigarette smoking, which delivers nicotine most rapidly; followed by nicotine nasal spray; then nicotine gum, inhaler, and lozenges; and lastly transdermal nicotine, which releases nicotine quite slowly.

The pharmacokinetics of nicotine differ in the fetus compared with the mother. Because nicotine needs to pass through the placenta before reaching the fetus, peak nicotine levels are not as high in the fetus as in the mother. In animals, peak nicotine concentrations in the fetal circulation occur 15–30 minutes after maternal dosing (Suzuki et al., 1974). The mechanism of clearance of nicotine from the fetus is via transfer back into the maternal circulation. Fetal renal clearance and metabolism accounts for only a small percentage of total clearance.

The fetus is immersed in amniotic fluid. Nicotine can enter the amniotic fluid either via fetal urine or directly via blood vessels of the amniochorionic membrane. Nicotine and cotinine levels in maternal blood and amniotic fluid are highly correlated (Luck & Nau, 1984). The average ratio of concentration in amniotic fluid vs. maternal blood is 1.54 for nicotine and 0.72 for cotinine. Because the fetus swallows amniotic fluid continually, amniotic fluid nicotine can be a source of ongoing exposure to the fetus, and this exposure may continue even when maternal blood nicotine concentrations fall to low levels.

**Possible adverse effects of nicotine on the pregnant mother**

Nicotine has been suspected of contributing both to adverse effects on pregnancy and to injury of the fetus. These concerns are based primarily on animal studies. Convincing evidence of the harm of nicotine per se in humans is lacking to date, but relatively little research with pure nicotine has been done in pregnant smokers. Definitive studies of the safety of nicotine in humans are still needed.

Several mechanisms by which nicotine might have adverse effects on pregnancy have been reported. The most widely discussed mechanism is uteroplacental insufficiency, or inadequate blood flow to the fetoplacental unit, which might contribute to fetal growth retardation and placental abruption. Nicotine is known to constrict blood vessels, both by release of catecholamines and possibly by reducing nitric oxide release (Benowitz & Gourlay, 1997). It is hypothesized that constriction of uteroplacental blood vessels decreases blood flow to the placenta and decreases the delivery of oxygen and nutrients to the fetus. Large intravenous doses of nicotine in pregnant monkeys and sheep substantially reduce uterine blood flow and produce acidosis and hypoxia in the fetus, supporting the uteroplacental insufficiency hypothesis (Resnik, Brink, & Wilkes, 1979; Suzuki, Minei, & Johnson, 1980). However, these studies have involved rapid administration of extremely high doses of nicotine, much higher than those to which mothers taking nicotine replacement therapy would be exposed.

Data on umbilical and placental blood flow in pregnant women smoking or receiving nicotine medications are inconsistent (see Dempsey & Benowitz, 2001, Appendix 1). A technical aspect of measurement of umbilical or placental blood flow in pregnant women deserves brief discussion. Blood flow cannot be measured directly in a pregnant woman. Blood flow is a function of velocity of flow and the diameter of the blood vessel. The velocity of blood flow in uterine, placental, and umbilical blood vessels can be measured using Doppler techniques. Blood flow velocity often is reported as a surrogate for blood flow. In studies of pregnant women, smoking or nicotine medication commonly increases maternal blood pressure and heart rate and increases fetal heart rate, but
changes in umbilical or placental blood flow velocity are usually small and remain within the range of normal variability.

Some controversy exists in the literature regarding the contribution of uteroplacental circulatory insufficiency to adverse pregnancy outcomes associated with smoking (Lambers & Clark, 1996). The argument against nicotine as a cause of uteroplacental insufficiency is that the uteroplacental circulation has considerable circulatory reserve. For the first two trimesters of pregnancy, the fetus is quite small and the placenta can easily provide more than adequate blood flow and nutrition. Possibly in the third trimester, when the fetus is larger, uteroplacental insufficiency could result in fetal injury, but even then the placental circulation has a considerable reserve. The placenta is a low-pressure system capable of tolerating the effects of intense uterine contraction during labor while still providing adequate blood flow to the fetus. Furthermore, it is not clear in general whether uteroplacental insufficiency is a significant cause of growth retardation (except when these changes are profound). The data reviewed above (and in more detail elsewhere) suggest that nicotine does not have significant effects on placental blood flow and that the hemodynamic effects of nicotine are unlikely to explain fetal growth retardation in smokers (Dempsey & Benowitz, 2001; Lambers & Clark, 1996).

Two other effects of nicotine have been mentioned as possible contributors to adverse outcomes of pregnancy. These effects are promoting platelet activation and inhibiting estrogen synthesis. Nicotine has been shown in some animal studies to acutely activate platelets, but these studies have been done with rapid intravenous high doses of nicotine (Folts & Bonebrake, 1982). Human studies do not provide convincing evidence that nicotine activates platelets, particularly studies looking at transdermal nicotine (although smoking per se does activate platelets) (Benowitz, Fitzgerald, Wilson, & Zhang, 1993).

Plasma levels of estrogen are 10% lower in smokers compared with nonsmokers during pregnancy (Petridou, Panagiotopoulou, Katsouyanni, Spanos, & Trichopoulos, 1990). In vitro studies have shown that nicotine, cotinine, and the minor tobacco alkaloid anabasine (the latter found in tobacco smokers) inhibit the enzyme aromatase, which is involved in the metabolic conversion of androstenedione to estrogen (Barbieri, Gochberg, & Ryan, 1986). Conceivably, nicotine could contribute to this inhibition, although a number of other chemicals in tobacco smoke can also inhibit aromatase.

Potential Adverse effects of nicotine on the fetus

Nicotine may have adverse effects on the heart, lung, and brain of the fetus. Nicotine has been shown to affect fetal heart rate, resulting in small increases or decreases in heart rate and reducing heart rate variability (studies reviewed in Dempsey & Benowitz, 2001). The effects of nicotine replacement therapy generally have been less than those of cigarette smoking. The magnitude of effects of nicotine replacement therapy on the fetal circulation appears to be small and is not likely to compromise the fetus.

Studies of nicotine administered to pregnant monkeys suggest that nicotine alters lung development, resulting in lung hypoplasia (Sekhon et al., 1999). This effect appears to be mediated by actions of nicotine on α7 nicotinic cholinergic receptors present in various cells of the developing lung. The significance of nicotine-related impairment of fetal lung development for human exposure is not clear, but altered lung function has been reported in infants of mothers who smoke during pregnancy (Hanrahan et al., 1992).

The greatest concern regarding the effect of nicotine on the fetus is the possibility of a detrimental effect on brain development. Based on studies in rodents, nicotine is suspected to impair nerve generation and maturation (Slotkin, 1998). During the highly complex development of the brain, neurotransmitters function as trophic factors. At various points in time, particular neurotransmitters may initiate or terminate cellular proliferation, differentiation, migration, or apoptosis. Nicotine stimulates nicotinic cholinergic receptors (acetylcholine is the endogenous ligand for these receptors). Stimulation of nicotinic cholinergic receptors at inappropriate times (i.e., when acetylcholine is not present at significant levels) may interfere with normal fetal brain development. Inappropriate nicotinic cholinergic stimulation ends cell proliferation prematurely and initiates cellular differentiation in the fetal brain, resulting in a reduced number of neurons in selected areas of the brain (Slotkin, Cho, & Whitmore, 1987). In rats, such effects can be seen at doses of nicotine sufficiently low so as not to cause growth retardation. Gestational nicotine exposure is reported to have effects on the synthesis and release of a number of brain neurotransmitters including acetylcholine, norepinephrine, dopamine, and serotonin (Seidler, Levin, Lappi, & Slotkin, 1992). Nicotine also may affect the types and densities of neurotransmitter receptors at nerve endings. The effects of nicotine on brain development persist after nicotine is stopped.

Prenatal nicotine exposure has been associated with dose-dependent abnormalities in selected behaviors and responses to cognitive tests in rodents (Levin, Briggs, Christopher, & Rose, 1993; Shacka, Fennell, & Robinson, 1997). Males appear to be more highly affected than females. These behavioral changes are suspected to be related to the developmental effects of nicotine on brain development.
Another concern regarding fetal nicotine exposure is that it may increase the risk of sudden infant death syndrome (SIDS) in the newborn. Cigarette smoking during pregnancy is a risk factor for SIDS, although the effects of prenatal vs. postnatal exposure are difficult to separate (Anderson & Cook, 1997; Schoendorf & Kiely, 1992). One hypothesis is that SIDS results from an abnormality in the cardiovascular and respiratory response to hypoxia (the latter assumed to be secondary to transient sleep apnea or transient airway obstruction). In the normal rat, hypoxia causes massive catecholamine release from the adrenal medulla, which stimulates the heart and increases blood flow to the brain. Rats exposed to nicotine in utero have a reduced catecholamine response to hypoxia, potentially increasing their vulnerability to hypoxia (Slotkin, Lappi, McCook, Lorber, & Seidler, 1995). During hypoxic stress, neonatal rats with chronic nicotine exposure in utero are more likely to die than are the nonexposed rats.

In summary, the main fetal health concern about nicotine administered during pregnancy is fetal neuroteratogenicity. Although this phenomenon has been well established in rodents, how the animal data apply to humans is unclear. Insofar as a dose-response relationship appears to exist between nicotine and its effects on the brain in animals, it would make sense to expose humans to the lowest dose of nicotine that is adequate to promote cessation of smoking. Any potential risks of nicotine, of course, need to be balanced against the risks of cigarette smoking, which exposes the pregnant woman not only to nicotine but also to the well-established neuroteratogen carbon monoxide and to other toxins discussed previously.

Nicotine metabolism during pregnancy

The level of nicotine in the body after a particular dose of nicotine (derived either from smoking or from nicotine medication) depends on the rate of elimination (also referred to as clearance) by the smoker. Pregnancy substantially accelerates the clearance of both nicotine and its proximate metabolite cotinine. In a study of 10 pregnant smokers who received intravenous nicotine during pregnancy and again postpartum, the average clearance of nicotine was 26 ml/min/kg during pregnancy compared with 16 ml/min/kg postpartum (Dempsey, Jacob, & Benowitz, 2002). An even greater effect of pregnancy was found for cotinine, with a clearance of 1.5 ml/min/kg during pregnancy compared with 0.5 ml/min/kg postpartum. The half-life of cotinine during pregnancy averaged 9 hours, compared with 17 hours postpartum.

Although renal blood flow increases in pregnancy, the renal clearance of nicotine did not increase during pregnancy. Therefore, the increase in total clearance of nicotine must be due to accelerated metabolism. The mechanism by which pregnancy accelerates the metabolism of nicotine and cotinine is unclear. For nicotine, part of the increase in clearance may be explained by increased liver blood flow. Nicotine is a rapidly metabolized drug, and when liver blood flow goes up, its clearance increases. Pregnancy results in an increase in cardiac output, including an increase in liver blood flow. The increase in liver blood flow would be expected to increase nicotine clearance. Cotinine is a much more slowly metabolized drug, such that liver blood flow is not expected to affect its metabolism substantially. Thus, pregnancy likely increases the levels and activity of enzymes that metabolize cotinine. Whether the enzyme is CYP2A6, which is responsible for most cotinine metabolism in the nonpregnant individual, or whether other enzymes are induced remains to be determined.

Accelerated nicotine and cotinine metabolism during pregnancy has several implications. First, for individuals receiving nicotine replacement therapy, the blood levels of nicotine for any given dose will be lower in the pregnant smoker compared with the nonpregnant smoker. As a result, usual doses of nicotine replacement therapy for nonpregnant smokers may be inadequate for pregnant smokers. This may explain the lack of efficacy in the one clinical trial of transdermal nicotine in pregnancy (Wisborg, Henriksen, Jespersen, & Secher, 2000). Because the effect of pregnancy on nicotine metabolism varies from person to person, the use of therapeutic drug monitoring of nicotine might enhance the efficacy while minimizing the chance of excessive dosing of nicotine.

The implication of accelerated metabolism of cotinine during pregnancy is primarily in the use of cotinine to determine smoking status during pregnancy and for exposure estimation. Nicotine and cotinine levels, normalized for cigarette consumption, have been reported by others to be lower in pregnant smokers than in nonpregnant smokers (Rebagliato et al., 1998; Selby, Hackman, Kapur, Klein, & Koren, 2001). Assuming that the clearance of cotinine is accelerated two- to threefold, the resultant cotinine levels for any given level of nicotine intake would be one third to one half as high during pregnancy compared with the nonpregnant state. Therefore, the concentrations used to determine smoking vs. nonsmoking status, and the use of cotinine levels as a marker of second-hand smoke exposure, need to be adjusted downward during pregnancy.
Clinical studies of nicotine replacement therapy during pregnancy

A number of single-dose studies of nicotine gum during pregnancy have been reported. Nicotine gum chewing typically increases maternal and fetal heart rate, reduces fetal heart rate variability, and does not change or increases fetal blood flow (reviewed in detail in Dempsey & Benowitz, 2001).

In a study of ad libitum nicotine gum use for 5 days, 19 pregnant smokers took an average of five to eight pieces of 2-mg gum per day. Nicotine exposure was considerably less when nicotine gum was chewed than when cigarettes were smoked, and hemodynamic effects were less with gum than with smoking (Oncken et al., 1996). Neither cigarette smoking nor nicotine gum chewing increased umbilical or uterine resistance index; rather, both declined after nicotine exposure.

Several studies have examined nicotine levels and effects with transdermal nicotine administration during pregnancy. Oncken et al. (1997) studied 15 women who participated in a crossover comparison of ad libitum cigarette smoking vs. 21-mg patches, each for 8 hours. Maternal peak plasma nicotine concentrations during patch use averaged 16 ng/ml. Patch use was associated with increased maternal heart rate over time, but the increase was not different from that observed during smoking. Both smoking and patch use were associated with small increases in the resistance index in the uterine artery and a small decrease in the resistance index in the middle cerebral artery, but the smoking and patch conditions were not different from one another. Loss of heart rate reactivity was observed in one of the women while using the patch vs. seven of the women while smoking cigarettes. The loss of heart rate reactivity with patch use appears to be associated with an increase in fetal heart rate and is likely to represent an autonomic neural effect of nicotine rather than fetal distress. Wright et al. (1997) studied six women receiving a 21-mg patch for 6 hours. Nicotine patch use had no effect on fetal heart rate or fetal blood flow parameters. Ogburn et al. (1999) studied 21 pregnant smokers who received a 22-mg nicotine patch daily for 4 days during a supervised period of nonsmoking. Average afternoon plasma nicotine concentration ranged from 11.8 to 13.7 ng/ml while using the patch compared with 14.4 ng/ml ($SD=9.7$) when smoking. Baseline fetal heart rate was slightly but significantly lower while using the nicotine patch compared with smoking, but no difference was found in umbilical artery blood velocity or fetal reactivity. Schroeder et al. (2002) reported further data on the same women who continued 22-mg nicotine patch use for 8 weeks. Of the 21 women, 8 completed patch use without smoking for 8 weeks; 5 women discontinued the patch due to skin irritation. Serial ultrasound studies were performed on the eight women who completed patch use and showed no significant effects on gestational weight gain and no abnormal nonstress tests. These data are reassuring in finding no adverse hemodynamic effects of transdermal nicotine during pregnancy.

We are aware of only one clinical trial of nicotine replacement therapy in pregnant smokers. Wisborg et al. (2000) studied 250 pregnant women who smoked 10 or more cigarettes per day after the first trimester. The average was 14 cigarettes per day. The women received 15-mg nicotine patches (16 hours per day) for 8 weeks, followed by 10-mg patches over 16 hours for 3 weeks, or placebo. All women received moderately intensive smoking cessation counseling. The trial found no significant benefit of nicotine patches on smoking cessation. Cessation rates for nicotine vs. placebo-treated women were no different: 28% and 25%, respectively, at the fourth prenatal visit, and 15% vs. 14%, respectively, 1 year postpartum. Of note, however, the salivary cotinine levels at 8 weeks were similar in patch users (153 ng/ml) and in placebo-treated women (174 ng/ml). Because the patch users were receiving nicotine from the patch, the observation that their cotinine levels were similar to those of placebo patch wearers means that the nicotine patch users were taking in less nicotine from cigarette smoke compared with the placebo patch users. Thus, they must have been smoking fewer cigarettes or smoking less intensively. Most important, the birth weights of babies born to the patch-treated mothers was significantly higher (3,539 grams) compared with the birth weights of babies born to the placebo-treated mothers (3,381 grams; 95% CI = 25–291 grams). This observation suggests that reduced smoking while using concomitant nicotine replacement therapy may ameliorate the growth-retarding effects of cigarette smoking.

The reasons why nicotine replacement therapy did not work in the Wisborg trial may be related to the rapid metabolism of nicotine during pregnancy. It may well be that 15-mg nicotine patches are not adequate for a woman who metabolizes nicotine much faster compared with a nonpregnant woman. Another possibility is that these women were highly dependent smokers, and that nicotine patches, especially at lower doses, are not effective in treating highly dependent smokers—as compared with the benefit of 15-mg patches in less dependent smokers. Further trials are needed using different doses and other forms of nicotine replacement therapy.

Recommendations for nicotine replacement therapy to aid smoking cessation during pregnancy

Our review indicates that the risk of cigarette smoking during pregnancy is far greater than the risk of exposure to pure nicotine. The use of nicotine
replacement therapy is probably not without risk, although the magnitude of risk to the mother and fetus is unknown. On balance, the use of nicotine replacement therapy to aid smoking cessation during pregnancy seems reasonable. An unanswered question is whether nicotine replacement therapy in pregnancy is effective. The one published study of nicotine patches suggests that, at least at the 15-mg dose, transdermal nicotine is not effective in pregnant smokers (Wisborg et al., 2000). It is hoped that ongoing clinical trials will answer the question of efficacy in general. In the meantime, if a woman is unable to quit smoking despite behavioral therapy (and is, therefore, highly addicted), nicotine therapy should be considered.

The FDA pregnancy rating for nicotine gum is category C and for nicotine patches, inhaler, and nasal spray, category D (Table 3). The manufacturer’s warning states that pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. Of course, treatment with nicotine replacement therapy during pregnancy requires that the mother be well informed about the potential risks vs. benefits.

The following suggestions are made based on the available data on mechanisms of toxicity and on pharmacokinetic and pharmacodynamic considerations. Our recommendations have not been tested empirically and should be tested in future studies.

1. It is recommended that nicotine replacement therapy be used in combination with behavioral therapy. Many studies have shown that the combination of medication and behavioral therapy provides greater benefits than either alone (Fiore, Bailey, & Cohen, 1996). All available resources should be used to promote cessation in the individual pregnant smoker because of the high risk of adverse pregnancy outcome caused by smoking.

2. Selection of the dose of nicotine for a pregnant smoker should be guided primarily by evidence of the level effective to achieve cessation. However, because a dose-response relationship appears to exist between nicotine and the risk of fetal neurotoxicity, the lowest dose of nicotine that is effective for achieving cessation should be used. Determining this dose may be difficult. For ad libitum nicotine medications, such as nicotine gum, nasal spray, inhaler, or lozenge, subjects tend to use the product when they are craving a cigarette. In most studies, the exposure to nicotine from such products is considerably less than the exposure to nicotine from cigarette smoking.

Determining the appropriate dose of nicotine with the use of nicotine patches is more difficult. Given the rapid metabolism of nicotine in pregnant smokers, it makes sense to start with the highest available nicotine patch dose. However, the use of therapeutic drug monitoring should be considered. That is, one can measure the cotinine level of a smoker during ad libitum smoking (before treatment) and then measure it again during nicotine therapy. A comparison of the two levels can be used to adjust the dose of the nicotine patch, aiming for a similar cotinine level to that observed while smoking. Using this type of drug monitoring, one could ensure that the nicotine dose is adequate and that the woman is not exposed to more nicotine from medication than from cigarette smoking previously. The use of expired carbon monoxide to monitor patient compliance with smoking cessation also should be considered. If the woman’s carbon monoxide level is not

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decreasing despite nicotine replacement therapy, it may be prudent to discontinue the therapy.

If one assumes that the efficacy of the various nicotine replacement products is similar (which appears to be the case in nonpregnant smokers), it makes sense for *ad libitum* dose forms to be the preferred initial therapy for most pregnant smokers because the daily dose of nicotine taken in from the *ad libitum* products is usually less than that from nicotine patches.

3. The nicotine delivery system should be individualized according to the patient’s symptoms. For example, in a woman with nausea and vomiting due to pregnancy, oral formulations may be poorly tolerated and a patch may be preferred.

4. When nicotine patches are used, it makes most sense to use the patch for 16 hours rather than for 24 hours. Available data suggest that 16-hour dosing is as effective as 24-hour dosing (Daughton et al., 1991). Patch use for 16 hours reduces daily exposure to nicotine and theoretically would minimize the risk of toxicity.

5. Pharmacotherapy should be initiated as early in pregnancy as possible. If smoking cessation occurs in the first 16 weeks of pregnancy, most or all of the adverse effects of cigarette smoking are avoided (MacArthur & Knox, 1988). The sooner cessation occurs thereafter, the better. Once it is clear that behavioral therapy is not working for a pregnant smoker, the use of pharmacotherapy should be considered.

6. In addition to the specific recommendations for nicotine therapy for pregnant smokers, we recommend the creation of a national registry for nicotine therapy during pregnancy. All efficacy studies could report their pregnancy outcome data to the registry. Individual patients who use nicotine therapy outside of an efficacy study also could be reported. Only through the systematic prospective collection of safety data from such registries can we better understand the safety and toxicity of nicotine replacement therapy during pregnancy, especially for uncommon to rare outcomes such as placental abruption or placenta previa.

**Bupropion during pregnancy**

The only nonnicotine drug approved for use in smoking therapy is bupropion. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine. Bupropion has been used as an antidepressant drug for many years. It is not teratogenic in animal studies conducted by the manufacturer, and limited reproductive data are available from human studies. Thus, the FDA pregnancy rating for bupropion is category B (see Table 3). We are unaware of any data on the kinetics and metabolism of bupropion during pregnancy.

Of possible relevance with respect to safety, bupropion is available in two formulations: immediate and sustained release. For smoking cessation, the sustained-release formulation (Zyban) is used, typically at maximal dose of 300 mg/day. For depression, bupropion (marketed as Wellbutrin) is available either as sustained release (100 mg or 150 mg per tablet) or immediate release (75 mg or 100 mg per tablet). Generic bupropion is available as an immediate-release formulation. For the treatment of depression, doses of up to 450 mg/day are recommended. Seizures have occurred (discussed more fully below) primarily with the use of immediate-release bupropion, in higher doses such as those used for depression.

The major side effects of bupropion in nonpregnant smokers are insomnia, dry mouth, and sympathetic nervous stimulation with mild hypertension. The experience with immediate-release bupropion as used for depression revealed a potential to produce seizures (0.1% incidence at 300 mg/day and 0.4% at 450 mg/day). These seizures were more common in people with a seizure risk or predisposition (history of prior seizures, head injury, alcoholism, sedative drug abuse) and in individuals with eating disorders (anorexia nervosa or bulimia). In trials of bupropion for smoking cessation, seizures have been extremely rare. However, if seizures were to occur during pregnancy, they could have extremely damaging effects on the fetus.

Two prospective observational studies of bupropion use during pregnancy involving a total of 450 women are ongoing (Chan, Hincharson, Selby, & Koren, 2003; GlaxoSmithKline, 2002). One is a worldwide pregnancy registry run by GlaxoSmithKline and the other (Chan et al., 2003) is being conducted by the Mother Risk Program in Toronto, Canada. Neither has reported the occurrence of seizures among pregnant women using bupropion.

GlaxoSmithKline has maintained a bupropion pregnancy registry since 1997. The majority (86.5%) of the women in the registry took bupropion for depression. Bupropion was used for smoking cessation by 11.5% of the women and for combined depression and smoking cessation by 2%. No data regarding the doses of bupropion or the duration of use were reported. To date, 668 pregnancies have been registered, and data are available for 333 pregnancy outcomes. Of the 333 pregnancy outcomes, 266 pregnancies had onset of exposure to bupropion during the first trimester, 50 during the second trimester, and 18 during the third trimester. With second and third trimester exposures, there were 66 live births, one spontaneous abortion, and one case of fetal demise. No birth defects were reported in babies of women who began bupropion use during the second and third trimesters.
Among the 266 pregnancies in which the mother began bupropion use during the first trimester, there were 216 live births, 31 spontaneous abortions, and 11 elective abortions (one elective abortion for trisomy 21 or Down's syndrome). Seven birth defects occurred among the live births. One newborn had bilateral club feet, one newborn had Klinefelter's syndrome, and five infants had a variety of cardiac defects. The observed birth defect rate for first trimester exposure was 3.9% (95% CI = 1.7–7.2). This is an observational study with no control groups. As defined by the Centers for Disease Control criteria for birth defects, the baseline rate for birth defects in the general population is 3% (range = 2%–5%) (GlaxoSmithKline, 2002). The Collaborative Perinatal Project (a large prospective pregnancy outcome study) reported a baseline frequency of 5%/7% for birth defects. At the present time, the “sample size of the registry is of insufficient size to reliably compute a birth defect risk, and no conclusions can be made regarding a possible teratogenic risk of Bupropion” (GlaxoSmithKline, 2002, summary statement by the Advisory Board).

The GlaxoSmithKline registry also accepts retrospective reports (outcomes of pregnancies known at the time of the report), but, appropriately, these data are not included in calculation of birth defect rates. Eleven birth outcomes with birth defects have been reported to the registry, all involving first trimester exposure to bupropion. Many of these defects involved multiple defects, and karyotyping was reported for only two outcomes (karyotyping was normal for both). Two of the retrospective cases involved hypoplastic hearts. Retrospective data are useful for identifying unusual or unique defects or a large increase in an uncommon birth defect. Multiple reports of the same unique or unusual birth defect associated with a medication not formerly used during pregnancy would prompt concern about an association between the birth defect and the exposure. The GlaxoSmithKline retrospective birth defect data are not unique, unusual, or rare. No conclusions can be drawn from these retrospective data.

The spontaneous abortion rate among women who used bupropion during the first trimester was 12% (prospective cohort). The reported cumulative estimated risk of spontaneous abortion in the general population is 14%/22% (similar to that observed with use of bupropion) (Kline, Stein, & Susser, 1989).

The Mother Risk Program in Toronto, Canada, also is conducting a prospective observational study of bupropion use during pregnancy (Chan et al., 2003). Preliminary results have been published. Data are available for 81 pregnancy outcomes. In 56 live births, no major malformations occurred. There were 16 miscarriages and 8 therapeutic abortions. The majority (69%) of the pregnant women took bupropion for depression, whereas 31% used it for smoking cessation. No dose or duration of use data were given. The miscarriage rate among those taking bupropion for depression was 21%, compared with 16% for those using it for smoking cessation. Women who took bupropion for smoking cessation reported that they had smoked fewer cigarettes per day compared with their prepregnancy smoking rate, and 40% quit smoking completely. The authors stated that these were preliminary findings and no definitive conclusions could be drawn.

These limited birth defect data suggest that the use of bupropion during pregnancy is safe, particularly if the alternative is smoking. No data indicate whether bupropion is more or less toxic than nicotine replacement therapy. The following recommendations are made with respect to the use of bupropion during pregnancy:

1. The efficacy of bupropion as an aid to smoking cessation during pregnancy is unknown. Based on its efficacy in smokers who are not pregnant, bupropion should be considered if a woman is unable to quit smoking despite behavioral therapy.

2. Pregnancy outcome data from bupropion efficacy studies or from individual use should be reported to the GlaxoSmithKline pregnancy registry (1-800-336-2176, toll free; or 1-910-256-0549, call collect) or to the Mother Risk Program (1-800-670-6126, selection 3, leave message).

3. The greatest concern with the use of bupropion is the risk of seizures. Prenatal care providers should apply the same contraindications as those used for nonpregnant adults, with the following caveat: bupropion should be stopped if the woman has a history of pre-eclampsia, develops any signs of pre-eclampsia, or develops any other pregnancy conditions that predispose her to seizures. Also, because of the increased incidence of seizures with bupropion use among women with eating disorders, it would be prudent for pregnant women with severe nausea and vomiting not to use bupropion.

**Nicotine replacement therapy vs. bupropion as pharmacotherapy for smoking cessation during pregnancy**

Nicotine has an FDA pregnancy classification of C or D, whereas bupropion has a classification of B (see Table 3). Based on the FDA classification, one might recommend bupropion use over nicotine replacement therapy. It should be recognized, however, that there are hundreds of animal studies of nicotine in pregnancy and of cigarette smoking and pregnancy. Relatively few studies on bupropion and pregnancy have been conducted. The FDA category C or D for nicotine is a result of considerable research in animals and of the known deleterious effects of cigarette smoking on reproduction. Cigarette smoking or nicotine does not appear to be a teratogen in the strict
sense of the word (i.e., producing anatomical defects) (Dempsey & Benowitz, 2001). The GlaxoSmithKline registry and the Mother Risk Program are collecting teratogen data. We know less about bupropion and reproduction than we know about nicotine and reproduction. We should not interpret the lack of data regarding bupropion as a lack of risk. No recommendation is made as to which pharmacotherapy (nicotine or bupropion) is preferable. The choice between nicotine replacement therapy and bupropion should be based mainly on the mother’s preference and on contraindications regarding bupropion.

Nicotine replacement therapy and breast feeding

Although breast feeding is strictly speaking not part of pregnancy, the issue of nicotine replacement therapy beyond the end of pregnancy, and in particular to prevent relapse to smoking postpartum, is clearly relevant. The dose of nicotine taken in by an infant from breast milk is the mathematical product of the volume of milk consumed and the concentration of nicotine in the milk. In neonates, the volume of milk ingested is about 900 ml/day, increasing to 1,500 ml/day as the baby grows. Nicotine distributes rapidly from the maternal bloodstream to and from breast milk (Dahlstrom, Lundell, Curvall, & Thapper, 1990; Luck & Nau, 1985). The mean elimination half-life of nicotine is similar in breast milk and in serum. Therefore, the level of nicotine in breast milk is highly dependent on how many cigarettes have been smoked since the last feeding and on the time of the last cigarette prior to feeding. The same would be true for use and timing of the last dose of nicotine medication.

When the mother smokes a cigarette, the route of nicotine exposure differs between the mother and the baby. The mother’s exposure is via the lungs, whereas the baby absorbs the nicotine through the gastrointestinal tract. After inhalation into the lungs, the full dose of nicotine is absorbed. However, considerable first-pass metabolism of nicotine occurs after oral administration (metabolism by the liver before entry into the systemic circulation). In adults, the systemic bioavailability of nicotine after oral administration is 30%–40% (Benowitz, Jacob, Denaro, & Jenkins, 1991). The oral bioavailability of nicotine in the infant is not known but is likely to be much less than 100%.

The concentrations of nicotine in breast milk and serum are highly correlated (Dahlstrom et al., 1990; Luck & Nau, 1985). However, nicotine is present in higher concentrations in milk than in serum (ratio = 2.5–2.9). The ratio is higher because the pH of breast milk is relatively acidic (pH = 6.8–7.0) compared with serum (7.4). Nicotine is more highly ionized and, therefore, partitions into the more acidic medium.

The dose of nicotine taken by the infant from breast milk can be estimated using the pharmacokinetic data described above. Assume that the concentration of nicotine in the serum of a heavy smoker averages 50 ng/ml (this is on the high end of levels seen in smokers of 20 or more cigarettes per day). One can assume a nicotine level of about 20 ng/ml for a nicotine patch user. If the baby drinks 0.9 liters of milk per day and one assumes a ratio of nicotine in milk to serum of 2.5, this means an ingestion of 113 μg nicotine per day by the baby of a smoker or 45 μg per day by the baby of the patch user. For a 4.5-kg baby, this would amount to 25 μg/kg/day and 10 μg/kg/day, respectively.

Using the more direct approach of measuring nicotine concentrations in the milk of individual mothers who smoked cigarettes and estimating milk consumption by weighing their infants before and after a feeding, Dahlstrom et al. (1990) determined an average daily nicotine dose of 6 μg/kg/day. Because the infant is taking nicotine orally with some degree of first-pass metabolism, the systemic dose is probably even less than is estimated by these methods. In contrast, nicotine intake in a 70-kg adult smoking 20 cigarettes per day or using a 21-mg nicotine patch is about 300 μg/kg/day. Thus, with a maternal exposure consistent with full-dose nicotine replacement (patch) therapy, the daily exposure normalized for the weight of the infant is 30 times lower than the exposure of the mother. Serum concentrations of nicotine have been measured in infants of breast-feeding mothers and were found to be quite low (range = 0–1.6 ng/ml) with an infant-to-maternal serum ratio of 0.06, supporting the idea that infant exposure is quite low (Luck & Nau, 1985).

Thus, the exposure of the infant to nicotine from a mother using nicotine replacement therapy is quite small compared with that of an adult smoker or compared with an adult using nicotine replacement therapy. It is unlikely that the low level of exposure is hazardous to the infant. In contrast, good evidence indicates that exposure to environmental tobacco smoke by the respiratory route is hazardous to the infant. Provision of nicotine replacement therapy to the mother, resulting in her not smoking, would be of great potential benefit to the infant because of reduced exposure to harmful second-hand smoke. On balance, the benefits of breast feeding and smoking abstinence during the postpartum period greatly outweigh the risks of nicotine replacement therapy in the postpartum period.

Breast milk production is lower in smokers compared with nonsmokers (Selby et al., 2001). The components of cigarette smoke responsible for the reduced milk production are unknown. If something other than nicotine is responsible, then nicotine
replacement therapy to aid smoking cessation postpartum may have the additional benefit of preserving breast milk production.

The formulation of nicotine replacement therapy may affect the level of nicotine in breast milk. Transdermal nicotine would provide a steady level of nicotine in plasma and thus in breast milk, and the mother could not control the level of nicotine in the breast milk except by changing the strength of the patch. Mothers who use nicotine medications intermittently might minimize the nicotine in their milk by prolonging the duration between nicotine administration and breast feeding.

**Bupropion and breast feeding**

Several case reports and one unpublished study have examined bupropion and breast feeding (Baab, Peindl, Piontek, & Wisner, 2002; Briggs, Samson, Ambrose, & Schroeder, 1993; Haas, Kaplan, Barenboim, Jacob, & Benowitz, 2004). Bupropion and its metabolites were undetectable in the plasma of three infants of breast-feeding mothers who were chronically taking bupropion for depression (Baab et al., 2002; Briggs et al., 1993).

Haas et al. studied 10 breast-feeding mothers who were discontinuing breast feeding (Haas et al., 2004). The mothers took bupropion and pumped their milk three times per day during the study period. After 7 days of sustained-release bupropion, the mothers were assumed to be at a steady state. Samples of serum and breast milk were obtained and analyzed quantitatively for bupropion, hydroxybupropion, erythrohydroxybupropion, and threo hydrobupropion. The average breast milk bupropion level was 45 ng/ml (range = 4.2–168.3), which was less than 0.2% of the weight normalized maternal dose of bupropion.

The metabolites of bupropion are known to have pharmacological activities similar to or less than those of bupropion. Haas et al. calculated the infant daily dose of bupropion based on the molar sum or bupropion and its three metabolites in breast milk (Haas et al., 2004). They calculated an infant daily dose that was 2% of the maternal weight normalized dose of bupropion. An infant dose of less than 10% of maternal dose of a drug has been used as a guideline for drug safety during breast feeding (Bennett, 1996). The mothers in this study were not breast feeding their infants while taking bupropion; thus, no data are available regarding plasma or urine levels in infants.

Data summarized here suggest that breast-feeding mothers can be included in efficacy studies of bupropion for relapse prevention or smoking cessation in the postpartum period. Further studies of bupropion that include breast-feeding mothers should document infant exposure to bupropion and metabolites by analyzing infant plasma samples for bupropion and its metabolites.

**Conclusion**

Cigarette smoke contains thousands of chemicals, many of which are reproductive toxins. The foremost toxin in cigarette smoke is carbon monoxide, a potent fetal toxin. Nicotine has been shown to be toxic to the developing fetus in animal studies. Although the use of nicotine replacement products may not be completely without risk, the risk is certainly much less than that of cigarette smoke. It is reasonable to consider the use of nicotine replacement therapies as an adjunct to smoking cessation in pregnant women who cannot quit smoking with behavioral treatments alone. Available clinical trial data suggest that nicotine replacement therapy is safe during pregnancy, although its efficacy in aiding cessation has not been demonstrated. This may be because of inadequate doses or inappropriate selection of nicotine dose form for the highly addicted pregnant smoker. Recommendations for smoking cessation therapy include the use of intermittent delivery formulations because these would be expected to give a smaller daily dose than continuous delivery formulations such as the patch. However, some smokers—because of nausea and vomiting during pregnancy—may be unable to tolerate oral formulations, and in that case patch use is preferred. If patches are used, it is recommended that they be used for 16 rather than 24 hours, to minimize total daily exposure to the fetus. The initial selection of the strength of the patch should be similar or higher than the patch strength that would have been selected for a nonpregnant female. It is also suggested that therapeutic drug monitoring be evaluated as a way to optimize the efficacy of nicotine replacement therapy while minimizing potential toxic exposures. It is recommended that all patients treated with nicotine replacement therapy be reported to a pregnancy registry that collects obstetrical outcome data, so as to better determine the overall safety and risk profile of nicotine replacement therapy during pregnancy. We recommend the use of nicotine replacement therapy for smoking cessation for women who breast feed. The dose of nicotine delivered in breast milk from nicotine replacement therapy is small, the risk to the baby is minimal, and the benefit of a smoke-free environment is large.

Bupropion is an alternative pharmacotherapy to nicotine replacement therapy. Bupropion is contraindicated in women with risk factors for seizures or a history of eating disorders. It also is recommended that all patients be reported to a bupropion registry.

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