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REVIEW ARTICLE

Early life insult from cigarette smoke may be predictive of chronic diseases later in life

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Abstract

Evidence is rapidly accumulating that links cigarette smoke (CS) exposure *in utero* with the development of a variety of disease pathologies in the older offspring including, type 2 diabetes, obesity, certain childhood cancers and respiratory disorders. The role that the fetal environment plays in these late-onset outcomes and the underlying cellular/molecular mechanisms by which these CS-induced effects may occur are currently unknown. Although we are becoming more aware of the fact that prenatal insult can underlie childhood/adult diseases, critical knowledge gaps still exist including gene–environment interactions, and how a CS-induced imbalance in immune dynamics (i.e. T_H1/T_H2) might affect asthma development and/or exacerbation later in life. In this mini-review we introduce the concept of sexual dimorphism in CS-induced late-onset disease outcomes, as well as explore the mechanisms by which CS exposure *in utero* can lead to cardiovascular, cancer and respiratory abnormalities in the exposed offspring. By addressing such questions using animal models, appropriate intervention strategies can be developed that will help to protect children's health and their long-term quality of life.

Keywords: *Cigarette smoke; prenatal exposure; respiratory disease; fetal insult*

Introduction

Previous research has clearly shown that babies, prenatally exposed to cigarette smoke (CS), are at increased risk for a number of perinatal consequences including low birth weight (LBW), preterm birth (PTB) and sudden infant death syndrome. In addition, evidence is rapidly accumulating that links CS exposure *in utero* with the development of a variety of disease pathologies in the older offspring including, type 2 diabetes, obesity (Oken et al. 2005) certain childhood cancers (i.e. leukaemias, lymphomas and central nervous system tumours) (Magnani et al. 1990, Murphy et al. 2003, Ng et al. 2005), and respiratory disorders (Penn et al. 2007). However, despite these consequences, more than 70% of women who smoke continue to do so throughout their pregnancy (http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=39853, May 2007). Taken together with those women exposed involuntarily (via environmental tobacco smoke (ETS)) to CS, about 2 million babies are born each year that have been exposed to CS *in utero* (Byrd et al. 1995).

Tobacco smoke contains at least 60 known or suspected carcinogens, along with pulmonary irritants, cilia toxicants, cardiotoxins, teratogens, and immunotoxicants (Fowles & Bates 2000), some of which can pass the placenta (Rhainds & Levallois 1997, Lackmann et al. 1999, Pichini et al. 2000, Perera et al. 2004). For example, in a study that measured benzo(a)pyrene (BaP) DNA adducts in the serum of smoking mothers and their prenatally exposed newborns, adducts were observed at a higher percentage in the neonate compared with the directly exposed mothers (Perera et al. 2004). These studies once again demonstrate that the fetus is not 'just a small adult' when it comes to toxic insult, and is an extremely vulnerable subpopulation for the toxic effects of environmental chemicals (Dietert & Piepenbrink 2008).

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Perinatal outcomes associated with maternal smoking

Preterm birth (PTB; <37 weeks' gestation), a well-known outcome of smoking during pregnancy, is usually also associated with low birth weight (LBW; <2500 g), which is the single most important factor determining neonatal mortality (Ventura et al. 1998). According to the American Lung Association, maternal smoking accounts for up to 15% of all preterm deliveries, ~20–30% of all low-birth-weight babies and ~10% of all stillborn births (http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=39853, May 2007).

Prenatal CS exposure and preterm birth in a murine model: the role of maternal hormone levels

Whilst the link between smoking during pregnancy and adverse perinatal health outcomes such as preterm delivery (PTD) and LBW is well-established, the exact mechanism(s) by which CS acts to bring about such effects is still being examined. A few studies have indicated that unfractionated CS can act as an antiestrogen by affecting the 2-hydroxylation pathway of estradiol metabolism leading to increased production of 2-hydroxyestrogens, which have minimal estrogenic activity and are rapidly cleared from the circulation (Michnovicz et al. 1986, Tanko & Christiansen 2004). As maternal hormone levels are critical for maintenance of pregnancy and parturition, this laboratory examined the effects of mainstream CS (MCS) exposure on hormonal secretion patterns in pregnant female mice (Ng et al. 2006).

Results from these studies demonstrated that in the absence of any overt maternal or neonatal effects (i.e. no change in litter size, female to male sex ratio or post-implantation loss), gestational duration was significantly ($p < 0.05$) decreased in smoke-exposed pregnant females compared with control dams. Gestational duration in smoke-exposed mice was shortened by 3.4% that is equivalent to a 1.3-week reduction in a human pregnancy, placing it in the PTD category (<37 weeks) and, therefore, at increased risk for any pathologies associated with early delivery.

Concurrent, in this study, with a decrease in gestational duration was a dramatic increase in maternal serum estradiol (E2) levels and a decreased progesterone:E2 ratio (compared with air control counterparts evaluated on the same gestational day). As effects on gestational duration and hormone homeostasis were observed after exposure to a maternal CS dose equivalent to smoking <1 pack of cigarettes per day, the need for smoking cessation even for light-to-moderate pregnant smokers is further underscored.

Adverse perinatal outcomes may be associated with maternal genetic susceptibility to CS

In a recent study by Wang et al. (2002), the effects of maternal smoking on infant birth weight were influenced by specific metabolic gene polymorphisms of the mother. Specifically, results demonstrated that a subgroup of pregnant women with the cytochrome P450 1A1 (*CYPIA1*) MspI variant genotype and/or the glutathione *S*-transferase theta 1 (*GSTT1*) deletion genotype were particularly susceptible to the adverse effects of smoking during pregnancy. The greatest reduction in birth weight, gestational duration and birth-weight ratio was observed in infants whose smoking mother had either one or both of the aforementioned polymorphisms, suggesting that maternal genotype plays a role in CS-induced effects on birth weight and gestational duration.

Prenatal CS exposure and later life respiratory disease

Childhood asthma is a widespread, chronic inflammatory disease of the airways, characterized by a dysregulated T-helper (T_H) type-2 response to inhaled antigens that leads to the production of allergic antibodies (i.e. IgE), infiltration into the airways and lung tissues of T lymphocytes and eosinophils, airway hyper-responsiveness (AHR), mucus cell hyperplasia and airway tissue remodelling (Melgert et al. 2005). Asthma, the number one cause of missed school days due to a chronic disease, is one of the highest ranked causes of paediatric hospitalizations in America (National Academy on an Aging Society, 1999). Although atopy and allergic disease may be associated with multiple susceptibility genes (Larché 2007), childhood asthma has also been linked to environmental factors, including, most notably, maternal smoking during pregnancy (Gilliland et al. 2001).

Epidemiological studies have revealed a strong link between CS exposure *in utero* and the development of asthma and asthma-like symptoms in the offspring (Cook & Strachan 1999). In a cross-sectional study that investigated the respiratory health of school-aged children (part of the Southern California Children's Health Study), physician-diagnosed asthma and a number of asthma-related symptoms (e.g. wheezing) and outcomes (i.e. medication and/or hospitalization), were associated with maternal smoking while pregnant (Gilliland et al. 2001). In another study, data were collected prospectively from parents (shortly after birth) regarding family history of asthma, parental occupations and maternal smoking during pregnancy; medical records of the infant were analysed retrospectively when the child reached 1 year of age (Dezateux et al. 1999).

Findings demonstrated that although infants exposed to CS *in utero* did not have diminished airway conductance (i.e. increased airway resistance) prior to 8 weeks of age, these same children were more likely to wheeze during their first year of life compared with those born to non-smoking mothers. These results suggest that prenatal exposure to CS may produce asthma-related effects that persist into childhood.

A study in 2003 (Noakes et al. 2003), that used cord blood to compare cytokine responses to allergens (e.g. ovalbumin (OVA) and house dust mites (HDM)), in neonates from smoking mothers (compared with those from non-smoking mothers), revealed that maternal smoking during pregnancy was associated with increased neonatal T_H2 cytokine responses to the allergens, suggesting that smoking during pregnancy can alter neonatal response to subsequent antigen challenge.

Prenatal CS exposure and asthma-related responses in a murine model

As mothers who smoke during pregnancy are not likely to stop after the baby is born, distinguishing asthma-related effects due to pre- versus post-natal exposure to CS is extremely difficult. Thus, laboratory animal models for which CS exposures can be limited to defined periods of time can be extremely useful.

In this regard, a number of studies have investigated the effects of *in utero* exposure to ETS in conjunction with allergen sensitization on asthma-related effects in a murine model. For example, Penn et al. (2007) examined Balb/c mice exposed prenatally to ETS and the offspring subsequently sensitized with OVA. Pulmonary function was assessed via whole body plethysmography (a non-invasive technique for measuring airway resistance) and results revealed that airway responsivity was not only enhanced in OVA-exposed mice (compared with non-sensitized animals), but that prenatal exposure to ETS, in combination with OVA-sensitization, increased airway reactivity greater than either agent alone. These results are consistent with a study by Seymour et al. (1997) that demonstrated that levels of serum IgE and IgG1 (key components of allergic asthma) were greater in OVA-sensitized Balb/c mice that were also exposed to ETS than sensitized mice exposed to air. These findings further the argument that exposure to ETS intensifies asthma-related outcomes.

Ongoing research in this laboratory using OVA-sensitized pregnant CD1 mice subsequently exposed to MCS revealed that offspring born to 'such dams' were less sensitive to challenge with the non-specific bronchoconstricting agent, acetylcholine (Grabowski et al. 2008). These findings are supported by a 2004 study (Melgert et al. 2004) in which OVA-sensitized C57B1/6J mice, subsequently exposed to MCS, demonstrated significantly reduced bronchoconstriction compared with OVA-challenged air control animals. Taken together, the results seem somewhat contradictory. However, it appears clear that 'atopy' in combination with CS exposure (either from direct exposure to CS or prenatal exposure) act together to modify the effects of either factor alone on airway health. More studies are urgently needed to understand more clearly the mechanisms by which synergistic/antagonistic effects between airway-modifying factors might occur.

Prenatal exposure to cigarette smoke and offspring cancer risk

Transplacental CS constituents

Several toxic constituents of CS including (but, not limited to) nicotine, some polycyclic aromatic hydrocarbons (PAHs), and certain metals (e.g. lead, nickel, zinc), can pass the placental barrier in humans (Rhainds & Levallois 1997, Lackmann et al. 1999, Pichini et al. 2000, Perera et al. 2004). Cadmium, while not thought to reach the fetus in any measurable amounts, accumulates in the placenta causing toxicity leading to detrimental effects on the developing fetus (Nishijo et al. 2004).

Tumour susceptibility following prenatal CS exposure in a murine model

The risk of developing childhood cancer following prenatal CS exposure is still being actively debated (Sasco & Vainio 1999). However, mounting epidemiological evidence indicates an association between prenatal CS exposure and subsequent development of certain childhood cancers (i.e. central nervous system tumours, leukaemia and lymphomas) (Magnani et al. 1990, Fillippini et al. 1994, 2000, Schuz et al. 2001). Thus, studies were carried out in this laboratory to provide biological plausibility for the epidemiological findings and to explore potential mechanism(s) by which prenatal CS exposure could lead to cancer development later in life. Pregnant $B_6C_3F_1$ mice were exposed to either air or MCS from gestational day (GD) 4 to parturition. At 5-weeks of age, male and female offspring were injected with cultured lymphoma cells and tumour incidence, growth rate and time to tumour formation (compared with the air exposed controls) were examined. Results demonstrated that prenatal exposure to CS increased tumour incidence (>2-fold) and tumour growth rate in the juvenile male offspring (Ng et al. 2006). Concurrent with the increase in tumour incidence/growth rate, prenatally exposed male offspring also demonstrated reduced cytotoxic T-lymphocyte (CTL) activity critical for the recognition and destruction of developing

neoplasms. Findings from this study not only provide biological plausibility for the epidemiological findings, but also demonstrate the suppressive effects of prenatal CS exposure on tumour surveillance mechanisms in the offspring, and differences between the sexes in response to prenatal exposure to CS and tumour susceptibility.

Conclusions and future directions

The adverse health effects due to maternal smoking during pregnancy are becoming more evident each year. While in some cases, smoking while pregnant may result in immediately apparent adverse health outcomes (e.g. birth defects, PTB and LBW) other pathologies may only manifest in the child much later in life (e.g. asthma, type 2 diabetes, obesity or childhood cancers). The role that the fetal environment may play in these late-onset outcomes and the underlying cellular/molecular mechanisms by which these CS-induced effects may occur are currently unknown.

Although we are becoming more aware of the fact that prenatal insult can underlie childhood/adult diseases, critical knowledge gaps still exist including gene–environment interactions, and how a CS-induced imbalance in T_H1/T_H2 dynamics might affect asthma development/exacerbation later in life. In this laboratory we are addressing the question of sexual dimorphism in CS-induced disease outcomes, as well as exploring the mechanisms by which CS exposure *in utero* can lead to behavioural, cardiovascular and respiratory abnormalities in the exposed offspring. By addressing such questions using animal models, appropriate intervention strategies can be developed that will help to protect children's health and their long-term quality of life.

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