Prenatal Nicotine Exposure and Sudden Infant Death Syndrome (SIDS)

Jocelyn Tabor

Writer's Comment: Although smoking is no longer the hip and trendy habit that it was in the 1950s, cigarettes remain popular, especially in foreign countries. As a Californian, I had never had much exposure to tobacco smoke until I went to Germany as an exchange student for one year after high school. I was amazed by the number of students my age who were smokers and wondered why such a health-conscious country would allow such a hazardous epidemic. Years later, during my last year at UC Davis, I stumbled into a lab that happened to study the cardiovascular consequences of cigarette smoke. As a neurobiology major, I was fascinated by the proposed neural pathways of nicotine exposure and wanted to study other harmful effects of smoking. I was reminded of a German acquaintance who had smoked throughout her pregnancy and given birth to a baby with a serious heart defect, and so I decided to review current literature regarding prenatal tobacco smoke exposure. I hope this review of prenatal tobacco smoke exposure and sudden infant death syndrome provides sufficient scientific evidence to convince women, especially those who are pregnant, to avoid tobacco use.

—Jocelyn Tabor

Instructor's Comment: Jocelyn's work in my Science Writing course (UWP 104E) was superb throughout the quarter. She tackled every assignment with the same level of commitment and thoroughness she demonstrates here in this fine review paper. This is the most difficult assignment of the quarter—students are required to research their topics in the scientific literature, and then synthesize the results of several primary research papers in their review articles. Not satisfied with looking at the five to eight papers I had suggested, Jocelyn read no less than twenty articles. The result is a persuasive analysis of the existing research on the relationship between prenatal nicotine exposure and SIDS. What's even more impressive is the clarity with which Jocelyn lays out her very technical analysis, making this a paper that is not only smart but readable.

—Pamela Demory, University Writing Program

Introduction

According to the American Cancer Society, an estimated 23% of men and 19% of women in the U.S. smoke cigarettes (1). Additionally, an estimated 20% of women in the U.S. who smoke continue to do so during pregnancy, despite numerous campaigns by government and health professionals (2). Epidemiological evidence links maternal smoking to many health risks, including increased occurrence of spontaneous abortion, low birth weight, and sudden infant death syndrome (SIDS) (3, 4). In fact, Lewis and colleagues report a nearly 70% increased risk of SIDS when maternal smoking is present (5).

SIDS is a condition characterized by sudden, unexplained death in clinically healthy infants, and is the leading cause of death in postneonatal children (3, 6). Although observers have reported decreased heart rate and gasping in SIDS babies immediately premortem, most cases of SIDS are identified only by autopsy (3, 6). In addition to environmental tobacco smoke (ETS), risk factors for SIDS include prone sleeping position and maternal bed-sharing (3, 7). SIDS also correlates with a younger, less-educated, or lower socioeconomic maternal demographic (3).

The nature of SIDS as a sudden, often unexplained condition makes it extremely difficult to study, as researchers must often gather evidence post-mortem or study previously-correlated risk factors. Within the limitations of current SIDS research, significant studies have been done on mechanisms of SIDS death, possible risk factors, and the roles of nicotine and environmental tobacco smoke. Although a number of studies have identified nicotine as a neuroteratogen, the exact mechanisms by which it affects the fetus are unknown (8-11). Current research suggests that nicotine acts at the level of the heart and brainstem to induce pharmacodynamic and pharmacological changes (6, 8, 10, 12-14). These alterations to the delicate neurohomeostasis of the young brain and heart may result in increased incidence of respiratory infections or decreased ability to tolerate hypoxia, both of which are thought to contribute to SIDS mortality (6, 8, 10, 14-16). As epidemiological studies demonstrate a strong correlation between ETS exposure and SIDS, it is imperative to elucidate exact mechanisms of nicotine-induced hypersensitivity in order to prevent future SIDS mortality. Although health

professionals already combat SIDS predisposition by advocating smoking cessation and proper prenatal care, current research could aid in the development of fetal nicotine antagonists or other effective therapies that eliminate reliance on maternal tobacco cessation. This review attempts to unify current research into tobacco smoke exposure and SIDS through an investigation of mechanisms of SIDS mortality with respect to the specific pharmacodynamic interactions of nicotine.

Nicotine Concentration and Metabolism

Although nicotine is addictive and teratogenic, it is only one of over 4,700 compounds contained in cigarette smoke (17). Thus, the terms "nicotine" and "environmental tobacco smoke" are not interchangeable when discussing the overall effects of cigarette smoking. In terms of fetal health, however, many studies have shown that nicotine is both able to cross the placental barrier and biologically active in fetal tissues (9, 18). Jauniaux and colleagues studied the concentrations of nicotine and its primary biological metabolite cotinine in maternal and fetal tissues from smokers and pregnant women living with smokers (18). They reported similar concentrations in maternal and fetal circulation during the first and second trimester, and slight decreases in fetal cotinine concentration vs. maternal levels in the third trimester (18). These correlations occurred in both the second-hand smoke exposure subjects and active smokers (18). Dempsey et al. attribute the similarities in maternal and fetal nicotine and cotinine levels to increased nicotine metabolism with decreased nicotine excretion during pregnancy (9). While studying the feasibility of transdermal nicotine administration as an alternative to smoking during pregnancy, Dempsey and colleagues observed increased metabolic clearance of nicotine paired with low excretion, which maintains relatively constant plasma concentrations (9). Thus, although many women decrease their smoking habits during pregnancy, a consistent concentration of nicotine may reach the fetus. Authors of both studies agree that maturation of the placenta within the third trimester allows for some added protection and filtration of teratogenic compounds (9, 18). For the majority of a pregnancy, however, the fetus is subject to significant nicotine levels (up to 3.07 ng/ml) if exposed to maternal smoking

or ETS (2). According to a study of human infants by Dwyer et al., nicotine levels in this range correspond to an odds ratio of up to 3.88 for developing SIDS (2). Coupled with the proposed bioactivity of nicotine, these findings make nicotine the most important component of cigarette smoke in terms of sudden infant death.

Overview of SIDS Mortality

Although a thorough discussion of the role of nicotine in facilitating SIDS death occurs with respect to each mechanism in the topics to follow, we must first identify the accepted mechanisms of SIDS mortality. While a small amount of research points to an increased incidence of respiratory infection in SIDS infants, the majority of findings implicate decreased hypoxia tolerance as the main mechanism of SIDS mortality (8, 10, 14-16). Hypoxia occurs normally in infants during sleep apnea, when sleeping in prone position, or when asleep in loose bedding (11). In response to decreased oxygen or increased carbon dioxide levels, infants normally exhibit a dramatic increase in respiration, including gasping, and an increase in heart rate (6). After nicotine exposure, however, infants are less able to recover from hypoxia, instead exhibiting decreases in cardiac activity and ventilation (5, 11, 14). Researchers have measured this effect directly in neonatal humans by presenting a hypoxia challenge while measuring heart rate, respiratory rate, and nicotine levels (5). Lewis et al. report that during hypoxia, 54% of infants exposed to prenatal nicotine did not awaken, compared to 15% of controls (5). This finding provides significant evidence that nicotine interferes with the ability to detect and respond to hypoxia, leading to potentially life-threatening events, including SIDS.

Fetal Nicotine Bioactivity

Changes in Cholinergic Receptor Activation

One of the foremost theories on nicotine bioactivity postulates that many of the deleterious consequences of prenatal nicotine exposure are due to changes in cholinergic receptors. Cholinergic receptors are found throughout the body and are important in autonomic regulation of cardiac function and respiratory efforts (8). In the heart, parasympathetic vagal innervation terminates on M2-

muscarinic receptors, while sympathetic neurons use β-adrenergic receptors. Slotkin and colleagues studied the effects of prenatal nicotine exposure on these receptor subtypes using rats as an animal model (8). Exposing the rats to nicotine levels similar to light (2 mg/day) and heavy (6 mg/day) smokers, they observed a 25% increase in M2 receptor binding, with no significant difference between the groups (8). Additionally, they found a decrease in β receptor binding at both levels (8). Neff et al. also observed an increase in M2 receptor binding and parasympathetic activation, although they did not examine sympathetic activity (12). These findings indicate that nicotine leads to an increase in inhibitory parasympathetic control while decreasing stimulatory sympathetic control, yielding an overall decrease in cardiac contractile strength. If this model is also true for humans, it may explain why infants exposed to prenatal nicotine have an overall decrease in heart rate during life-threatening situations, opposite of what is expected in a healthy heart.

Many researchers also believe that nicotine acts at receptors within the brainstem during prenatal nicotine exposure. Although often examined separately, brainstem and cardiac activity are integrally related. Receptors in the brainstem transmit information to cardiac sympathetic and parasympathetic neurons, as well as regions that regulate respiration and blood pressure (3). Unlike in the heart, however, Slotkin et al. reported a decrease in M2 receptor binding in the rat brainstem (8). Using monkeys as an animal model, the same group of researchers observed upregulation of brainstem nicotinic receptors, suggesting that nicotine may act on different receptor subtypes in each organ or exhibit species-specific differences (10). Slotkin and colleagues believe this increase in nicotinic receptor activation is enough to produce cellular damage due to over-stimulation when nicotine is subsequently administered, possibly producing the brainstem damage noted by Menihan et al. during autopsies of SIDS infants (3, 10). Slotkin et al. and Hafstrom et al. also report nicotine-induced brainstem abnormalities in the rat and lamb, respectively, and cite this damage as a possible cause for increased SIDS mortality during respiratory distress (8, 15). Conditions such as prone sleeping position and loose bedding create hypoxic environments for many infants. The aforementioned mechanism may explain why SIDS infants are significantly more

likely to die during hypoxic conditions, as damaged brainstem structures may be unable to detect or compensate for decreased oxygenation.

In order to test the hypothesis that nicotine acts at brainstem receptors to effect reduced hypoxia tolerance, Hafstrom et *al*. examined the effects of mild hypoxia during sleep in lambs that had been prenatally exposed to nicotine (15). These animals demonstrated reduced ventilation (69% oxygen saturation vs. 80% oxygen saturation) and heart rate (20% increase vs. 42% increase) compared to controls (15). Hafstrom and colleagues attribute this attenuated response to brain stem abnormalities as well as to changes in chemoreceptor activation, which will be discussed later (15). As this study presented a very small treatment group (n=7) and an uncommon animal model, it is difficult to predict whether the changes observed are true figures or an artifact of natural variability and unproven methods. In a similar study, Huang et al. attributes reduced cardiac response to hypoxia in nicotine-treated rats to activation of a strong excitatory vagal pathway not found in control animals (6). As vagal excitation produces cardiac inhibition, this pathway would likely use parasympathetic M2 receptors in the heart. These findings further substantiate the theory that nicotine reduces hypoxia tolerance in young animals, although the exact contributions of receptors in the heart and brainstem remain unknown.

Dopamine Transmission and Peripheral Chemoreceptor Activation

Although the majority of research points to changes in cholinergic receptors as the mechanism of nicotine action with regard to SIDS, some researchers believe nicotine may act on peripheral chemoreceptors as well (15, 19). Chemoreceptors detect changes in blood levels of dissolved gases, such as carbon dioxide, and are activated during hypoxia (15). Studies using the rat and cat have demonstrated the presence of nicotinic receptors on carotid body chemoreceptors, and nicotine is thought to act at these receptors to inhibit dopamine release (15). A decrease in dopamine transmission may then lead to decreased oxygen sensitivity in the chemoreceptors, facilitating death by hypoxia (15). Using rats as an animal model, Holgert et al. examined the effects of prenatal nicotine exposure on carotid body dopamine release (19). Researchers observed

a 54% decrease in dopamine release, which they attribute to the direct binding of nicotine to cholinergic receptors (19). Furthermore, they believe this decrease in dopamine may attenuate the activity of peripheral chemoreceptors, resulting in reduced sensitivity to fluctuations in blood oxygen (19). This finding further supports the view that inability to respond to hypoxia is the main mechanism of SIDS mortality, as peripheral chemoreceptors reflect an important sensor in the blood oxygenation reflex arc. More research is necessary, however, to elucidate the mechanism by which dopamine decreases chemoreceptor sensitivity, and establish the extent to which this mechanism contributes to SIDS mortality.

One study was able to link peripheral chemoreceptor activity to the widely accepted cholinergic receptor activation hypothesis. Lewis et al. indirectly measured activity at peripheral chemoreceptors by inducing hypercapnia and hypoxia in human infants (5). As hypercapnia yielded much higher arousal in infants of smokers than hypoxia (100% of infants vs. 46%), the authors concluded that peripheral chemoreceptors were functioning but that brainstem hypoxia detection, which cannot respond to hypercapnia, was not working properly (5). This finding supports a link between both theories herein stated: nicotine may affect brainstem cholinergic receptors, rendering them unable to detect hypoxia while also acting at peripheral chemoreceptors to decrease neurotransmission of dopamine, although the detrimental effects of nicotine at the latter receptors remain unproven.

Upregulation of Pro-Inflammatory Mediators

Cigarette smoke is known to cause an inflammatory response in humans, leading to bronchitis, asthma and other respiratory symptoms (16). Gordon et al. report that nicotine-induced upregulation of inflammatory mediators may also contribute to SIDS death, as an excess of inflammatory factors can lead to tissue damage and death, especially in young animals (16). To test this theory, Gordon and co-workers measured plasma levels of interleukin-6 (IL-6), interferon-γ (IFN), and interleukin-1β (IL-10) in smokers and non-smokers (16). For IFN, they observed a significant increase in smokers vs. non-smokers (131.9 pg/ml vs. 60.5 pg/ml), with similar patterns for the other two inflammatory mediators (16). As they failed to

examine infants, however, their discussion of a possible relationship to SIDS mortality cannot be substantiated, and their experimental results hold little validity in the scope of this review. Although Gordon et al. present an interesting new theory, lack of research into this topic and incomplete methodology award little credibility at this time to their proposal that nicotine upregulation of inflammatory mediators is an important contributor to SIDS death.

Conclusion

Sudden infant death syndrome is a devastating condition for infants and families, as it kills without warning and leaves few biological clues. Although no demographic is immune, epidemiological studies demonstrate strong correlations between younger, less-educated, lower socioeconomic level mothers and SIDS occurrence in their infants, with maternal smoking linked as the strongest risk factor. As cigarette smoke contains a plethora of natural and artificial compounds, researchers must rely on experimental evidence to expose nicotine as the causal agent in increased SIDS risk. While many studies have demonstrated the teratogenic effects of prenatal nicotine exposure and the ability of nicotine to cross the placental barrier in high concentrations, researchers cannot exclude other ETS components as possible fetal toxins. Although research has not yet elucidated other components of tobacco smoke as teratogenic, it remains possible that the deleterious effects observed are due to other metabolites, alone or in combination with nicotine.

Given the large body of experimental and epidemiological evidence that nicotine can contribute to SIDS mortality, much current research focuses on elucidating the exact mechanisms of nicotine's teratogenic effects. The most fully researched theory implicates nicotine as a catalyst of receptor-level modification. In the heart, nicotine may lead to increased parasympathetic inhibition and decreased sympathetic tone, resulting in an attenuated cardiac response during stress. In the brainstem, nicotine likely causes nicotinic cholinergic receptor upregulation, resulting in over-stimulation and subsequent damage to structures that regulate breathing, heart rate, and blood pressure. This neural degeneration leads to diminished ability to detect and respond to life-threatening events such as hypoxia, although peripheral chemoreceptor activation may

also play a role. Regardless of mechanism, most researchers agree that normal hypoxic events are the ultimate catalysts of SIDS mortality in both healthy and nicotine-exposed infants.

Although scientists do not agree on a single mechanism of SIDS death or nicotine action within the fetal circulation, the findings from many labs show significant similarities. As researchers discover links between nicotine metabolism during pregnancy, bioactivity, and SIDS mortality, the potential for early detection and prevention increases. Though rates of smoking are decreasing in the United States, worldwide tobacco use is increasing, and cessation rates during pregnancy can be less than 10% in some areas (11). These figures demonstrate a scientific obligation to protect infants from the deleterious consequences of fetal nicotine exposure despite maternal tobacco use. With increased pharmacodynamic research into exact receptor subtypes and brain regions affected, future research can focus on specific receptor-site antagonists or nicotine-targeting antibodies, neutralizing the teratogenic threat. Although additional research is required in the field of nicotine-related SIDS mortality to elucidate exact mechanisms and receptor characteristics, current research clearly indicates that women, especially those within populations established as "high risk," should avoid tobacco use during pregnancy.

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