The Role of Nicotine in the Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease
Implications for Dangers of E-Cigarettes

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Abstract

Use of e-cigarettes, especially among the young, is increasing at near-exponential rates. This is coupled with a perception that e-cigarettes are safe and with unlimited advertising geared toward vulnerable populations, the groups most likely to smoke or vape during pregnancy. There is now wide appreciation of the dangers of maternal smoking during pregnancy and the lifelong consequences this has on offspring lung function, including the increased risk of childhood wheezing and subsequent asthma. Recent evidence strongly supports that much of the effect of smoking during pregnancy on offspring lung function is mediated by nicotine, making it highly likely that e-cigarette use during pregnancy will have the same harmful effects on offspring lung function and health as do conventional cigarettes. In fact, the evidence for nicotine being the mediator of harm of conventional cigarettes may be most compelling for its effects on lung development. This raises concerns about both the combined use of e-cigarettes plus conventional cigarettes by smokers during pregnancy as well as the use of e-cigarettes by e-cigarette–only users who think them safe or by those sufficiently addicted to nicotine to not be able to quit e-cigarette usage during pregnancy. Thus, it is important for health professionals to be aware of the risks of e-cigarette usage during pregnancy, particularly as it pertains to offspring respiratory health.

Keywords: lung development; pulmonary function; asthma; nicotinic receptor

In the last few years, use of e-cigarettes has increased rapidly, especially among middle school and high school students (1). This increase in use is coupled with a perception of safety that has yet to be proven. Although e-cigarettes are obviously safer than conventional cigarettes, there are several areas of concern about e-cigarette safety. Concerns include the potential for lifetime addiction to nicotine, eventual transition to conventional tobacco use, and the health effects of nicotine by itself. Surveys also suggest that increasing numbers of people are using e-cigarettes alone (1–3). Thus, in considering the safety of e-cigarettes, it is not just a matter of comparing the safety of e-cigarettes to conventional cigarettes; safety must be compared with the use of no tobacco-derived products at all.

One critical area of e-cigarette safety is its continued use during pregnancy. The combination of the addictive nature of nicotine with the perception of relative safety suggests that e-cigarette use during pregnancy will likely increase (4). Although nicotine replacement therapy has been used during pregnancy (5, 6), on the basis that nicotine alone will be safer than conventional cigarette use, the potential continued use of e-cigarettes by e-cigarette–only users during pregnancy raises heightened safety concerns of e-cigarette use during pregnancy. The fact that about half of conventional cigarette users continue to smoke while pregnant (7, 8) suggests that significant numbers of e-cigarette users will also continue e-cigarette use during pregnancy, thus exposing the fetus to nicotine. As described later, the developing lung is particularly sensitive to the effects of nicotine, suggesting that e-cigarette use during pregnancy may affect lung development.

E-Cigarette Usage and Characteristics

E-cigarettes, also referred to as electronic nicotine delivery devices, consist of a battery and heating element that heat a nicotine solution (e-juice) to deliver vaporized

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nicotine to the user. The nicotine solution typically contains propylene glycol or vegetable glycerin as a vehicle for the nicotine and various flavoring agents. The heating element can be combined with nicotine solution (cartomizers) or separate from the solution. Newer designs provide variable voltage, such that higher voltage can deliver higher levels of nicotine (9). Users can purchase mass market brands sold by tobacco companies (e.g., Blu made by Lorilard, Greensboro, NC; Vuse made by Reynolds, Winston-Salem, NC); from larger independent companies (NJoy made by NJoy, Inc., Scottsdale, AZ); or more custom designs assembled from batteries, vaporizers, and liquid tanks sold by small vape shops and online. There are literally thousands of choices and untold numbers of flavors and nicotine liquids, all with essentially no regulation at this point in time.

Critical elements in considering the health effects of the type of e-cigarette used are potential dose of nicotine delivered, potential contaminants, constituents, and heat-generated byproducts. For this Perspective, the focus will be on potential effects of nicotine, which is present in the vast majority of e-cigarettes. Recent studies by Talih and colleagues (9) demonstrate that nicotine delivery by e-cigarettes can be modeled primarily as a concentration of nicotine concentration in the e-juice, temperature of the vaporizer, and volume of the puff. In practical terms, this means that depending on the puff volume and nicotine concentration, e-cigarettes deliver as high or higher amounts of nicotine as do conventional e-cigarettes (9, 10). As e-cigarette users become more experienced, they tend to take higher-volume puffs and obtain higher levels of nicotine equaling the nicotine levels achieved by smokers of conventional cigarettes (9, 10).

Concern about the potential health effects of e-cigarettes has been driven by recent studies showing an almost exponential increase in their use (11) and the use of e-cigarettes beginning to exceed use of conventional cigarettes. For example, in one study, use of tobacco products in high school students in Hawaii was 17% (e-cigarettes only), 12% (dual use), and 3% (cigarettes only) (3). Between 2011 and 2013, the number of never-smoking youth who used e-cigarettes increased threefold, from 79,000 to more than 263,000 (11). Intention to smoke conventional cigarettes was 43.9% among ever–e-cigarette users and 21.5% among never users (12). Seventy-one percent of adolescent e-cigarette users consider e-cigarettes less harmful than conventional cigarettes (13). Recent prospective studies show the use of e-cigarettes significantly increases likelihood of conventional cigarette use (14, 15). Remarkably, a recent survey of pregnant women showed nearly 40% did not realize e-cigarettes contained nicotine or could be addictive, and 40% believed them to be less harmful than traditional cigarettes (4).

At present there is little regulation of e-cigarette advertising and marketing, and e-cigarette companies are using similar strategies of advertising as previously used by conventional cigarette companies, with significant advertising focused at younger potential users (16–18). This period of unregulated advertising and marketing has the potential to create a new generation of women of childbearing age addicted to nicotine. In this Perspective, we concentrate on the potential risks of maternal e-cigarette use during pregnancy on offspring lung development. Other areas of concern about e-cigarette safety have been recently reviewed by Grana and colleagues (19).

Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease

Prevalence of Smoking during Pregnancy

Smoking during pregnancy is the largest preventable cause of low birth weight, prematurity, intrauterine growth restriction, and perinatal mortality (20, 21); sadly, more than 50% of smokers who become pregnant continue to smoke (7, 8). The incidence of smoking during pregnancy varies widely across the United States, with at least 12% of pregnant women continuing to smoke (22). Birth cohort studies from Europe have shown an incidence ranging from 17 to 39% of pregnant smokers (23). Smoking in pregnancy is a unique morbidity in that smoking is addictive, heavily advertised (24, 25), and, as discussed below, certain genotypes significantly increase the likelihood of nicotine addiction/failure to quit (26, 27). There are also complex societal underpinnings to smoking in pregnancy, because teen pregnancy, low income, low education, and living with a smoker are important factors increasing the odds of smoking during pregnancy, with a gradient linking the number of risk factors to the percentage of smoking (28). The estimated number of pregnant smokers is also likely underestimated; studies have shown at least 20% of pregnant smokers lie about their habit (29), which is even more concerning in the context of vapers, who may already believe vaping to be safe during pregnancy (4). Because the major addictive component of cigarette smoke is nicotine, these data strongly imply that at least 50% of vapers will continue to vape while pregnant despite best efforts at cessation (7, 8).

Effect of Maternal Smoking during Pregnancy on Offspring Lung Function and Lung Disease

Smoking during pregnancy adversely affects fetal lung development, causing offspring to fail to reach maximum lung function in childhood with subsequent lifelong decreases in pulmonary function (30, 31). At birth and before any significant exposure to postnatal smoke, infants born to smokers show decreased pulmonary function tests (PFTs), with decreased respiratory flows and respiratory compliance and altered tidal breathing patterns (31–33). These changes lead to increased wheezing, hospitalization for respiratory infections, and increased childhood asthma (34). Several birth cohort studies with longitudinal PFT data have demonstrated that smoking during pregnancy is associated with persistent PFT deficits in expiratory flows. A 21-year follow up of mothers and their children recruited into a longitudinal prebirth cohort demonstrated in 2,409 adults that there were continued decreases in the FEV_1 and forced expiratory flow (FEF) between 25 and 75% of FVC (or mid–mean expiratory flow [MMEF]) in men with *in utero* smoke exposure after accounting for maternal smoking after pregnancy (30). Moshammer and colleagues (35) studied more than 20,000 children aged 6 to 12 years old across Europe and North America and found *in utero* smoke was associated with decreases

in lung function parameters, with a 4% lower MMEF corresponding to a 40% increase in risk of poor lung function (defined as MMEF $<$ 75% of expected). This study also showed that small decreases in the MMEF in the general population of healthy school children were associated with a relevant increase in the number of children with clinical poor lung function. Cunningham and colleagues (36) studied 8,800 children 8 to 12 years of age and showed reduced FEFs if mothers smoked during pregnancy; the decreased flows were not explained by postnatal smoke exposure. Although reductions in respiratory flows are the most commonly reported effect of maternal smoking on respiratory function, alterations in tidal breathing (32, 33) and decreased compliance (37–39) have also been frequently reported.

The 1986 United States Surgeon General's report stated that there was sufficient evidence that involuntary or secondhand smoke was associated with adverse respiratory health effects in children. Before and since then, many studies have been published showing increased wheezing, increased hospitalizations for respiratory infections, increased bronchitis, and increased incidence of childhood asthma in children born to smoking mothers (40–43). Several recent large studies have been able to separate out the effect of *in utero* versus postnatal smoke on childhood respiratory health. A pooled analysis of eight European birth cohorts (23) involving 21,000 children demonstrated that smoking only during pregnancy was associated with wheeze at 4 to 6 years of age with an adjusted odds ratio (OR) of 1.39 (95% confidence interval [CI], 1.08–1.77) and with asthma at 4 to 6 years of age with an adjusted OR of 1.65 (95% CI, 1.18–2.31). A large meta-analysis of 79 prospective studies (44) found the strongest effect from prenatal maternal smoking was on asthma in children 2 years of age or younger (OR, 1.85; 95% CI, 1.35–2.53). Preterm delivery (i.e., before 37 weeks of gestation) is increased in pregnant smokers and interrupts normal lung development/alveolar formation in itself even without the additional adverse effects of nicotine (31). As discussed later, animal studies demonstrate that nicotine is the key mediator of *in utero* smoke exposure on lung development, so vaping during pregnancy will also have significant adverse effects on fetal lung development.

Genetic Influences on Likelihood of Smoking during Pregnancy and Relative Effect of Smoking on Fetal Outcomes

Recent studies have also indicated the key role of genotype relative to the development of asthma, sensitivity to maternal smoking, and difficulty in quitting smoking. Notably, several common polymorphisms are linked in terms of sensitivity of offspring to maternal smoking. In particular, common deletions or structural polymorphisms in the glutathione transferase genes, which play a key role in antioxidant defenses, increase both the risk of asthma and sensitivity of the fetus to maternal smoking (45, 46). Similarly, the common structural polymorphism of the α_5 nicotinic receptor, in which residue 398 is mutated from an Asp to an Asn (rs16969968), increases nicotine addiction, makes quitting more difficult, and increases the risk of lung cancer and chronic obstructive pulmonary disease (26, 47). Consistent with this, we recently demonstrated that the maternal genotype for rs16969968 significantly increased the effects of maternal smoking on offspring pulmonary function (32). Pregnant mothers with this genotype who vape would also potentially have an increased risk of vaping having significant effects on offspring pulmonary function. Thus, it is likely that the same genotypes that increase risk of smoking during pregnancy will increase the risk of vaping during pregnancy and also enhance the degree to which vaping during pregnancy affects lung development and offspring lung function.

Effects of Prenatal Nicotine Exposure on Lung Development and Offspring Respiratory Disease

Effects of Prenatal Nicotine Exposure on Lung Development and Function

Studies on the effects of prenatal nicotine on lung development have primarily been performed in animals, but comparison of the effects induced by prenatal nicotine alone in animal models versus sequelae of maternal smoking during pregnancy indicate which effects are mediated by nicotine. Studies of the effects of nicotine on lung development have been performed in mice, rats, sheep, and monkeys, with striking similarities of observed effects between species. As described above, the clearest, most consistently measured effect of maternal smoking during pregnancy on offspring respiratory health is decrease in FEF (30, 33, 35, 36). In both monkeys and mice, exposure to prenatal nicotine alone, at levels similar to that of smokers, causes similar decreases in FEF (48–50). In one study, pregnant rhesus monkeys were infused subcutaneously with nicotine at 1.5 mg/kg/d or saline from Day 26 to 160 of gestation (term is 165 d). Cesarean sections were done at 160 days and pulmonary function measured at 24 hours of age. The prenatal nicotine exposure caused significant decreases in lung volume, FEV during the first 0.2 seconds, peak tidal expiratory flow during tidal breathing, and MMEF when compared with offspring of saline-treated control animals (49, 50). Pulmonary resistance was significantly increased; static and dynamic lung compliance were decreased, although not significantly; and there were substantial increases in airway collagen (Figure 1).

Studies in mice have suggested the potential mechanism by which prenatal nicotine exposure leads to decreased expiratory flow in offspring. *In vitro*, in embryonic murine lung explants, nicotine stimulated lung branching and dysanaptic lung growth in a dose-dependent fashion (51, 52), and this effect of nicotine was dependent on the presence of α7 nicotinic acetylcholine receptors (nAChRs) (51). This was further studied *in vivo* in a murine model of *in utero* nicotine exposure in which pregnant mice were treated with nicotine from gestation Day 7 to postnatal Day 14. This combination of pre- and postnatal nicotine exposure (which would be most comparable to mid- to late-gestation exposure in a human pregnancy) caused significant decreases in FEF in the offspring, just as observed in humans and monkeys (48). A primary mediator of this effect again appeared to be the α7 nAChR, as prenatal nicotine exposure strongly up-regulated levels of α7 nAChR in airways (Figures 1A and 1B), and the effect of nicotine was lost in α7 nAChR knockout mice (48). The critical period for perinatal nicotine exposure to alter FEFs was further studied by exposing mice to

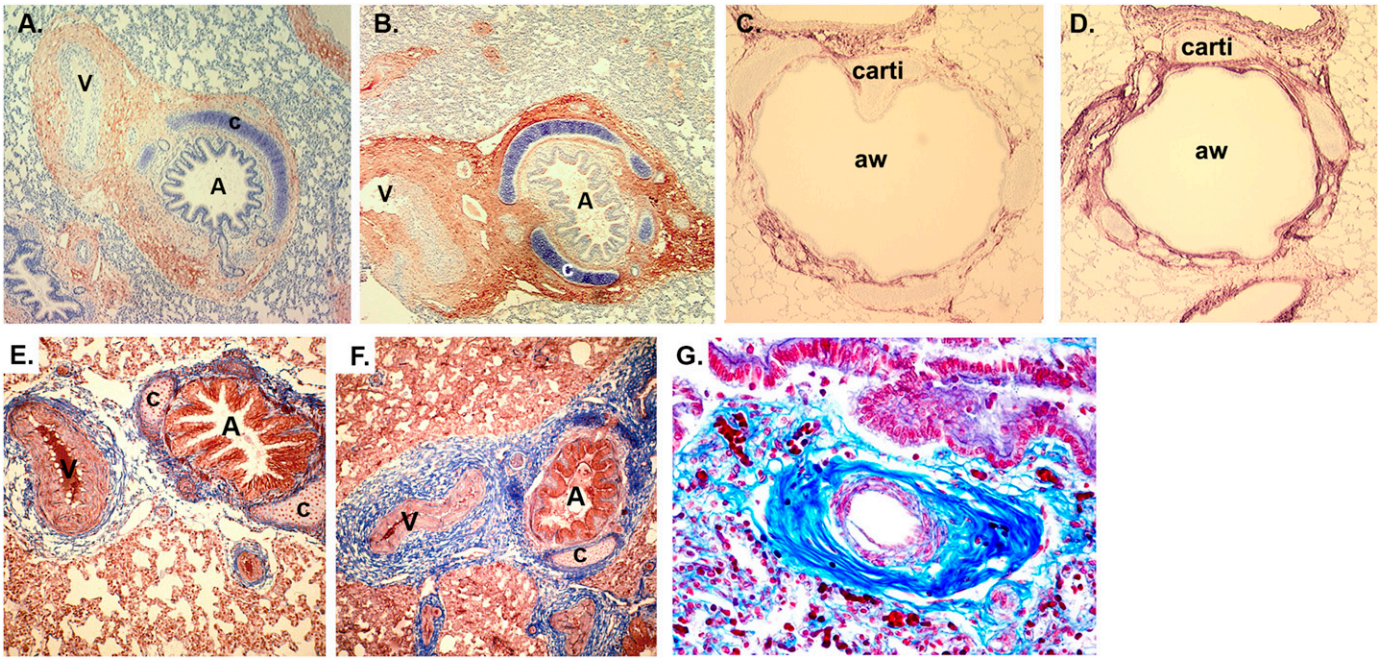

Figure 1. Prenatal nicotine exposure increases α7 nicotinic acetylcholine receptors (nAChRs), collagen, and trichrome staining in a parallel manner (56, 57). (*A*) α7 nAChR immunoreactivity (*red*) in lung from control 134-day fetal monkey. Magnification, ×100. (*B*) α7 nAChR immunoreactivity (*red*) in lung from nicotine-exposed 134-day fetal monkey. Magnification, ×100. (*C*) Collagen III immunostaining of control 134-day fetal monkey lung. Magnification, ×100. (*D*) Collagen III immunostaining of nicotine-treated 134-day fetal monkey lung. Magnification, ×100. (*E*) Masson trichrome–stained control 134-day fetal monkey lung. Magnification, ×100. (*F*) Masson trichrome–stained nicotine-exposed 134-day fetal monkey lung. Magnification, ×100. (*G*) Trichrome-stained human lung from infant who had sudden infant death syndrome whose mother smoked during pregnancy. Magnification, ×200. Reprinted by permission from Reference 60. A = airway; aw = airway; c = cartilage; carti = cartilage; V = vessel.

nicotine during gestation Days 7 to 21, gestation Days 14 to postnatal Day 7, and postnatal Days 3 to 15. Only exposure from prenatal Day 14 to postnatal Day 7 was effective in decreasing offspring FEF. This time period in mouse lung development corresponds to the tail end of the pseudoglandular period through the canalicular and saccular periods, but before most alveolarization has occurred (53, 54). This timing thus suggests a primary effect of nicotine on airway growth. This was confirmed by stereologic analysis of airway size and diameter, which showed increased number of airways of small diameter with nicotine treatment. Thus, prenatal nicotine exposure may lead to decreased FEF by simulating epithelial cell growth and lung branching to result in longer and more torturous airways, thereby forcing airflows through narrower tubes. This is consistent with effects of cigarette smoke, which Sekhon and colleagues (55) have shown to cause airway proliferation in rats.

The studies in mice and monkeys point to additional mechanisms of the action of nicotine on lung development. First, immunohistochemistry in mice, rats, and monkeys shows abundant expression of multiple nicotinic-receptor subtypes in developing lung. Particularly striking are high levels of α7 nAChR in airway epithelial cells and in fibroblasts surrounding airways and vessels (Figure 1A). Treatment of pregnant rhesus monkeys with low levels of nicotine designed to simulate the nicotine exposure of pregnant human smokers caused marked increases of levels of α7 nAChR in airway epithelial cells and fibroblasts in fetal monkey lung (Figures 1A and 1B). There were also increases in collagen and connective tissue in a similar distribution as the increase in α7 nAChR (Figures 1C–1F) (56–58). Similar effects of prenatal nicotine exposure increasing lung collagen were also seen in mice (48). The increased collagen and decreased elastin may underlie the decreased respiratory compliance observed in some studies in the offspring of mothers who smoked during pregnancy (37–39). Prenatal nicotine exposure also leads to thickening of walls surrounding airways and pulmonary vessels in monkeys (58), and this has also been reported in offspring of smokers (Figure 1G) (59, 60). In particular, the patterns of collagen expression observed in airways of offspring of smokers are strikingly similar to those observed in lungs of animals exposed just to nicotine (56–58) (Figure 1G). Morphologic alterations in lung caused by prenatal nicotine exposure also extend to alveoli, with simplification leading to increased alveolar volume but decreased alveolar surface area observed in both rats (61) and monkeys (56), and are again similar to reports of the effects of prenatal smoke exposure on alveolar structure (62–64) observed in rats, monkeys, and humans.

The proliferative effects of maternal smoking during pregnancy and prenatal nicotine exposure on the proliferation of pulmonary type II cells and pulmonary neuroendocrine cells are also similar. In animal studies, prenatal nicotine exposure has been shown to increase surfactant mRNA and protein in mice, rats, monkeys, and lambs (52, 56, 65, 66). Consistent with this, nAChRs are expressed on type II cells (56). This is also consistent with the increased levels of surfactant in amniotic

Table 1. Comparison of the Effects of Maternal Smoking during Pregnancy and the Effects of Nicotine Exposure from Animal Models during Pregnancy on Lung Development and Function

Category	Effect	Smoke Exposure	Nicotine Exposure	Smoke Exposure References	Nicotine Exposure References
Pulmonary function	Decreased forced expiratory flow	Yes	Yes	30–36	48–50
	Decreased compliance*	Yes	Maybe	37–39, 94	56
	Altered flow ratio†	Yes	Unknown	32, 33	
Respiratory illness	Increased airway reactivity/asthma/ wheeze‡	Yes	Yes	23, 31, 44, 82	48, 79–81
	Decreased arousal/increased apnea§	Yes	Yes	86, 87, 95	88–90
	Increased respiratory infections/ hospitalizations/altered immune function‖	Yes	Yes	40–43	96–98
Anatomic and cellular changes	Increased connective tissue/airway wall thickening	Yes	Yes	59, 60, 99	56–58
	Increased narrow and smaller airways	Yes	Yes	55	48, 51, 52, 79
	Altered alveolar geometry	Yes	Yes	56, 61	62–64, 100
	Increased type 2 cells/surfactant	Yes	Yes	67, 68	52, 56, 65, 66
	Increased NEB/PNEC	Yes	Yes	69, 70, 94	56, 101, 102
Mechanistic underpinnings	Oxidative mechanisms underlying effects	Yes	Yes	32, 45, 46	49, 78
	Respiratory effects modified by nAChR SNPs/knockouts	Yes	Yes	32	48, 51, 52
	Modified levels of nAChR expression	Yes	Yes	60	56, 89, 91, 92
General	Decreased birth weight¶	Yes	No	103, 104	49, 50, 103, 105, 106
	Prematurity	Yes	Yes	103, 107	103, 108–110

Definition of abbreviations: nAChR = nicotinic acetylcholine receptor; NEB = neuroepithelial bodies; PNEC = pulmonary neuroendocrine cells; SNP = single-nucleotide polymorphism.
*Most, though not all, studies show an effect. In animal studies there is a downward trend.
†Ratio of time to peak tidal expiratory flow to expiratory time.
‡In animal studies, increased airway reactivity is used as a surrogate for asthma and wheeze.
§Correlates of increased risk of sudden infant death syndrome in offspring of smokers.
‖Alterations in immune function in animals used as a surrogate for hospital admissions.
¶There is a downward trend in birthweight, but it is not statistically significant in most studies.

fluid of pregnant smokers (67, 68). Prenatal nicotine exposure also increases the numbers of pulmonary neuroendocrine cells and size of neuroepithelial bodies in monkeys and rodents (56), just as smoking during pregnancy increases the size and number of neuroepithelial bodies in offspring of smokers (69, 70). As for type II cells, this is consistent with expression of nAChR in pulmonary neuroendocrine cells (56, 71).

Oxidative mechanisms also appear to mediate both the effects of prenatal nicotine exposure on lung development and the effects of maternal smoking during pregnancy. Multiple reports demonstrate that prenatal nicotine exposure increases markers of oxidative damage (72–74), and, similarly, multiple reports also show that maternal smoking during pregnancy increases markers of oxidative damage (75–77). A fundamental role for reactive oxygen species in mediating the effects of both prenatal nicotine and maternal smoking is the ability of vitamin C supplementation during pregnancy to block both the effects of prenatal nicotine (49, 78) and maternal smoking (32) on lung development.

Effects of Prenatal Nicotine Exposure on Offspring Respiratory Disease

Data from animal studies on prenatal nicotine exposure also support a role of nicotine in smoking-induced lung disease, although this is more indirect, as we must rely on animal models for the human diseases. As discussed above, maternal smoking during pregnancy is linked to an approximately twofold increase in the risk of childhood asthma (23, 44). In mice, Wongtrakool and colleagues have shown that perinatal nicotine exposure increases airway reactivity (48). Similarly, prenatal nicotine exposure has also been shown to cause airway hyperreactivity in sheep (79) as well as increasing smooth muscle volume in distal bronchi. Rehan and colleagues have shown in rats that perinatal nicotine exposure increases methacholine-induced bronchial constriction in the offspring (80) and that this effect of nicotine can be passed on to subsequent generations (81). This suggests that nicotine exposure may increase the risk of asthma not just for the first generation of infants but also for generations to come. Such transgenerational effects have also been reported for the link between maternal smoking during pregnancy and asthma (82).

Finally, there is the well-described link between maternal smoking during pregnancy and the increased risk of offspring dying from sudden infant death syndrome (SIDS) (20, 83, 84). Although the causes of SIDS are multifactorial (85), the link between maternal smoking and

SIDs remains incontrovertible. In fact, with the success of the "Back to Sleep" movement (83), the importance of maternal smoking as a risk factor for SIDS has nearly doubled. The mechanism by which maternal smoking increases the risk of SIDS is not completely understood, but infants born of smoking mothers show increased apneic events and decreased rates of arousal in response to the apneic events (86, 87). Further supporting the key role of nicotine, in a Swedish study of 600,000 pregnancies, the use of smokeless tobacco in pregnancy was associated with an even higher incidence of neonatal apnea than was conventional cigarette use (88). The key role for nicotine in mediating decreased arousal and increased apnea caused by maternal smoking is further supported by animal studies in both mice (89) and sheep (90), in which prenatal nicotine exposure blunts respiratory responses to hypoxia. Mechanisms for this may involve alterations in cholinergic signaling in brainstem, heart, and chemoreceptors induced by prenatal nicotine exposure (89, 91, 92).

Overall Comparison of Pulmonary Effects of *In Utero* Nicotine Exposure Versus Effects of *In Utero* Tobacco Product Exposure and Conclusions

As the data described above show, there is striking similarity between the effects of maternal smoking during pregnancy and the effects of prenatal nicotine exposure on offspring pulmonary function and respiratory disease. Although the data on the effects of nicotine alone derive primarily from animal studies, or can be inferred from the effects of smokeless tobacco, the striking similarity of findings in monkeys, mice, rats, sheep, and humans all support the direct effects of nicotine on lung development that mediate the deleterious effects of maternal smoking during pregnancy on offspring respiratory health. This comparison is summarized in Table 1, showing the comparable effects of conventional cigarettes and nicotine on lung development and disease. Thus, the findings summarized here strongly suggest that use of e-cigarettes during pregnancy will have the same effect on lung development and offspring lung health as does the use of conventional cigarettes.

The conclusion that nicotine mediates most of the effects of maternal smoking during pregnancy on lung development is supported not only by the similarity of effects but also by the similarity of underlying mechanisms of action. The effects of maternal smoking on lung development are mediated by nicotinic receptors, changes in airway geometry, effects on airway epithelial cell proliferation, and oxidative mechanisms. Similarly, animal models show that the effects of prenatal nicotine exposure are also mediated by these same mechanisms. Therefore, the likelihood that e-cigarettes affect lung development is supported by both descriptive and mechanistic data.

In expressing concerns about the effects of e-cigarettes on the developing fetus it is important to note that this is not a case of the lesser of two evils, as nicotine-replacement therapy during pregnancy (6, 93) for smokers is often considered. The safety of e-cigarettes during pregnancy must be compared with the use of no nicotine products during pregnancy, given the rapidly increasing numbers of e-cigarette–only users (1–3) and the addictive potential of nicotine that will likely drive a similar percentage of e-cigarette users to continue use during pregnancy, as is observed for smokers of conventional cigarettes. In addition, the perception of e-cigarettes as safe may also drive smokers to supplement cigarettes with e-cigarettes during pregnancy, thereby increasing nicotine exposure to the fetus.

Thus, in summary, the data presented here strongly support that e-cigarette usage during pregnancy will be as harmful to fetal lung development as is conventional cigarette usage. Limitations of this conclusion include a lack of comprehensive epidemiologic data on usage of e-cigarettes during pregnancy and limitations of animal models for asthma and SIDS. Nevertheless, the data are strong enough to raise major concerns, and it is hoped that education and regulation will prevent the effects of e-cigarettes on a new generation of infants. It is imperative that strong warnings about the dangers of e-cigarette use during pregnancy are imparted before this new generation of infants is affected. ■

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