

The Effect of *In Utero* Cigarette Smoke Exposure on Development of Respiratory Control: A Review

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Maternal cigarette smoking is the most modifiable risk factor for sudden infant death syndrome. Although the mechanism underlying the association between maternal smoking and sudden infant death syndrome is unknown, the effect of *in utero* cigarette smoke exposure on respiratory control development is speculated as the important causative mechanism. In human, several studies have linked maternal smoking and alterations in breathing pattern, ventilatory, and arousal responses in infants during the early postnatal age. Cigarette contains many compounds, but nicotine has been identified as the main culprit underlying changes in respiratory control. Further investigations in animal models have demonstrated that perinatal nicotine exposure results in alteration in baseline ventilation, ventilatory response to hypoxia, arousals, and autoresuscitation processes in developing animals. The mechanisms underlying the effect of nicotine exposure on respiratory control may be related to modulation of neurotransmitters and signal transductions mediating ventilatory control and arousal responses. Findings from these studies will help to understand how perinatal cigarette smoke exposure interferes with respiratory control development, and may lead to more effective preventive strategies and therapeutic intervention for this significant health problem.

Introduction

CIGARETTE SMOKING DURING PREGNANCY is associated with significant perinatal morbidity, including premature delivery, low birth weight, and other neonatal morbidities, and mortality. Maternal smoking is the most modifiable risk factor for sudden infant death syndrome (SIDS), which is the leading cause of death in the first year of life. Although the mechanism underlying the association between maternal smoking and SIDS is unclear, the effect of maternal smoking on respiratory control has been proposed as the important causative mechanism.

Cigarette contains numerous compounds, including nicotine, tars, and carbon monoxide.^{1,2} However, several studies suggest that nicotine is the main culprit underlying changes in respiratory control. The exposure of nicotine during early development is associated with neurochemical changes in the developing brain especially cardiorespiratory control centers of the brainstem. The resultant physiologic changes in maturation of respiratory control can lead to alteration of respiratory patterns, ventilatory response, arousals, and autoresuscitation. In this article, the relationship between maternal cigarette smoke and SIDS will be explored. Then, we will summarize studies that evaluate the effect of maternal cigarette smoke on respiratory pattern, ventilatory, and arousal responses in infants and neonates. Finally, we will review basic research assessing the effect of

perinatal nicotine exposure on development of respiratory control in animal models.

Maternal Smoking and SIDS

SIDS is the leading cause of death of infants beyond 1 month of age in the United States. After the American Academy of Pediatrics released the recommendation of supine position of infants in sleep in 1992,³ the Back to Sleep campaign launched in 1994 was met with dramatic reductions in SIDS over the next few years.⁴ With fewer infants sleeping prone at this time, the rate of decline in SIDS has experienced a plateau, and there is renewal of interest in the association between smoking and SIDS. In fact, *in utero* cigarette smoke exposure has been identified as one of the major risk factors for SIDS in many epidemiological studies.⁵⁻⁹ Studies conducted following Back to Sleep campaigns examining the relationship between maternal smoking and SIDS demonstrated that infants of smoking mothers have a 2-fold to 5-fold elevated risk of SIDS.⁶ More recent studies indicate the odd ratios ranging from 3.3 to 6.0, which are higher than previously reported.¹⁰ Prenatal and postnatal exposure to tobacco smoke adversely affects maternal and child health and secondhand smoke exposure has been linked causally with SIDS.¹¹ In 1992, the U.S. Environmental Protection Agency first noted this association, and both prenatal exposure and postnatal smoke exposure were listed as independent risk factors for SIDS in a

1997 California Environmental Protection Agency report.¹² Numerous studies have further strengthened this relationship. Prematurity is an independent risk factor for SIDS,^{13–15} and prenatal exposure to cigarette smoke may have profound effects on the respiratory pattern during sleep in this vulnerable population. The amount of maternal smoking during pregnancy and nursing has been shown to influence the risk of SIDS in the newborn in proportion.¹⁶ The risk of SIDS increases by a factor of 2 with moderate smoking and 5 with heavy smoking. Milerad et al. have demonstrated the presence of nicotine and cotinine in pericardial fluid in victims of SIDS.¹⁷ There is conflicting evidence in studies examining the relationship between location of smoking and the risk of SIDS. Although Mitchell et al.¹⁸ did not find any difference in risk, irrespective of whether smoking was claimed to have occurred in or out of the house, Klonoff-Cohen et al. found that passive smoking in the infant's room increased the risk of SIDS.¹⁹ This latter study also noted that increasing cigarettes as well as total number of smokers were associated with a dose-response effect for SIDS, and that nursing was protective for SIDS in nonsmokers, but not in smokers. In addition, household (paternal) exposure to tobacco smoke had an independent additive effect.

The pathophysiologic mechanism underlying the association between maternal smoking and SIDS is currently unknown. Several pathophysiologic mechanisms have been proposed as causative mechanisms especially respiratory control abnormalities. In the subsequent sections, we will review studies evaluating the effect of *in utero* cigarette smoke exposure on development of breathing control in both human and animal models.

Maternal Smoking and Baseline Ventilation and Ventilatory Response in Infants

Maternal smoking has been shown to affect resting ventilation, breathing drive, and the hypoxic ventilatory response in infants. Infants born to smoking mothers were found to have altered baseline ventilation with decreased tidal volume and increased respiratory rate.^{20,21} Assessment of ventilatory drive of infants of smoking mother revealed conflicting results. Ueda et al. demonstrated that infants of smoking mothers had a decrease in respiratory drive as demonstrated by reduction in occlusion pressure (P0.1) and attenuation of ventilatory response to hypoxia.²² In addition, there was a dose-dependent relationship between the number of cigarettes smoked by the mother and the scale of decrease in ventilatory drive.²² Paternal smoking had no effect on baseline ventilation, respiratory drive, or ventilatory response to hypoxia.²² However, other investigators showed no significant change in baseline ventilation or ventilatory response to hypoxia or hypercapnia.^{23–25} Further studies on development of oxygen chemosensitivity showed no difference between infants born to smoking mother and control.^{20,26} The discrepancy among these studies could be attributed to several factors such as sleep stage, sleep position, and the amount of cigarette smoke exposure.²⁷

Maternal Smoking and Infant Apnea and Arousals

Maternal cigarette smoking has been shown to be associated with an increase in both central and obstructive ap-

nea.^{28–30} Toubas et al. found increased rate of central apnea in infants of smokers compared with nonsmokers.²⁸ Kahn et al. demonstrated an increase in frequency and duration of obstructive apnea and there was a dose-dependent relationship between the number of cigarette smoked and the occurrence of obstructive apnea.²⁹ In addition, paternal smoking during pregnancy added to the risk of obstructive apneas in infants, but smoking in the postnatal period did not seem to have such an effect.²⁹ This finding suggests the effect of maternal smoking on infant apnea is more likely to be from prenatal than postnatal exposure. The effect of maternal smoking on infant apnea was observed in preterm infants. Prematurity is one of the risk factors for SIDS,^{13–15} and prenatal exposure to cigarette smoke may have profound effects on respiratory pattern in these infants. Indeed, preterm infants exposed prenatally to cigarette smoke had increased respiratory events during rapid eye movement (REM) sleep, predominately due to obstructive events.³⁰ Since REM sleep represents a greater percentage of total sleep time in premature infants compared with term infants, the exposure to cigarette smoke could have more adverse effect in preterm infants. Of note, preterm infants enrolled in this study had stayed in the nursery for an average of 2 months before sleep studies; therefore, recent postnatal exposure to cigarette smoke was unlikely.³⁰ The lack of postnatal exposure implies that prenatal exposure to cigarette smoke has a long-lasting effect on respiratory control in these infants. Although there is no proven link between apnea and SIDS, the effect of perinatal nicotine exposure on infant apneas may have significant implications and may provide the link between maternal smoking and SIDS. Kato et al. compared respiratory patterns of 40 infants who subsequently died of SIDS with those of 607 healthy infants matched for sex and age.³¹ It was observed that infants who died of SIDS had experienced more frequent episodes of obstructive and mixed apnea before their terminal events, and these tended to be <15 s duration. This observation provided indirect evidence for a slower maturation of respiratory control in some infants who ultimately die of SIDS.

One of the important protective mechanisms during respiratory events, hypoxia, or hypercapnia is arousal. Animal studies revealed that arousal plays a key role in termination of apneic events,^{32,33} whereas gasping and autoresuscitation are important protective mechanisms during profound hypoxia and anoxia. In fact, recovery from sleep apnea or asphyxia is believed to occur early as a result of arousals and later as a result of gasping and autoresuscitation. Failure of arousal and autoresuscitation is postulated as an important mechanism in the pathophysiology of SIDS.^{34,35} Prenatal exposure to cigarette smokes interferes with this important protective mechanism. Several studies have found that infants born to smoking mothers had a significant decrease in arousal responses after obstructive events^{30,36} and hypoxia.^{23,25} One study suggested that the diminished arousal after respiratory events was observed in preterm infants of smokers and this change was noted only during active (REM) sleep.³⁰ The other study revealed that impaired hypoxic arousal response was more predominate during quiet (non-rapid eye movement [NREM]) sleep.²⁵ Another way of determining arousal response is by assessing the arousal threshold in response to external stimuli. A reduced arousal response to auditory stimuli was noted in infants of smoking mothers.^{37–39} Horne et al. showed that infants born to smoking mothers had a reduction in both spontaneous arousal and

arousal in response to air jet stimulation in quiet sleep at 2–3 months of age, which is the vulnerable period for SIDS.^{25,39}

Prenatal Nicotine Exposure and Development of Respiratory Control: Animal Model

Although cigarettes contain many chemical compounds, including nicotine, tars, and carbon monoxide,^{1,2} several studies have indicated that nicotine is the main culprit underlying changes in respiratory control. Nicotine acts through selective nicotinic cholinergic receptors and it influences the maturation of these receptors in the fetal brain, autonomic ganglia, and adrenal medulla.^{40,41} The distribution of gene family encoding $\alpha 5$ subunit of nicotinic acetylcholine receptors has been demonstrated in the caudal brainstem where cardiorespiratory areas are located.⁴² In human fetuses at midgestation, a high concentration of nicotine binding sites appears in tegmental nuclei, an area that is important in cardiopulmonary integration and arousal.⁴³ The nucleus of the solitary tract within the caudal brainstem is the first central relay of cardiopulmonary receptors, arterial baroreceptors, and chemoreceptors inputs.⁴⁴ Immunocytochemical studies have shown the presence of both cholinergic neurons and nicotinic receptors in the medial part of the nucleus of solitary tract.^{45,46} Microinjection of nicotine into the nucleus of solitary tract has been shown to modulate cardiovascular function.⁴⁷ Presynaptic modulation of glutamate release by nicotinic receptors is one possible means by which nicotine may mediate cardiorespiratory effects in the nucleus of solitary tract.⁴⁶ The following sections will review the effect of perinatal nicotine exposure on developmental of respiratory control in an animal model.

Prenatal nicotine exposure and baseline ventilation and ventilatory response

Several studies examined the effect of perinatal nicotine exposure on baseline ventilation and respiratory pattern in developing animals. Although one study showed no significant change in baseline ventilation,⁴⁸ most studies revealed that prenatal nicotine exposure affected baseline ventilation in the newborn.^{49–51} St.-John and Leiter demonstrated that nicotine-exposed neonatal rats had significant lower minute ventilation on room air, indicating the effect of prenatal nicotine exposure on eupneic ventilation.⁴⁹ Hafstrom et al. showed that nicotine-exposed developing lambs had similar ventilation at baseline, but had lower tidal volume and higher respiratory frequency.⁵⁰ Simakajornboon et al. examined the effect of prenatal nicotine exposure in developing rats and found no difference in minute ventilation or tidal volume, but nicotine-exposed pups had higher baseline respiratory frequency.⁵¹ For respiratory pattern, Robinson et al. demonstrated a higher frequency of apnea during both normoxia and hypoxia only in mice at day 0–3, and suggested that nicotine-exposed animals had delayed development of breathing pattern.⁵² Later study by Huang et al. found that prenatal nicotine exposure led to increased apnea frequency in the early postnatal period, but affected baseline tidal volume and respiratory frequency after second week of life.⁵³ These studies showed changes in baseline ventilation and respiratory pattern, but the disparity between various studies could be due to differences in the animal model or the route and the dose of nicotine exposure.

In addition to the effect on baseline ventilation, perinatal nicotine exposure modulates ventilatory response to hypoxia. Both direct nicotine infusion and prenatal nicotine exposure have been shown to attenuate the hypoxic ventilatory response in developing lambs.^{54,55} Bamford et al. demonstrated no significant change in hypoxic and hypercapnic ventilatory responses in nicotine-exposed developing rats.⁴⁸ The subsequent study by the same laboratory, however, revealed alteration in the dynamic ventilatory response after withdrawal of baseline peripheral chemoreceptor drive.⁵⁶ The recent study showed attenuation of both hypoxic and hypercapnic ventilatory responses in nicotine-exposed developing rats.⁵⁷

The mammalian response to hypoxia is biphasic. An initial increase in minute ventilation is followed by a decrease in minute ventilation, with the latter being termed hypoxic ventilatory depression.⁵⁸ The reduction in ventilation during hypoxic ventilatory depression is more predominant in developing animals.⁵⁹ Simakajornboon et al. examined the effect of prenatal nicotine exposure on specific component of the biphasic hypoxic ventilatory response. Prenatal nicotine exposure is associated with mild attenuation of the peak hypoxic ventilatory response and a significant reduction in the magnitude of hypoxic ventilatory depression.⁵¹ The effect of prenatal nicotine exposure on hypoxic ventilatory depression may have significant functional implications. Previous studies have shown that activation of platelet-derived growth factor (PDGF)- β receptors occurred in brainstem regions, such as the nucleus of solitary tract during hypoxic ventilatory depression in adult rats, which may underlie a critical role in neuroprotection and survival strategies during hypoxic deprivation.⁶⁰ Such a mechanism could provide an additional explanation for the relatively high tolerance to hypoxia exhibited by brainstem neurons,⁶¹ an observation further reinforced by the high levels of PDGF- β receptor expression within the caudal brainstem regions underlying the hypoxic ventilatory response.⁶⁰

Prenatal nicotine exposure and arousal response and autoresuscitation

The important survival mechanism during severe hypoxemia or anoxia is the ability to autoresuscitate by gasping. Failure to autoresuscitate during prolonged apnea has been postulated to play a role in SIDS.^{34,35} Developing animals are more tolerant of anoxic conditions, and gasping and autoresuscitation are important mechanisms for survival in immature animals. Several studies have revealed that prenatal nicotine exposure interferes with arousal and autoresuscitation in developing animals. Acute nicotine infusion attenuated normal autoresuscitation following apnea in newborn piglets.⁶² Hafstrom et al. demonstrated a delayed arousal response to hypoxia during quiet in prenatal nicotine-exposed lambs.⁶³

Fewell and Smith examined the effect of perinatal nicotine exposure on the ability of developing rats to autoresuscitate from apnea during hypoxia.⁶⁴ Perinatal nicotine exposure did not affect the duration of gasping during anoxia, but it reduced the number of successful autoresuscitations during repeated anoxic exposure.⁶⁴ The effect of prenatal nicotine exposure on the gasping pattern during a single hypoxic exposure and autoresuscitation during repeated hypoxic exposure was age dependent such that the effect was predominate in the early postnatal age.⁶⁵ In addition, nicotine exposure impaired the ability of developing animals

to autoresuscitate from intermittent hypoxia in a dose-dependent manner.⁶⁶

Laryngeal chemoreflex plays an important role in inhibiting breathing and protect the airway from aspiration. However, laryngeal chemoreflex stimulation can lead to an exaggerated apnea and bradycardia. This mechanism has been linked to SIDS in 1 case report.⁶⁷ Sundell et al. showed that postnatal nicotine exposure impaired the ability to terminate laryngeal chemoreflex-induced apnea in young lambs during both normoxia and hypoxia.⁶⁸

Prenatal nicotine exposure and neuromodulators mediating hypoxic ventilatory and arousal responses

The neuronal molecular mechanism underlying the effect of nicotine on the peripheral chemoreceptor component of hypoxic ventilatory response has been investigated. Holgert et al. evaluated the effect of postnatal nicotine exposure on signal transduction in the carotid body and found that nicotine may interfere with postnatal oxygen sensitivity resetting of the peripheral chemoreceptor by increasing tyrosine hydroxylase and dopamine content in the carotid body.⁶⁹ Later study by Gauda et al. demonstrated that prenatal nicotine exposure upregulated tyrosine hydroxylase mRNA levels in the peripheral chemoreceptors of newborn rats.⁷⁰ Because the resetting of oxygen sensitivity is believed to be due to the rapid change in carotid body dopamine content and turnover that takes place around birth, prenatal nicotine exposure may interfere with this process.^{20,69}

In developing animals, certain receptors and second messenger systems are important modulators of neuronal activity underlying generation and maintenance of baseline ventilation and the hypoxic ventilatory response. Several lines of evidence have indicated that the early hypoxic response is primarily mediated thorough N-methyl-D-aspartate receptors.⁷¹⁻⁷³ The intracellular domain of N-methyl-D-aspartate receptor-1 contains serine/threonine residues that can be phosphorylated by protein kinase C, particularly at serine residues 890 and 896.^{74,75} Previous studies have demonstrated that protein kinase C activation mediates critical components of the hypoxic ventilatory response, and selective protein kinase C translocation occurred in the dorsocaudal brainstem during hypoxia.⁷⁶⁻⁷⁸ In addition, protein kinase C isoforms are developmentally regulated and overall ventilatory output may be more critically dependent on protein kinase C activity in immature animals.⁷⁹ Prenatal nicotine exposure has been shown to interfere with neuromodulators mediating central control of the hypoxic ventilatory response. Simakajornboon et al. showed that protein kinase C- β and protein kinase C- δ were upregulated in the caudal brainstem of nicotine-exposed developing animals.⁵¹ Both protein kinase C isoforms have been previously shown to be the most likely candidates underlying functional roles in generation of respiratory drive and in modulation of the hypoxic ventilatory response.^{78,80} The upregulation of specific protein kinase C isoforms previously identified as playing an important role in respiratory control may account for modulation of the hypoxic ventilatory response in nicotine-exposed developing animals. The mechanism underlying the effect of nicotine on protein kinase C activity is currently unknown. Some studies suggest that nicotine may directly affect protein kinase C activity through

the nicotinic receptors.^{81,82} The other putative mechanism may involve the indirect effect of nicotine on protein kinase C through N-methyl-D-aspartate glutamate receptors.⁸³ Indeed, nicotine specifically alters the channel property of glutamate receptors in neurons mediating inspiratory drive.⁵²

As previously mentioned, prenatal nicotine exposure modulates hypoxic ventilatory depression. Several neuromodulators, including γ -amino-butyric-acid (GABA), serotonin, adenosine, and opioid receptors, have shown to play an important role in hypoxic ventilatory depression. The GABA-mediated mechanism has been shown to mediate hypoxic ventilatory depression and has been implicated in the development of respiratory control.⁸⁴⁻⁸⁷ There are data linking nicotine to potentiation of γ GABA-mediated inhibition of respiratory system.^{88,89} The effect of prenatal nicotine exposure on the hypoxic ventilatory depression may have significant functional implications. A previous study has shown that activation of PDGF- β receptors occurs in brainstem regions, such as the nucleus of solitary tract, during hypoxic ventilatory depression in adult rats; this activation may play a critical role in neuroprotective and survival strategies during hypoxic deprivation.⁹⁰ Subsequently, study confirmed that hypoxia-induced phosphorylation of PDGF- β receptors in the caudal brainstem of adult rats was temporally associated with activation of the anti-apoptotic mechanism via PI3-kinase-dependent phosphorylation of both the Akt and BAD pathways.⁹¹ The recent study demonstrated that prenatal nicotine exposure was associated with a reduction of PDGF- β receptor activation in the caudal brainstem during hypoxia leading to attenuation of anti-apoptotic process through Akt/BAD pathways and subsequent acceleration of early apoptotic markers.⁹² The effects of nicotine exposure on apoptosis in neural cells have been investigated with conflicting results. Although some studies have suggested that nicotine exposure leads to an increase in apoptotic cells in certain brain areas,^{93,94} other studies have reported that nicotine exerts protective effects and may reduce apoptosis and promote neural cell survival.^{95,96} Interestingly, 1 study indicated that nicotine exposure caused significant cell death in undifferentiated or immature cells, but spared the same cells when differentiation was induced.⁹³ The effect of prenatal nicotine exposure on the apoptotic process in the developing brain may have significant clinical implication. Several studies have demonstrated that infants who succumbed to SIDS had evidence of apoptosis of neurons and glial cells in certain area of brainstem.^{97,98} Apoptosis of neural cells in the cardiorespiratory areas of the brainstem may lead to attenuation of hypoxic and arousal responses in SIDS victims.

Nitric oxide (NO) has been identified as a putative neurotransmitter in hypoxic chemotransduction pathway and anoxia-induced gasping and autoresuscitation in immature animals.^{99,100} It has dual effects; neuronal NO synthase plays a significant role in sustaining ventilation during the late phase of biphasic hypoxic ventilatory response,¹⁰¹⁻¹⁰³ whereas endothelial NO synthase exerts an inhibitory effect at the carotid body.^{104,105} In addition, anoxia-induced gasping is modulated by NO mechanisms, and higher NO concentration in the brainstem of developing animals may favor early autoresuscitation during prolonged asphyxia.^{99,100} Hasan et al. demonstrated that cigarette-smoke-exposed pups had a decrease in neuronal NO synthase expression within the caudal brainstem without any changes in

endothelial NO synthase expression.¹⁰⁶ The reduction in neuronal NO synthase expression by prenatal exposure to cigarette smoke may account for reduced ability to mount or sustain an appropriate ventilatory response to hypoxia, decreased anoxia-induced gasping, and may ultimately enhance the susceptibility for SIDS.¹⁰⁶

Conclusion

Perinatal exposure to cigarette smoke is the most modifiable risk factor for SIDS. The effect of *in utero* cigarette smoke exposure on respiratory control is speculated as an important causative mechanism. Numerous studies have linked maternal smoking and changes in breathing pattern, ventilatory, and arousal responses in infants during the early postnatal age when they are vulnerable to SIDS. Further investigation in animal models has identified nicotine as the main culprit underlying changes in respiratory control. Perinatal nicotine exposure results in alteration in baseline ventilation, ventilatory response to hypoxia, arousals, and autoresuscitation processes in developing animals, although conflicting findings exist among studies. The mechanisms underlying the effect of nicotine on maturation of respiratory control may be related to modulation of neurotransmitters and signal transductions mediating ventilatory control and arousal responses.

There is much evidence that prenatal nicotine exposure is harmful to both mother and infant. The importance of education of women of child bearing age cannot be over-emphasized and should be considered paramount in reducing the most modifiable risk factor for SIDS. Specific intervention programs are important in addressing the issue of smoking in pregnancy and provide dissemination of guidelines in culturally appropriate ways. Such programs should have mechanisms to track effect on smoking cessation in the short term, and SIDS trends in the long term. The ability to assess outcomes directly related to specific interventions is important to maximize the impact of the specific intervention within the scope of cultural, geographic, and social limitations.

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