Possible Teratogenicand long term Effects of Nicotine

Abd El-Monem Awad Hegazy, Manar Mohamady Khatab, Doaa Mohammed Yousef Abd Al-Hamid, Reham Helmy Abdel-Kareem

Human Anatomy and Embryology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Manar Mohamady Khatab

Email: aymanmashal00@gmail.com

Conflict of interest: None declared

Funding: No funding sources

Abstract

Background: In addition to increasing the likelihood of negative health outcomes in adult children, cigarette smoking during pregnancy is linked to a plethora of obstetrical, fetal, and developmental issues. An alternative to smoking that is safer for pregnant women is nicotine replacement therapy (NRT), which was developed as a pharmacotherapy for smoking cessation. Very few short-term human trials have assessed the safety of NRT usage during pregnancy; however, data about the long-term impacts of developing nicotine exposure in humans is now unavailable. Nevertheless, research on animals has shown that nicotine is a crucial component in many of the negative consequences of maternal cigarette smoking on children. These consequences include infertility, type 2 diabetes, obesity, high blood pressure, abnormal brain development, and breathing problems.

Keywords: Teratogenic, long term Effects of Nicotine

TobRegul Sci. ™ 2023; 9(1): 7684 – 7708

DOI: doi.org/10.18001 /TRS.9.1.544

Introduction:

It has been well documented that cigarette smoking during pregnancy is associated with a number of adverse obstetrical outcomes including: spontaneous abortion (George et al., 2006), placenta previa (Chelmow et al., 1996; Faiz and Ananth, 2003; Hung et al., 2007), placental abruption (Ananth et al., 1999), preterm birth (Fantuzzi et al., 2007; Kolas et al., 2000), stillbirth (Hogberg and Cnattingius, 2007; Wisborg et al., 2001), fetal growth restriction (Hammoud et al., 2005; Nordentoft et al., 1996), low birth weight (Bernstein et al., 2005; Jaddoe et al., 2008), and sudden infant death syndrome (SIDS) (Mitchell and Milerad, 2006). Smoking cessation or at least reduction of cigarette smoking during pregnancy can ameliorate damage to the developing fetus (Lindley et al., 2000; Pickett et al., 2003). Indeed,

smoking cessation programs based on behavioral therapy, which are implemented during pregnancy, have been shown to reduce the incidence of low birth weight and preterm birth (Lumley et al., 2004).

Although cigarette smoking during pregnancy is associated with adverse fetal, obstetrical, and developmental outcomes, 15–20% of all women smoke throughout the duration of pregnancy (Andres and Day, 2000; Bergmann et al., 2003), despite intentions to refrain from smoking during that period (Okuyemi et al., 2000). Approximately 75% of pregnant smokers report the desire to quit smoking (Ruggiero et al., 2000), but only 20–30% successfully abstain from smoking during pregnancy and half of these women relapse within 6 months of parturition (Ebert and Fahy, 2007). Smoking cessation is most effective if implemented before pregnancy or prior to the initiation of prenatal care (Tong et al., 2008). For most women, nicotine dependence is a significant element of their smoking behavior (Okuyemi et al., 2000), and the highly addictive nature of nicotine makes smoking cessation difficult. Indeed, the majority of adverse physiological symptoms associated with smoking cessation (cravings, irritability, restlessness, anxiety, and increased appetite) have been attributed to nicotine withdrawal (Glynn et al., 2009). Therefore, nicotine replacement therapy (NRT) has been widely developed as a pharmacotherapy of smoking cessation and is considered to be of benefit for pregnant women who are highly dependent and have been unable to quit smoking by other means (Benowitz and Dempsey, 2004; Okuyemi et al., 2000; Ontario Medical Association [OMA], 2008; Peters and Morgan, 2002).

In pregnant women who smoke or use NRT, nicotine crosses the placenta, concentrates in fetal blood and amniotic fluid, and is detectable in breast milk during lactation (Jordanov, 1990; Lambers and Clark, 1996; Luck and Nau, 1987). Indeed, during the first week of life, urinary cotinine levels in infants of smoking mothers who are exclusively breast-fed are significantly higher than those who are only bottle fed (fully breast-fed median 801 ng cotinine/mg creatinine [range 325–1693] vs. fully bottle fed median 65 ng cotinine/mg creatinine [range 28–101]; Schwartz-Bickenbach et al., 1987). Therefore, maternal NRT use results in both fetal and neonatal exposure to nicotine. NRT in the form of gum, nasal spray, and lozenges is currently classified as a Pregnancy Category C drug, whereas the transdermal nicotine patch is classified in pregnancy as Category D (Benowitz and Dempsey, 2004; Pauly and Slotkin, 2008). Based on these U.S. Food and Drug Administration classifications, it is generally agreed that the risk to the fetus of continued smoking outweighs any potential adverse effects of NRT (Glynn et al., 2009; OMA, 2008). Furthermore, NRT is thought of as a safer alternative to smoking during pregnancy because the mother and fetus are exposed to one chemical instead of the thousands of chemicals found in cigarette smoke (Glynn et al., 2009; OMA, 2008). It has also been argued that because NRT usually delivers a dose of nicotine that is equivalent to smoking 10 cigarettes a day, the fetus will be exposed to much less nicotine than children born to women who smoke heavily during pregnancy (Oncken and Kranzler, 2003). The OMA currently

recommends that NRT should be made available to pregnant women who are unable to quit smoking using nonpharmacologic means (OMA, 2008). In addition, the Committee on Safety of Medicines (CSM) and Medicines and Healthcare Regulatory Authority (MHRA) in the United Kingdom recently changed their policy to recommend NRT to pregnant and breastfeeding mothers, stating that although there is a theoretical risk that nicotine could cause harmful effects, in practice, none have been found to date (Action on Smoking and Health, 2005). However, there are several issues with the OMA and CSM/MHRA recommendations. First, NRT use compared with placebo does not appear to increase the probability of successful smoking cessation during pregnancy. Although NRT is highly effective for smoking cessation in non–pregnant smokers (reviewed in Glynn et al., 2009), there is currently no evidence to suggest that NRT use is effective for smoking cessation in pregnant women (assessed by meta-analysis in Lumley et al., 2004). These findings may be attributed to the increased rate of nicotine metabolism in pregnant versus non–pregnant smokers (60% higher nicotine clearance and 140% higher cotinine clearance during pregnancy; Dempsey et al., 2002) or may relate to the low adherence to NRT among pregnant smokers (Fish et al., 2009). Despite the lack of evidence to support the efficacy of NRT use during pregnancy, the percentage of pregnancies in which NRT was prescribed has increased steadily between 1998 and 2004 (Coleman, 2008). Second, nicotine may not be the "safe" chemical in cigarettes as was previously assumed. Notably, in their recently updated smoking cessation document, the OMA has acknowledged that there is no safe dose of nicotine during pregnancy (OMA, 2008).

Ginzel et al. (2007) have recently raised concerns about NRT use during pregnancy, based on evidence of fetotoxicity and neuroteratogenicity associated with maternal nicotine exposure. Moreover, maternal smoking is associated with numerous adverse cardiovascular, respiratory, endocrine, and metabolic outcomes in the offspring (Beratis et al., 1996; Bergmann et al., 2003; Blake et al., 2000; Jensen et al., 1998; Lannero et al., 2006; Montgomery and Ekbom, 2002; Oken et al., 2008; Power and Jefferis, 2002; Sharpe and Franks, 2002; Syme et al., 2009; Toschke et al., 2002; Weinberg et al., 1989; Wideroe et al., 2003), yet the effects of nicotine exposure alone on these outcomes have not been comprehensively evaluated. To date, reviews that evaluate the safety of NRT use during pregnancy generally consider the acute risks of nicotine exposure on the developing fetus and, in some cases, the long-term neurological effects. The goal of this review is to assess the current evidence regarding the long-term effects of fetal and neonatal nicotine exposure, an area of research that has been overlooked in the safety assessment of NRT use during pregnancy. We will also consider the potential contribution of nicotine to the long-term toxicity associated with cigarette smoke exposure during fetal and neonatal development.

Go to:

NRT USE DURING PREGNANCY: HUMAN TRIALS

There are an extremely limited number of trials examining the safety of NRT in humans, all of which focus on obstetrical outcomes and the short-term toxicological effects on the fetus. A report by Morales-Suarez-Varela et al. (2006) showed an increased prevalence of specific malformations in pregnant NRT users compared with both nonsmokers and smokers, whereas Strandberg-Larsen et al. (2008) showed in the same cohort (Danish National Birth Cohort) that NRT use during pregnancy was not associated with an increased risk of stillbirth. A recent, open-label randomized trial by Pollak et al. (2007), comparing cognitive-behavioral therapy (CBT) with or without NRT, was the first large trial to demonstrate efficacy of NRT for smoking cessation during pregnancy (but not postpartum). Unfortunately, this trial was stopped early because of increased incidence of "serious adverse events" in the CBT + NRT group compared with the CBT arm; however, because of the open-label design of this trial and other confounding factors, it is difficult to make conclusions about these data (Pollak et al., 2007). Nicotine gum and patches have been shown to increase maternal blood pressure and heart rate, as well as fetal heart rate, but to a lesser degree than cigarette smoking (reviewed in Dempsey and Benowitz, 2001). Although smoking is clearly associated with intrauterine growth restriction (Kolas et al., 2000; Williams et al., 1997), the role of nicotine in causing this effect is unclear. Two randomized control trials have found that birth weights were significantly higher in women using nicotine gum (Oncken et al., 2008) or nicotine patch (Wisborg et al., 2000) compared with smokers receiving placebo controls. Notably, in both of these studies, serum cotinine levels were actually lower in the NRT group than the placebo group (Oncken et al., 2008; Wisborg et al., 2000). Furthermore, both the NRT and placebo groups included women who quit smoking, those who reduced cigarette consumption, and those who did not change smoking behaviors, thus making analyses of the role of nicotine alone on birth weight in these studies difficult to interpret (Oncken et al., 2008; Wisborg et al., 2000). Conversely, data from the 2004 Phase V Pregnancy Risk Assessment Monitoring System indicated that self-reported NRT use during pregnancy was associated with a 2-fold increased risk of low birth weight compared with nonsmokers, whereas a 1.3-fold increased risk was observed in smokers versus nonsmokers (Gaither et al., 2009). Therefore, it is difficult to ascertain the role of nicotine in the increased incidence of low birth weight associated with maternal smoking because nicotine exposure in humans may actually be lower in women using NRT. Results from the ongoing smoking, nicotine and pregnancy trial, a double-blind placebo-randomized control trial of NRT in pregnancy (Coleman, 2007), which is expected to end in 2012, should help to clarify the effects of NRT use during pregnancy on birth weight.

Currently, there are no prospective epidemiological studies that examine NRT use during pregnancy and the incidence of adult-onset disease in the offspring. However, considerable insight into the long-term effects of developmental nicotine exposure can be gained from animal models. The general consensus among clinicians is that more information is needed about the risks of NRT use during pregnancy before well-informed definitive recommendations can be made to pregnant women (Crawford et al., 2008; Herbert et al., 2005; Lumley et al.,

2009; Oncken and Kranzler, 2009; Osadchy et al., 2009). Although we agree that there is limited information available from human trials with NRT during pregnancy, there is substantial evidence in animal models that can contribute to dialogue on this subject. Therefore, this review will evaluate a broader spectrum of outcomes than has been previously examined, including the long-term consequences of fetal and neonatal nicotine exposure in animal studies and the potential contribution of nicotine to the increased incidence of adult-onset diseases in humans following maternal smoking during pregnancy.

LONG-TERM EFFECTS OF FETAL AND NEONATAL EXPOSURE TO NICOTINE

Neurobehavioral Outcomes

The long-term consequences of fetal and neonatal exposure to nicotine on the central nervous system have been extensively studied in numerous animal models and are reviewed in detail elsewhere (reviewed in Dwyer et al., 2009; Pauly and Slotkin, 2008; Winzer-Serhan, 2008). Briefly, nicotine has been clearly established as a neuroteratogen that compromises the development of critical neural pathways in the developing brain (Dwyer et al., 2009; Pauly and Slotkin, 2008; Winzer-Serhan, 2008). Numerous long-term neurological effects have also been documented following prenatal nicotine exposure, which are thought to explain many of the adverse neurobehavioral outcomes in the offspring of women who smoke during pregnancy. For instance, epidemiological studies have demonstrated that prenatal tobacco exposure is associated with numerous adverse postnatal neurobehavioral outcomes, such as attention-deficit hyperactivity disorder, learning disabilities, behavioral problems, and increased risk of nicotine addiction (reviewed in Cornelius and Day, 2009; Dwyer et al., 2009; Pauly and Slotkin, 2008; Rogers, 2009; Winzer-Serhan, 2008). Similarly, prenatal nicotine exposure in rodents causes postnatal hyperactivity, cognitive impairment, increased anxiety, somatosensory deficits, persistent neurochemical alterations, changes in sensitivity to nicotine, alterations in nicotine self-administration and altered patterns of neural cell survival, and synaptogenesis (reviewed in Dwyer et al., 2009; Pauly and Slotkin, 2008; Winzer-Serhan, 2008). Evidence from animal studies strongly points to nicotine as a key chemical involved in mediating the long-term neurological effects of developmental cigarette smoke exposure.

Metabolic Outcomes

Because it is well established that maternal cigarette smoking results in intrauterine growth restriction (Andres and Day, 2000; England et al., 2001; Robinson et al., 2000; Wideroe et al., 2003) and that low birth weight is a significant risk factor for the development of obesity, hypertension, and type 2 diabetes (Barker, 1998; Barker and Clark, 1997; Godfrey and Barker, 2000, 2001; Ong and Dunger, 2002; Seckl, 2001), it has been suggested that the association of cigarette smoking with an increased risk of adverse postnatal health outcomes is simply a reflection of intrauterine growth restriction. However, maternal smoking increases the risk of adult-onset diseases in the offspring even after adjustment for a wide range of confounding

factors including birth weight, socioeconomic status, and maternal diet (Power and Jefferis, 2002; Syme et al., 2009; Von et al., 2002; Wideroe et al., 2003), suggesting that it may be a direct effect of intrauterine exposure to the chemicals in cigarette smoke that accounts for the increased risk of adverse health outcomes in the offspring of women who smoke during pregnancy. Indeed, recent epidemiological studies have shown a strong relationship between maternal smoking and subsequent obesity, hypertension, and type 2 diabetes in the offspring (Bergmann et al., 2003; Montgomery and Ekbom, 2002; Oken et al., 2008; Power and Jefferis, 2002; Syme et al., 2009; Toschke et al., 2002; Wideroe et al., 2003). Of the 4000 chemicals in cigarette smoke, animal studies suggest that fetal exposure to nicotine alone may result in postnatal metabolic alterations associated with obesity, type 2 diabetes, and hypertension. This hypothesis is supported by work from our laboratory, which demonstrated that maternal nicotine exposure during pregnancy and lactation in rats results in increased adiposity and/or increased body weight (Gao et al., 2005; Holloway et al., 2005), altered perivascular adipose tissue composition and function (Gao et al., 2008), elevated blood pressure (Gao et al., 2008), and impaired glucose homeostasis (Holloway et al., 2005) postnatally. In our animal model, female rats are injected daily with either nicotine bitartrate (1.0 mg/kg/day) or saline (vehicle) for 2 weeks prior to mating, 3 weeks during gestation (fetal development), and 3 weeks during lactation (neonatal development). The dose of nicotine used in our animal model results in maternal serum cotinine concentrations of 136 ng/ml (Holloway et al., 2006), which is within the range of cotinine levels reported in women who are considered “moderate smokers” (80–163 ng/ml) (Eskenazi and Bergmann, 1995). In addition, this dose of nicotine results in serum cotinine concentrations of 26 ng/ml in the nicotine-exposed offspring at birth (Holloway et al., 2006), which is also within the range (5–30 ng/ml) observed in infants nursed by smoking mothers (Luck and Nau, 1985). The following sections will evaluate findings from our animal model as well as similar models of developmental nicotine exposure by others in the field.

Obesity.

Prenatal nicotine exposure in rats has been shown to result in increased postnatal body weight (Gao et al., 2005; Newman et al., 1999; Somm et al., 2008) and higher levels of body fat in the fetus at gestational day 20 (Williams and Kanagasabai, 1984) and offspring during adulthood (Gao et al., 2005; Oliveira et al., 2009; Somm et al., 2008). It has been suggested that prenatal nicotine exposure may result in increased adiposity/body weight via alterations in the central endocrine control of body weight homeostasis. The signals for body weight regulation and energy balance are ultimately integrated in the hypothalamus, which is arguably the most important center in the brain for the regulation of appetite and body weight homeostasis (Hillebrand et al., 2002; Kalra et al., 1999; Wilding, 2002). Wideroe et al. (2003) suggested that the underlying mechanism for the reported association between maternal smoking and childhood overweight may be inappropriate changes in the hypothalamic regulation of energy homeostasis resulting in increased appetite. Indeed, nicotinic acetylcholine receptors (nAChR) are widely distributed in

the hypothalamus (Jo et al., 2002; Li et al., 2003), and Grove et al. (2001) have shown that in utero exposure to nicotine in the rhesus macaque can alter hypothalamic expression of both neuropeptide Y and proopiomelanocortin (POMC) messenger RNA (mRNA), regulators of appetite and satiety, in the neonate. Similarly, neonatal rats treated with nicotine also have significantly upregulated levels of POMC mRNA in the arcuate nucleus, an effect that was blocked by dihydro-β-erythroidine, an α4β2 nAChR antagonist (Huang and Winzer-Serhan, 2007). These results suggest that the nicotine-induced alterations in body weight homeostasis may be regulated by changes in hypothalamic control mechanisms during fetal life.

Type 2 diabetes.

We have demonstrated that in rats, nicotine exposure alone, during pregnancy and lactation, results in endocrine and metabolic changes in the adult offspring (i.e., 26 weeks of age) that are consistent with the disturbed glucose metabolism that may lead to type 2 diabetes (Holloway et al., 2005). In humans, type 2 diabetes results from a progressive reduction in the ability of the pancreas to produce sufficient insulin to maintain normal glucose homeostasis and compensate for any underlying resistance to the action of insulin (Butler et al., 2003; Marchetti et al., 2006). Impaired insulin secretion may be because of a reduced number of insulin-secreting cells (i.e., beta cell mass) and/or abnormal insulin secretion from the beta cells (i.e., beta cell function). Insulin resistance, a reduced sensitivity to insulin action, is also a major component of the pathophysiology of type 2 diabetes and can be characterized by defective insulin signaling in insulin target tissues and/or impaired insulin-stimulated glucose transport in skeletal muscle.

In rats, fetal and neonatal exposure to nicotine adversely affects pancreatic development and postnatal beta cell survival and function (Bruin et al., 2007b, 2008a,b,c). Beta cell mass is determined by a balance of beta cell size, replication, neogenesis, and apoptosis (Bouwens and Rooman, 2005; Hill, 2005; Rhodes, 2005). We have demonstrated that fetal and neonatal nicotine exposure caused a permanent loss of beta cell mass beginning at birth, which was attributed to increased levels of beta cell apoptosis and a decreased capacity for islet cell proliferation compared with saline controls (Bruin et al., 2007b). This is similar to humans with type 2 diabetes, in which the primary cause of impaired beta cell mass is increased apoptosis (Butler et al., 2003). Furthermore, Somm et al. (2008) have assessed the effects of prenatal nicotine exposure on beta cell neogenesis in a similar animal model. In their study, fetal and neonatal exposure to nicotine resulted in reduced islet size and number, as well as a reduction in beta cell neogenesis, as determined by impaired islet gene expression of Pdx-1, Pax-6, Nkx6.1, and insulin (Somm et al., 2008). Regardless of the treatment protocol, nicotine-exposed offspring subsequently developed glucose and insulin intolerance, hyperinsulinemia, and increased body weight during adulthood (Holloway et al., 2005; Somm et al., 2008). Taken together, these studies show clearly that in animals, fetal and neonatal exposure to nicotine has profound effects on fetal and neonatal pancreatic development resulting in abnormal glucose homeostasis in adulthood.

Our laboratory has further examined the mechanism by which fetal and neonatal nicotine causes loss of beta cell mass and function. We propose that nicotine binds to the nAChR on the developing beta cell, causing an increase in the production of intracellular reactive oxygen species (Bruin et al., 2008b). Because the antioxidant defense system in the beta cells is known to be relatively low compared with other cell types (Lenzen et al., 1996; Tiedge et al., 1997), beta cells are particularly susceptible to oxidative stress. Notably, we have shown increased oxidative damage specifically to mitochondrial proteins in the pancreas of nicotine-exposed neonates (Bruin et al., 2008b). Indeed, mitochondrial dysfunction appears to be a central defect in beta cells following nicotine exposure. First, loss of beta cell mass in nicotine-exposed neonates was attributed to increased mitochondrial-mediated beta cell apoptosis (Bruin et al., 2008a). Second, a progressive deterioration of mitochondrial structure and function was observed with increasing age following cessation of nicotine treatment at weaning (Bruin et al., 2008c). Finally, these mitochondrial defects were associated with impaired glucose-stimulated insulin secretion in isolated islets and reduced insulin granule biosynthesis (Bruin et al., 2008c), both of which likely contributed to the altered glucose homeostasis in this animal model.

Prenatal nicotine exposure also causes impaired insulin sensitivity in the peripheral tissues, another hallmark of type 2 diabetes. Somm et al. (2008) reported an increased glucose response following an insulin challenge in nicotine-exposed offspring relative to saline controls during adulthood. Furthermore, we have shown significantly reduced insulin receptor protein expression (Bruin et al., 2007a) and uptake of radiolabeled insulin (Labiris et al., 2006) in skeletal muscle at 26 weeks of age following fetal and neonatal nicotine exposure. Therefore, maternal nicotine exposure may cause impaired glucose homeostasis in offspring as a result of both defective insulin secretion (caused by impaired pancreatic beta cell mass and function) and reduced peripheral insulin sensitivity.

Cardiovascular Outcomes

Hypertension is one of the health consequences associated with in utero exposure to cigarette smoking in humans (Beratis et al., 1996; Blake et al., 2000), and animal studies suggest that this effect may be mediated via nicotine. Indeed, fetal and neonatal nicotine exposure results in increased blood pressure during adulthood in both the normotensive Wistar-Kyoto rat strain (Gao et al., 2008) and a spontaneously hypertensive strain (Pausova et al., 2003). However, the mechanisms for blood pressure elevation in the offspring of the nicotine-exposed dams are not fully understood.

Results from other studies suggest that fetal and neonatal exposure to nicotine in rats causes elevated blood pressure postnatally because of endothelial dysfunction (Xiao et al., 2007) and/or changes in renal structure or function (Mao et al., 2009; Pausova et al., 2003). However, in our animal model, there was no evidence of either endothelial dysfunction or altered renal structure in the nicotine-exposed offspring at 6 months of age (Gao et al., 2008). Instead, data from these

experiments have shown that fetal and neonatal exposure to nicotine (1) changes the composition and amount of perivascular adipose tissue and (2) impairs the ability of the perivascular adipose tissue to attenuate the contractile response of blood vessels (Gao et al., 2005, 2008).

Because perivascular adipose tissue surrounds almost all systemic arteries and is an important modulator of vascular function (Gao et al., 2007; Gollasch and Dubrovska, 2004), these data suggest that the elevated postnatal blood pressure in nicotine-exposed offspring may be at least partly attributed to altered perivascular adipose tissue function.

Prenatal nicotine exposure also leads to stress-induced cardiac defects in the offspring. Nicotine-exposed rat offspring had elevated left ventricle myocardial infarct size and decreased postischemic recovery of left ventricle function following 25 min of ischemia during adulthood (Lawrence et al., 2008). Similarly, intolerance to neonatal hypoxia has been attributed to impaired maintenance of cardiac function following prenatal nicotine exposure (Slotkin et al., 1997). Control rats responded to hypoxic conditions with initial tachycardia and a subsequent slight decline in heart rate, whereas nicotine-exposed pups show no tachycardia and a rapid decline in heart rate (Slotkin et al., 1997). These effects also extended into adulthood with nicotine-exposed rats showing a higher incidence of arrhythmia in response to stress at 4–5 months of age compared with saline controls (Feng et al., 2010). Taken together, animal studies demonstrate that developmental nicotine exposure may play a key role in the increased risk of hypertension following maternal smoking (Beratis et al., 1996; Blake et al., 2000). Furthermore, nicotine-induced cardiac dysfunction may also be involved in the increased risk of SIDS in cigarette smoke–exposed neonates (Mitchell and Milerad, 2006).

Respiratory Outcomes

Lung development.

Epidemiological studies have associated maternal cigarette smoke exposure with a variety of adverse pulmonary function outcomes in the offspring. Maternal smoking during pregnancy doubles the risk of wheezing and asthma in offspring up to 2 years of age (Lannero et al., 2006) and is associated with diminished lung function parameters in children (Gilliland et al., 2000). The risk of the offspring developing asthma following maternal smoking during pregnancy remains elevated as the children reach school age, adolescence, and adulthood (Gilliland et al., 2001; Skorge et al., 2005). In addition, maternal smoking during pregnancy synergizes with personal smoking in later life to increase airflow limitations in chronic obstructive pulmonary disease (Upton, 2004).

Similarly, perinatal exposure to nicotine also has a profound impact on lung development and postnatal lung function. Because this topic has been reviewed in detail elsewhere (Campos et al., 2009; Hafstrom et al., 2005; Maritz, 2008), we will only highlight selected studies. For instance, nicotine can alter airway structure and mechanics in fetal monkeys, resulting in decreased

pulmonary function parameters such as forced expiratory volume, forced vital capacity, and expiratory reserve volume (Sekhon et al., 1999, 2001, 2002). In addition, nicotine impairs alveolarization in the lungs of perinatally exposed rats (Maritz, 2002; Maritz and Thomas, 1994; Maritz and Windvogel, 2003; Petre et al., 2008). Offspring of nicotine-treated lambs also had abnormal postnatal breathing patterns (Hafstrom et al., 2002a) and proximal airway obstruction (Sandberg et al., 2004). However, the long-term consequences of these changes in lung structure have not been well described. Maritz and Windvogel (2003) have followed offspring from their studies up to postnatal day 42 and have observed accelerated aging of the lungs, characterized by microscopic emphysema, enlarged alveolar volume, increased flattening of alveoli with age, and decreased internal surface area for gas exchange. Similarly, in our laboratory, nicotine exposure resulted in altered alveolarization and reduced lung vascularization in the neonates, suggesting that gas exchange might be compromised. However, these changes in lung structure in neonatal life did not translate into permanent functional changes in lung mechanics or airway responsiveness to a methacholine challenge during adulthood (Petre et al., 2008).

Hypoxia sensing.

Cigarette smoking during pregnancy is associated with an increased risk of SIDS (Mitchell and Milerad, 2006). Indeed, exposure to nicotine alone during gestation in rats results in increased mortality during a hypoxic challenge on the day after birth (Slotkin et al., 1995). As previously discussed, this effect has been attributed, in part, to the adverse consequences of maternal nicotine on the maintenance of postnatal cardiac function under conditions of ischemic stress (Lawrence et al., 2008; Slotkin et al., 1997). In addition, studies in lambs have shown that prenatal nicotine exposure alters the lung mechanical response to hypoxia (Sandberg et al., 2007) and blunts the major cardiorespiratory defense systems to hypoxia (i.e., heart rate and ventilatory and arousal responses) (Hafstrom et al., 2002b). It has been proposed that these defects may all be attributed to the deficient adrenomedullary catecholamine release observed during hypoxia in nicotine-exposed neonatal rats (Slotkin et al., 1995). Indeed, in our animal model, there is an impaired ability of adrenomedullary chromaffin cells to respond to hypoxic stress following fetal nicotine exposure (Buttigieg et al., 2008). Nicotine treatment of primary chromaffin cells (isolated from neonates) in culture blunted hypoxia-induced catecholamine secretion (Buttigieg et al., 2009). Similarly, significantly lower levels of catecholamines were detected in umbilical cord blood of smokers compared with nonsmokers (Oncken et al., 2003). Therefore, prenatal nicotine exposure blunts the neonatal response to hypoxia via a combination of respiratory, cardiovascular, and adrenal chromaffin cell defects.

Fertility Outcomes

It has been well documented that there is a significant association between smoking and reduced fertility among females (Augood et al., 1998; Greenlee et al., 2003; Hughes and Brennan, 1996; Hull et al., 2000; Shiverick and Salafia, 1999) and males (Kunzle et al., 2003; Vine,

1996). Furthermore, cotinine (the metabolite of nicotine), cadmium (a heavy metal in cigarette smoke), and benzo[a]pyrene (a polyaromatic hydrocarbon in cigarette smoke) have been detected in the follicular fluid of women who smoke (Neal et al., 2008; Younglai et al., 2002; Zenzes et al., 1995), demonstrating that chemicals present in cigarette smoke can accumulate in the ovary. It has been suggested that impaired fertility in women who smoke may be the result of a combination of impaired oocyte function and viability, decreased fertilization rates, altered ovarian steroidogenesis, depleted ovarian reserves, and increased chromosomal abnormalities in oocytes (Harrison et al., 1990; Klonoff-Cohen et al., 2001; Ness et al., 1999; Van Voorhis et al., 1996; Zenzes et al., 1995).

In human populations, there is also evidence to suggest that fetal exposure to cigarette smoke is associated with reduced fertility during adulthood in both men and women (Jensen et al., 1998; Sharpe and Franks, 2002; Weinberg et al., 1989). Data from animal studies suggest that nicotine exposure may be a critical component in the development of adverse reproductive effects in the offspring of women who smoke. In our animal model, nicotine exposure during fetal and neonatal development resulted in reduced fertility, dysregulation of ovarian steroidogenesis, and altered follicle dynamics in female offspring (Holloway et al., 2006). Furthermore, developmental nicotine exposure resulted in reduced granulosa cell proliferation, increased ovarian cell apoptosis, and decreased ovarian angiogenesis during adulthood compared with saline controls (Petrik et al., 2009), an effect that may be mediated, in part, via changes in the intra-ovarian growth insulin-like growth factor system (Cesta et al., 2009).

The results for male offspring appear to be less profound than the changes observed in the females. There were some transient defects noted in the histopathology of nicotine-exposed testes during the peripubertal period (7 weeks of age), including increased spermatid retention, seminiferous tubule vacuolization, leukocyte and germ cell infiltration into epididymal ducts, and germ cell exfoliation and depletion in seminiferous tubules (Anzar et al., 2006). However, these structural changes were not evident during adulthood (i.e., 26 weeks of age) and were not associated with adverse functional outcomes at either age (Lagunov et al., 2009). Therefore, fetal and neonatal nicotine exposure appears to play an important role in the infertility reported in female offspring of smoking mothers, but the role in male offspring remains unclear. This is consistent with a study in Danish dizygotic twins, which reported that the female twin had reduced fecundity following in utero cigarette smoke exposure, whereas the fecundity of the male twin was unaffected (Jensen et al., 2006).

Childhood Cancers

Prenatal exposure to tobacco smoke has been associated with an increased risk of childhood cancers, including childhood brain tumors and leukemia/lymphoma (Sasco and Vainio, 1999). The long-term effects of fetal and neonatal nicotine exposure on cancer development are not well studied, but there is certainly biological plausibility to suggest that this may be an area of risk.

Nicotine and its metabolites are known to both initiate and promote tumor growth (Catassi et al., 2008; Martin et al., 2009; Zheng et al., 2007). The fetus may be particularly vulnerable to these effects because of its reduced detoxification abilities (Perera et al., 2004).

Nicotine can be transformed to the carcinogenic compound, the tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Notably, although NRT users have reduced urinary levels of NNK metabolites compared with smokers, nicotine from NRT was transformed to these tobacco-specific carcinogens (Hatsukami et al., 2004). NNK and its metabolites have been detected in the urine of newborns born to mothers who smoked cigarettes during pregnancy, indicating placental transfer of this carcinogen (Lackmann et al., 1999). It can be assumed that women using NRT during pregnancy would also expose the fetus to NNK, although likely at lower levels. Notably, NNK is a transplacental carcinogen in the Syrian golden hamster, even at low doses (Schuller et al., 1994). Offspring of pregnant hamsters treated with NNK develop tumors in various different tissues, including the respiratory tract, pancreas, liver, and adrenal glands (Correa et al., 1990; Schuller et al., 1993, 1994). Therefore, fetal and neonatal exposure to nicotine, via NRT or cigarette smoking, may similarly increase the long-term risk of developing cancer, although more research is needed to verify this hypothesis.

References:

[1] Action on Smoking and Health. Guidance for Health Professionals on Changes in the Licensing Arrangements for Nicotine Replacement Therapy. 2005. Available at: http://www.ash.org.uk/files/documents/ASH_445.pdf. [Google Scholar]

[2] Ananth CV, Smulian JC, Vintzileos AM. Incidence of placental abruption in relation to cigarette smoking and hypertensive disorders during pregnancy: a meta-analysis of observational studies. Obstet. Gynecol. 1999;93:622–628. [PubMed] [Google Scholar]

[3] Andres RL, Day MC. Perinatal complications associated with maternal tobacco use. Semin. Neonatol. 2000;5:231–241. [PubMed] [Google Scholar]

[4] Anzar M, Buhr M, Mirshokraei P, Holloway AC. Fetal and Neonatal Exposure to Nicotine Adversely Affects Testicular and Epididymal Function in Rats. Omaha, NE: Society for the Study of Reproduction; 2006. [Google Scholar]

[5] Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. Hum. Reprod. 1998;13:1532–1539. [PubMed] [Google Scholar]

[6] Barker DJ. In utero programming of chronic disease. Clin. Sci. 1998;95:115–128. [PubMed] [Google Scholar]

[7] Barker DJ, Clark PM. Fetal undernutrition and disease in later life. Rev. Reprod. 1997;2:105–112. [PubMed] [Google Scholar]

[8] Benowitz N, Dempsey D. Pharmacotherapy for smoking cessation during pregnancy. Nicotine Tob. Res. 2004;6(Suppl. 2):S189–S202. [PubMed] [Google Scholar]

[9] Beratis NG, Panagoulias D, Varvarigou A. Increased blood pressure in neonates and infants whose mothers smoked during pregnancy. J. Pediatr. 1996;128:806–812. [PubMed] [Google Scholar]

[10] Bergmann KE, Bergmann RL, Von KR, Bohm O, Richter R, Dudenhausen JW, Wahn U. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. Int. J. Obes. Relat. Metab. Disord. 2003;27:162–172. [PubMed] [Google Scholar]

[11] Bernstein IM, Mongeon JA, Badger GJ, Solomon L, Heil SH, Higgins ST. Maternal smoking and its association with birth weight. Obstet. Gynecol. 2005;106:986–991. [PubMed] [Google Scholar]

[12] Blake KV, Gurrin LC, Evans SF, Beilin LJ, Landau LI, Stanley FJ, Newnham JP. Maternal cigarette smoking during pregnancy, low birth weight and subsequent blood pressure in early childhood. Early Hum. Dev. 2000;57:137–147. [PubMed] [Google Scholar]

[13] Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. Physiol. Rev. 2005;85:1255–1270. [PubMed] [Google Scholar]

[14] Bruin JE, Gerstein HC, Holloway AC. The effect of rosiglitazone on peripheral insulin signaling and glucose utilization pathways following fetal and neonatal exposure to nicotine in rats. 2007a 67th Annual American Diabetes Association Scientific Sessions. [Google Scholar]

[15] Bruin JE, Gerstein HC, Morrison KM, Holloway AC. Increased pancreatic beta cell apoptosis following fetal and neonatal exposure to nicotine is mediated via the mitochondria. Toxicol. Sci. 2008a;103:362–370. [PubMed] [Google Scholar]

[16] Bruin JE, Kellenberger LD, Gerstein HC, Morrison KM, Holloway AC. Fetal and neonatal nicotine exposure and postnatal glucose homeostasis: identifying critical windows of exposure. J. Endocrinol. 2007b;194:171–178. [PubMed] [Google Scholar]

[17] Bruin JE, Petre MA, Lehman MA, Raha S, Gerstein HC, Morrison KM, Holloway AC. Maternal nicotine exposure increases oxidative stress in the offspring. Free Radic. Biol. Med. 2008b;44:1919–1925. [PubMed] [Google Scholar]

[18] Bruin JE, Petre MA, Raha S, Morrison KM, Gerstein HC, Holloway AC. Fetal and neonatal nicotine exposure in Wistar rats causes progressive pancreatic mitochondrial damage and beta cell dysfunction. PLoS.One. 2008c;3:e3371. [PMC free article] [PubMed] [Google Scholar]

[19] Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003;52:102–110. [PubMed] [Google Scholar]

[20] Buttigieg J, Brown S, Holloway AC, Nurse CA. Chronic nicotine blunts hypoxic sensitivity in perinatal rat adrenal chromaffin cells via upregulation of KATP channels:

role of alpha7 nicotinic acetylcholine receptor and hypoxia-inducible factor-2alpha. J. Neurosci. 2009;29:7137–7147. [PMC free article] [PubMed] [Google Scholar]

[21] Buttigieg J, Brown S, Zhang M, Lowe M, Holloway AC, Nurse CA. Chronic nicotine in utero selectively suppresses hypoxic sensitivity in neonatal rat adrenal chromaffin cells. FASEB J. 2008;22:1317–1326. [PubMed] [Google Scholar]

[22] Campos M, Bravo E, Eugenin J. Respiratory dysfunctions induced by prenatal nicotine exposure. Clin. Exp. Pharmacol. Physiol. 2009;36:1205–1217. [PubMed] [Google Scholar]

[23] Catassi A, Servent D, Paleari L, Cesario A, Russo P. Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: implications on lung carcinogenesis. Mutat. Res. 2008;659:221–231. [PubMed] [Google Scholar]

[24] Cesta CE, Petrik JJ, Ambraska H, Holloway AC. In utero and lactational exposure to nicotine alters the intra-ovarian IGF system in adult female rats. Reprod. Biol. Insights. 2009;2:1–9. [Google Scholar]

[25] Chelmow D, Andrew DE, Baker ER. Maternal cigarette smoking and placenta previa. Obstet. Gynecol. 1996;87:703–706. [PubMed] [Google Scholar]

[26] Coleman T, Thornton J, Britton J, Lewis S, Watts K, Coughtrie MW, Mannion C, Marlow N, Godfrey C. Protocol for the smoking, nicotine and pregnancy (SNAP) trial: double-blind, placebo-randomised, controlled trial of nicotine replacement therapy in pregnancy. BMC Health Serv. Res. 2007;7:2. [PMC free article] [PubMed] [Google Scholar]

[27] Coleman T. Reducing harm from tobacco smoke exposure during pregnancy. Birth Defects Res. C. Embryo. Today. 2008;84:73–79. [PubMed] [Google Scholar]

[28] Cornelius MD, Day NL. Developmental consequences of prenatal tobacco exposure. Curr. Opin. Neurol. 2009;22:121–125. [PMC free article] [PubMed] [Google Scholar]

[29] Correa E, Joshi PA, Castonguay A, Schuller HM. The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone is an active transplacental carcinogen in Syrian golden hamsters. Cancer Res. 1990;50:3435–3438. [PubMed] [Google Scholar]

[30] Crawford JT, Tolosa JE, Goldenberg RL. Smoking cessation in pregnancy: why, how, and what next. Clin. Obstet. Gynecol. 2008;51:419–435. [PubMed] [Google Scholar]

[31] Dempsey D, Jacob P, III, Benowitz NL. Accelerated metabolism of nicotine and cotinine in pregnant smokers. J. Pharmacol. Exp. Ther. 2002;301:594–598. [PubMed] [Google Scholar]

[32] Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf. 2001;24:277–322. [PubMed] [Google Scholar]

[33] Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol. Ther. 2009;122:125–139. [PMC free article] [PubMed] [Google Scholar]

[34] Ebert LM, Fahy K. Why do women continue to smoke in pregnancy? Women Birth. 2007;20:161–168. [PubMed] [Google Scholar]

[35] England LJ, Kendrick JS, Gargiullo PM, Zahniser SC, Hannon WH. Measures of maternal tobacco exposure and infant birth weight at term. Am. J. Epidemiol. 2001;153:954–960. [PubMed] [Google Scholar]

[36] Eskenazi B, Bergmann JJ. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and postnatal smoke exposure. I. Effects on physical growth at age 5 years. Am. J. Epidemiol. 1995;142:S10–S18. [PubMed] [Google Scholar]

[37] Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: an overview and meta-analysis of observational studies. J. Matern. Fetal Neonatal Med. 2003;13:175–190. [PubMed] [Google Scholar]

[38] Fantuzzi G, Aggazzotti G, Righi E, Facchinetti F, Bertucci E, Kanitz S, Barbone F, Sansebastiano G, Battaglia MA, Leoni V, et al. Preterm delivery and exposure to active and passive smoking during pregnancy: a case-control study from Italy. Paediatr. Perinat. Epidemiol. 2007;21:194–200. [PubMed] [Google Scholar]

[39] Feng Y, Caiping M, Li C, Can R, Feichao X, Li Z, Zhice X. Fetal and offspring arrhythmia following exposure to nicotine during pregnancy. J. Appl. Toxicol. 2010;30:53–58. [PubMed] [Google Scholar]

[40] Fish LJ, Peterson BL, Namenek Brouwer RJ, Lyna P, Oncken CA, Swamy GK, Myers ER, Pletsch PK, Pollak KI. Adherence to nicotine replacement therapy among pregnant smokers. Nicotine Tob. Res. 2009;11:514–518. [PMC free article] [PubMed] [Google Scholar]

[41] Gaither KH, Brunner Huber LR, Thompson ME, Huet-Hudson YM. Does the use of nicotine replacement therapy during pregnancy affect pregnancy outcomes? Matern. Child Health J. 2009;13:497–504. [PubMed] [Google Scholar]

[42] Gao YJ, Holloway AC, Su LY, Takemori K, Lu C, Lee RM. Effects of fetal and neonatal exposure to nicotine on blood pressure and perivascular adipose tissue function in adult life. Eur. J. Pharmacol. 2008;590:264–268. [PubMed] [Google Scholar]

[43] Gao YJ, Holloway AC, Zeng ZH, Lim GE, Petrik JJ, Foster WG, Lee RM. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. Obes. Res. 2005;13:687–692. [PubMed] [Google Scholar]

[44] Gao YJ, Lu C, Su LY, Sharma AM, Lee RM. Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. Br. J. Pharmacol. 2007;151:323–331. [PMC free article] [PubMed] [Google Scholar]

[45] George L, Granath F, Johansson AL, Anneren G, Cnattingius S. Environmental tobacco smoke and risk of spontaneous abortion. Epidemiology. 2006;17:500–505. [PubMed] [Google Scholar]

[46] Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, Avol E, Peters JM. Maternal smoking during pregnancy, environmental tobacco smoke

exposure and childhood lung function. Thorax. 2000;55:271–276. [PMC free article] [PubMed] [Google Scholar]

[47] Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. Am. J. Respir. Crit. Care Med. 2001;163:429–436. [PubMed] [Google Scholar]

[48] Ginzel KH, Maritz GS, Marks DF, Neuberger M, Pauly JR, Polito JR, Schulte-Hermann R, Slotkin TA. Critical review: nicotine for the fetus, the infant and the adolescent? J. Health Psychol. 2007;12:215–224. [PubMed] [Google Scholar]

[49] Glynn DA, Cryan JF, Kent P, Flynn RA, Kennedy MP. Update on smoking cessation therapies. Adv. Ther. 2009;26:369–382. [PubMed] [Google Scholar]

[50] Godfrey KM, Barker DJ. Fetal nutrition and adult disease. Am. J. Clin. Nutr. 2000;71:1344S–1352S. [PubMed] [Google Scholar]

[51] Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr. 2001;4:611–624. [PubMed] [Google Scholar]

[52] Gollasch M, Dubrovska G. Paracrine role for periadventitial adipose tissue in the regulation of arterial tone. Trends Pharmacol. Sci. 2004;25:647–653. [PubMed] [Google Scholar]

[53] Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. Epidemiology. 2003;14:429–436. [PubMed] [Google Scholar]

[54] Grove KL, Sekhon HS, Brogan RS, Keller JA, Smith MS, Spindel ER. Chronic maternal nicotine exposure alters neuronal systems in the arcuate nucleus that regulate feeding behavior in the newborn rhesus macaque. J. Clin. Endocrinol. Metab. 2001;86:5420–5426. [PubMed] [Google Scholar]

[55] Hafstrom O, Milerad J, Sandberg KL, Sundell HW. Cardiorespiratory effects of nicotine exposure during development. Respir. Physiol. Neurobiol. 2005;149:325–341. [PubMed] [Google Scholar]

[56] Hafstrom O, Milerad J, Sundell HW. Altered breathing pattern after prenatal nicotine exposure in the young lamb. Am. J. Respir. Crit. Care Med. 2002a;166:92–97. [PubMed] [Google Scholar]

[57] Hafstrom O, Milerad J, Sundell HW. Prenatal nicotine exposure blunts the cardiorespiratory response to hypoxia in lambs. Am. J. Respir. Crit. Care Med. 2002b;166:1544–1549. [PubMed] [Google Scholar]

[58] Hammoud AO, Bujold E, Sorokin Y, Schild C, Krapp M, Baumann P. Smoking in pregnancy revisited: Findings from a large population-based study. Am. J. Obstet. Gynecol. 2005;192:1856–1862. discussion 1862–1863. [PubMed] [Google Scholar]

[59] Harrison KL, Breen TM, Hennessey JF. The effect of patient smoking habit on the outcome of IVF and GIFT treatment. Aust. N. Z. J. Obstet. Gynaecol. 1990;30:340–342. [PubMed] [Google Scholar]

[60] Hatsukami DK, Lemmonds C, Zhang Y, Murphy SE, Le C, Carmella SG, Hecht SS. Evaluation of carcinogen exposure in people who used “reduced exposure” tobacco products. J. Natl. Cancer Inst. 2004;96:844–852. [PubMed] [Google Scholar]

[61] Herbert R, Coleman T, Britton J. U.K. general practitioners' beliefs, attitudes, and reported prescribing of nicotine replacement therapy in pregnancy. Nicotine Tob. Res. 2005;7:541–546. [PubMed] [Google Scholar]

[62] Hill DJ. Development of the endocrine pancreas. Rev. Endocr. Metab. Disord. 2005;6:229–238. [PubMed] [Google Scholar]

[63] Hillebrand JJ, de Wied D, Adan RA. Neuropeptides, food intake and body weight regulation: a hypothalamic focus. Peptides. 2002;23:2283–2306. [PubMed] [Google Scholar]

[64] Hogberg L, Cnattingius S. The influence of maternal smoking habits on the risk of subsequent stillbirth: is there a causal relation? BJOG. 2007;114:699–704. [PMC free article] [PubMed] [Google Scholar]

[65] Holloway AC, Cuu DQ, Morrison KM, Gerstein HC, Tarnopolsky MA. Transgenerational effects of fetal and neonatal exposure to nicotine. Endocrine. 2007;31:254–259. [PubMed] [Google Scholar]

[66] Holloway AC, Kellenberger LD, Petrik JJ. Fetal and neonatal exposure to nicotine disrupts ovarian function and fertility in adult female rats. Endocrine. 2006;30:213–216. [PubMed] [Google Scholar]

[67] Holloway AC, Lim GE, Petrik JJ, Foster WG, Morrison KM, Gerstein HC. Fetal and neonatal exposure to nicotine in Wistar rats results in increased beta cell apoptosis at birth and postnatal endocrine and metabolic changes associated with type 2 diabetes. Diabetologia. 2005;48:2661–2666. [PubMed] [Google Scholar]

[68] Huang LZ, Winzer-Serhan UH. Nicotine regulates mRNA expression of feeding peptides in the arcuate nucleus in neonatal rat pups. Dev. Neurobiol. 2007;67:363–377. [PubMed] [Google Scholar]

[69] Hughes EG, Brennan BG. Does cigarette smoking impair natural or assisted fecundity? Fertil. Steril. 1996;66:679–689. [PubMed] [Google Scholar]

[70] Hull MG, North K, Taylor H, Farrow A, Ford WC. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. Fertil. Steril. 2000;74:725–733. [PubMed] [Google Scholar]

[71] Hung TH, Hsieh CC, Hsu JJ, Chiu TH, Lo LM, Hsieh TT. Risk factors for placenta previa in an Asian population. Int. J. Gynaecol. Obstet. 2007;97:26–30. [PubMed] [Google Scholar]

[72] Jaddoe VW, Troe EJ, Hofman A, Mackenbach JP, Moll HA, Steegers EA, Witteman JC. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr. Perinat. Epidemiol. 2008;22:162–171. [PubMed] [Google Scholar]

[73] Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, Ernst E, Bonde JP, Skakkebaek NE, Olsen J. Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. Am. J. Epidemiol. 1998;148:992–997. [PubMed] [Google Scholar]

[74] Jensen TK, Joffe M, Scheike T, Skytthe A, Gaist D, Petersen I, Christensen K. Early exposure to smoking and future fecundity among Danish twins. Int. J. Androl. 2006;29:603–613. [PubMed] [Google Scholar]

[75] Jo YH, Talmage DA, Role LW. Nicotinic receptor-mediated effects on appetite and food intake. J. Neurobiol. 2002;53:618–632. [PMC free article] [PubMed] [Google Scholar]

[76] Jordanov JS. Cotinine concentrations in amniotic fluid and urine of smoking, passive smoking and non-smoking pregnant women at term and in the urine of their neonates on 1st day of life. Eur. J. Pediatr. 1990;149:734–737. [PubMed] [Google Scholar]

[77] Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. Endocr. Rev. 1999;20:68–100. [PubMed] [Google Scholar]

[78] Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-Fallopian transfer. Hum. Reprod. 2001;16:1382–1390. [PubMed] [Google Scholar]

[79] Kolas T, Nakling J, Salvesen KA. Smoking during pregnancy increases the risk of preterm births among parous women. Acta Obstet. Gynecol. Scand. 2000;79:644–648. [PubMed] [Google Scholar]

[80] Kunzle R, Mueller MD, Hanggi W, Birkhauser MH, Drescher H, Bersinger NA. Semen quality of male smokers and nonsmokers in infertile couples. Fertil. Steril. 2003;79:287–291. [PubMed] [Google Scholar]

[81] Labiris R, Truman T, Farncombe T, Guenther K, Valiant J, Gerstein HC, Holloway AC. In vivo evaluation of insulin distribution in an animal model of type 2 diabetes using 99mTc-labelled human insulin. 2006 Annual Meeting of the Society of Nuclear Medicine, San Diego, CA. [Google Scholar]

[82] Lackmann GM, Salzberger U, Tollner U, Chen M, Carmella SG, Hecht SS. Metabolites of a tobacco-specific carcinogen in urine from newborns. J. Natl. Cancer Inst. 1999;91:459–465. [PubMed] [Google Scholar]

[83] Lagunov A, Sadeu JC, Bruin JE, Woynillowicz AK, Foster WG, Holloway AC. Effect of fetal and lactational exposure to nicotine on spermatogenesis in Wistar rats. 2009 Canadian Fertility and Andrology Society 55th Annual Meeting, Montreal, QC. [Google Scholar]

[84] Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. Semin. Perinatol. 1996;20:115–126. [PubMed] [Google Scholar]

[85] Lannero E, Wickman M, Pershagen G, Nordvall L. Maternal smoking during pregnancy increases the risk of recurrent wheezing during the first years of life (BAMSE) Respir. Res. 2006;7:3. [PMC free article] [PubMed] [Google Scholar]

[86] Lawrence J, Xiao D, Xue Q, Rejali M, Yang S, Zhang L. Prenatal nicotine exposure increases heart susceptibility to ischemia/reperfusion injury in adult offspring. J. Pharmacol. Exp. Ther. 2008;324:331–341. [PMC free article] [PubMed] [Google Scholar]

[87] Lenzen S, Drinkgern J, Tiedge M. Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. Free Radic. Biol. Med. 1996;20:463–466. [PubMed] [Google Scholar]

[88] Li MD, Kane JK, Konu O. Nicotine, body weight and potential implications in the treatment of obesity. Curr. Top Med. Chem. 2003;3:899–919. [PubMed] [Google Scholar]

[89] Lindley AA, Becker S, Gray RH, Herman AA. Effect of continuing or stopping smoking during pregnancy on infant birth weight, crown-heel length, head circumference, ponderal index, and brain:body weight ratio. Am. J. Epidemiol. 2000;152:219–225. [PubMed] [Google Scholar]

[90] Luck W, Nau H. Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. J. Pediatr. 1985;107:816–820. [PubMed] [Google Scholar]

[91] Luck W, Nau H. Nicotine and cotinine concentrations in the milk of smoking mothers: influence of cigarette consumption and diurnal variation. Eur. J. Pediatr. 1987;146:21–26. [PubMed] [Google Scholar]

[92] Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst. Rev. 2009 CD001055. [PMC free article] [PubMed] [Google Scholar]

[93] Lumley J, Oliver SS, Chamberlain C, Oakley L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst. Rev. 2004 CD001055. [PubMed] [Google Scholar]

[94] Mao C, Wu J, Xiao D, Lv J, Ding Y, Xu Z, Zhang L. The effect of fetal and neonatal nicotine exposure on renal development of AT(1) and AT(2) receptors. Reprod. Toxicol. 2009;27:149–154. [PMC free article] [PubMed] [Google Scholar]

[95] Marchetti P, Del Prato S, Lupi R, Del Guerra S. The pancreatic beta-cell in human Type 2 diabetes. Nutr. Metab. Cardiovasc. Dis. 2006;16(Suppl. 1):S3–S6. [PubMed] [Google Scholar]

[96] Maritz GS. Maternal nicotine exposure during gestation and lactation of rats induce microscopic emphysema in the offspring. Exp. Lung Res. 2002;28:391–403. [PubMed] [Google Scholar]

[97] Maritz GS. Nicotine and lung development. Birth Defects Res. C Embryo Today. 2008;84:45–53. [PubMed] [Google Scholar]

[98] Maritz GS, Thomas RA. The influence of maternal nicotine exposure on the interalveolar septal status of neonatal rat lung. Cell Biol. Int. 1994;18:747–757. [PubMed] [Google Scholar]

[99] Maritz GS, Windvogel S. Chronic maternal nicotine exposure during gestation and lactation and the development of the lung parenchyma in the offspring. Response to nicotine withdrawal. Pathophysiology. 2003;10:69–75. [PubMed] [Google Scholar]

[100] Martin JW, Mousa SS, Shaker O, Mousa SA. The multiple faces of nicotine and its implications in tissue and wound repair. Exp. Dermatol. 2009;18:497–505. [PubMed] [Google Scholar]

[101] Mitchell EA, Milerad J. Smoking and the sudden infant death syndrome. Rev. Environ. Health. 2006;21:81–103. [PubMed] [Google Scholar]

[102] Montgomery SM, Ekbom A. Smoking during pregnancy and diabetes mellitus in a British longitudinal birth cohort. BMJ. 2002;324:26–27. [PMC free article] [PubMed] [Google Scholar]

[103] Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use, and congenital malformations. Obstet. Gynecol. 2006;107:51–57. [PubMed] [Google Scholar]

[104] Neal MS, Zhu J, Foster WG. Quantification of benzo[a]pyrene and other PAHs in the serum and follicular fluid of smokers versus non-smokers. Reprod. Toxicol. 2008;25:100–106. [PubMed] [Google Scholar]

[105] Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, Kline J. Cocaine and tobacco use and the risk of spontaneous abortion. N. Engl. J. Med. 1999;340:333–339. [PubMed] [Google Scholar]

[106] Newman MB, Shytle RD, Sanberg PR. Locomotor behavioral effects of prenatal and postnatal nicotine exposure in rat offspring. Behav. Pharmacol. 1999;10:699–706. [PubMed] [Google Scholar]

[107] Nordentoft M, Lou HC, Hansen D, Nim J, Pryds O, Rubin P, Hemmingsen R. Intrauterine growth retardation and premature delivery: the influence of maternal smoking and psychosocial factors. Am. J. Public Health. 1996;86:347–354. [PMC free article] [PubMed] [Google Scholar]

[108] Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. Int. J. Obes. 2008;32:201–210. [PMC free article] [PubMed] [Google Scholar]

[109] Okuyemi KS, Ahluwalia JS, Harris KJ. Pharmacotherapy of smoking cessation. Arch. Fam. Med. 2000;9:270–281. [PubMed] [Google Scholar]

[110] Oliveira E, Moura EG, Santos-Silva AP, Fagundes AT, Rios AS, Abreu-Villaca Y, Nogueira Neto JF, Passos MC, Lisboa PC. Short- and long-term effects of maternal

nicotine exposure during lactation on body adiposity, lipid profile, and thyroid function of rat offspring. J. Endocrinol. 2009;202:397–405. [PubMed] [Google Scholar]

[111] Oncken C, Dornelas E, Greene J, Sankey H, Glasmann A, Feinn R, Kranzler HR. Nicotine gum for pregnant smokers: a randomized controlled trial. Obstet. Gynecol. 2008;112:859–867. [PMC free article] [PubMed] [Google Scholar]

[112] Oncken CA, Henry KM, Campbell WA, Kuhn CM, Slotkin TA, Kranzler HR. Effect of maternal smoking on fetal catecholamine concentrations at birth. Pediatr. Res. 2003;53:119–124. [PubMed] [Google Scholar]

[113] Oncken CA, Kranzler HR. Pharmacotherapies to enhance smoking cessation during pregnancy. Drug Alcohol Rev. 2003;22:191–202. [PubMed] [Google Scholar]

[114] Oncken CA, Kranzler HR. What do we know about the role of pharmacotherapy for smoking cessation before or during pregnancy? Nicotine Tob. Res. 2009;11:1265–1273. [PMC free article] [PubMed] [Google Scholar]

[115] Ong KK, Dunger DB. Perinatal growth failure: the road to obesity, insulin resistance and cardiovascular disease in adults. Best Pract. Res. Clin. Endocrinol. Metab. 2002;16:191–207. [PubMed] [Google Scholar]

[116] Ontario Medical Association (OMA) Rethinking stop-smoking medications: treatment myths and medical realities [update 2008] Ontario. Medical Rev. 2008;75:22–34. [Google Scholar]

[117] Osadchy A, Kazmin A, Koren G. Nicotine replacement therapy during pregnancy: recommended or not recommended? J. Obstet. Gynaecol. Can. 2009;31:744–747. [PubMed] [Google Scholar]

[118] Pauly JR, Slotkin TA. Maternal tobacco smoking, nicotine replacement and neurobehavioural development. Acta Paediatr. 2008;97:1331–1337. [PubMed] [Google Scholar]

[119] Pausova Z, Paus T, Sedova L, Berube J. Prenatal exposure to nicotine modifies kidney weight and blood pressure in genetically susceptible rats: a case of gene-environment interaction. Kidney Int. 2003;64:829–835. [PubMed] [Google Scholar]

[120] Perera FP, Tang D, Tu YH, Cruz LA, Borjas M, Bernert T, Whyatt RM. Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage. Environ. Health Perspect. 2004;112:1133–1136. [PMC free article] [PubMed] [Google Scholar]

[121] Peters MJ, Morgan LC. The pharmacotherapy of smoking cessation. Med. J. Aust. 2002;176:486–490. [PubMed] [Google Scholar]

[122] Petre MA, Labiris RN, Inman MD, Holloway AC. Fetal and neonatal exposure to nicotine disrupts postnatal lung development. 2008 Annual Meeting of the American Thoracic Society, Toronto, ON, May. [PMC free article] [PubMed] [Google Scholar]

[123] Petrik JJ, Gerstein HC, Cesta CE, Kellenberger LD, Alfaidy N, Holloway AC. Effects of rosiglitazone on ovarian function and fertility in animals with reduced fertility following

fetal and neonatal exposure to nicotine. Endocrine. 2009;36:281–290. [PubMed] [Google Scholar]

[124] Pickett KE, Wakschlag LS, Dai L, Leventhal BL. Fluctuations of maternal smoking during pregnancy. Obstet. Gynecol. 2003;101:140–147. [PubMed] [Google Scholar]

[125] Pollak KI, Oncken CA, Lipkus IM, Lyna P, Swamy GK, Pletsch PK, Peterson BL, Heine RP, Brouwer RJ, Fish L, et al. Nicotine replacement and behavioral therapy for smoking cessation in pregnancy. Am. J. Prev. Med. 2007;33:297–305. [PMC free article] [PubMed] [Google Scholar]

[126] Power C, Jefferis BJ. Fetal environment and subsequent obesity: a study of maternal smoking. Int. J. Epidemiol. 2002;31:413–419. [PubMed] [Google Scholar]

[127] Rhodes CJ. Type 2 diabetes-a matter of beta-cell life and death? Science. 2005;307:380–384. [PubMed] [Google Scholar]

[128] Robinson JS, Moore VM, Owens JA, McMillen IC. Origins of fetal growth restriction. Eur. J. Obstet. Gynecol. Reprod. Biol. 2000;92:13–19. [PubMed] [Google Scholar]

[129] Rogers JM. Tobacco and pregnancy. Reprod. Toxicol. 2009;28:152–160. [PubMed] [Google Scholar]

[130] Ruggiero L, Tsoh JY, Everett K, Fava JL, Guise BJ. The transtheoretical model of smoking: comparison of pregnant and nonpregnant smokers. Addict. Behav. 2000;25:239–251. [PubMed] [Google Scholar]

[131] Sandberg K, Poole SD, Hamdan A, Arbogast P, Sundell HW. Altered lung development after prenatal nicotine exposure in young lambs. Pediatr. Res. 2004;56:432–439. [PubMed] [Google Scholar]

[132] Sandberg KL, Poole SD, Hamdan A, Minton PA, Sundell HW. Prenatal nicotine exposure transiently alters the lung mechanical response to hypoxia in young lambs. Respir. Physiol. Neurobiol. 2007;156:283–292. [PubMed] [Google Scholar]

[133] Sasco AJ, Vainio H. From in utero and childhood exposure to parental smoking to childhood cancer: a possible link and the need for action. Hum. Exp. Toxicol. 1999;18:192–201. [PubMed] [Google Scholar]

[134] Schuller HM, Jorquera R, Lu X, Riechert A, Castonguay A. Transplacental carcinogenicity of low doses of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone administered subcutaneously or intratracheally to hamsters. J. Cancer Res. Clin. Oncol. 1994;120:200–203. [PubMed] [Google Scholar]

[135] Schuller HM, Jorquera R, Reichert A, Castonguay A. Transplacental induction of pancreas tumors in hamsters by ethanol and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Cancer Res. 1993;53:2498–2501. [PubMed] [Google Scholar]

[136] Schwartz-Bickenbach D, Schulte-Hobein B, Abt S, Plum C, Nau H. Smoking and passive smoking during pregnancy and early infancy: effects on birth weight, lactation

period, and cotinine concentrations in mother's milk and infant's urine. Toxicol. Lett. 1987;35:73–81. [PubMed] [Google Scholar]

[137] Seckl JR. Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Mol. Cell Endocrinol. 2001;185:61–71. [PubMed] [Google Scholar]

[138] Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, Lindstrom J, Spindel ER. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. J. Clin. Invest. 1999;103:637–647. [PMC free article] [PubMed] [Google Scholar]

[139] Sekhon HS, Keller JA, Benowitz NL, Spindel ER. Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. Am. J. Respir Crit. Care Med. 2001;164:989–994. [PubMed] [Google Scholar]

[140] Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. Maternal nicotine exposure upregulates collagen gene expression in fetal monkey lung. Association with alpha7 nicotinic acetylcholine receptors. Am. J. Respir. Cell Mol. Biol. 2002;26:31–41. [PubMed] [Google Scholar]

[141] Sharpe RM, Franks S. Environment, lifestyle and infertility—an inter-generational issue. Nat. Cell Biol. 2002;4(Suppl):s33–s40. [PubMed] [Google Scholar]

[142] Shiverick KT, Salafia C. Cigarette smoking and pregnancy I: ovarian, uterine and placental effects. Placenta. 1999;20:265–272. [PubMed] [Google Scholar]

[143] Skorge TD, Eagan TM, Eide GE, Gulsvik A, Bakke PS. The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood. Am. J. Respir. Crit. Care Med. 2005;172:61–66. [PubMed] [Google Scholar]

[144] Slotkin TA, Lappi SE, McCook EC, Lorber BA, Seidler FJ. Loss of neonatal hypoxia tolerance after prenatal nicotine exposure: implications for sudden infant death syndrome. Brain Res. Bull. 1995;38:69–75. [PubMed] [Google Scholar]

[145] Slotkin TA, Saleh JL, McCook EC, Seidler FJ. Impaired cardiac function during postnatal hypoxia in rats exposed to nicotine prenatally: implications for perinatal morbidity and mortality, and for sudden infant death syndrome. Teratology. 1997;55:177–184. [PubMed] [Google Scholar]

[146] Somm E, Schwitzgebel VM, Vauthay DM, Camm EJ, Chen CY, Giacobino JP, Sizonenko SV, Aubert ML, Huppi PS. Prenatal nicotine exposure alters early pancreatic islet and adipose tissue development with consequences on the control of body weight and glucose metabolism later in life. Endocrinology. 2008;149:6289–6299. [PubMed] [Google Scholar]

[147] Strandberg-Larsen K, Tinggaard M, Nybo Andersen AM, Olsen J, Gronbaek M. Use of nicotine replacement therapy during pregnancy and stillbirth: a cohort study. BJOG. 2008;115:1405–1410. [PubMed] [Google Scholar]

[148] Syme C, Abrahamowicz M, Mahboubi A, Leonard GT, Perron M, Richer L, Veillette S, Gaudet D, Paus T, Pausova Z. Prenatal exposure to maternal cigarette smoking and

accumulation of intra-abdominal fat during adolescence. Obesity (Silver Spring) 2009 Advance Access published on October 29, 2009; doi: 10.1038/oby.2009.354. [PubMed] [Google Scholar]

[149] Tiedge M, Lortz S, Drinkgern J, Lenzen S. Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells. Diabetes. 1997;46:1733–1742. [PubMed] [Google Scholar]

[150] Tong VT, England LJ, Dietz PM, Asare LA. Smoking patterns and use of cessation interventions during pregnancy. Am. J. Prev. Med. 2008;35:327–333. [PubMed] [Google Scholar]

[151] Toschke AM, Koletzko B, Slikker W, Jr, Hermann M, Von KR. Childhood obesity is associated with maternal smoking in pregnancy. Eur. J. Pediatr. 2002;161:445–448. [PubMed] [Google Scholar]

[152] Upton MN. Effects of parental smoking on the respiratory health of adults. Thorax. 2004;59:274–276. [PMC free article] [PubMed] [Google Scholar]

[153] Van Voorhis BJ, Dawson JD, Stovall DW, Sparks AE, Syrop CH. The effects of smoking on ovarian function and fertility during assisted reproduction cycles. Obstet. Gynecol. 1996;88:785–791. [PubMed] [Google Scholar]

[154] Vine MF. Smoking and male reproduction: a review. Int. J. Androl. 1996;19:323–337. [PubMed] [Google Scholar]

[155] Von KR, Toschke AM, Koletzko B, Slikker W., Jr Maternal smoking during pregnancy and childhood obesity. Am. J. Epidemiol. 2002;156:954–961. [PubMed] [Google Scholar]

[156] Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. Am. J. Epidemiol. 1989;129:1072–1078. [PubMed] [Google Scholar]

[157] Wideroe M, Vik T, Jacobsen G, Bakketeig LS. Does maternal smoking during pregnancy cause childhood overweight? Paediatr. Perinat. Epidemiol. 2003;17:171–179. [PubMed] [Google Scholar]

[158] Wilding JP. Neuropeptides and appetite control. Diabet. Med. 2002;19:619–627. [PubMed] [Google Scholar]

[159] Williams CM, Kanagasabai T. Maternal adipose tissue response to nicotine administration in the pregnant rat: effects on fetal body fat and cellularity. Br. J. Nutr. 1984;51:7–13. [PubMed] [Google Scholar]

[160] Williams LA, Evans SF, Newnham JP. Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant. BMJ. 1997;314:1864–1868. [PMC free article] [PubMed] [Google Scholar]

[161] Winzer-Serhan UH. Long-term consequences of maternal smoking and developmental chronic nicotine exposure. Front. Biosci. 2008;13:636–649. [PubMed] [Google Scholar]

[162] Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. Obstet. Gynecol. 2000;96:967–971. [PubMed] [Google Scholar]

[163] Wisborg K, Kesmodel U, Henriksen TB, Olsen SF, Secher NJ. Exposure to tobacco smoke in utero and the risk of stillbirth and death in the first year of life. Am. J. Epidemiol. 2001;154:322–327. [PubMed] [Google Scholar]

[164] Xiao D, Huang X, Lawrence J, Yang S, Zhang L. Fetal and neonatal nicotine exposure differentially regulates vascular contractility in adult male and female offspring. J. Pharmacol. Exp. Ther. 2007;320:654–661. [PubMed] [Google Scholar]

[165] Younglai EV, Foster WG, Hughes EG, Trim K, Jarrell JF. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch. Environ. Contam. Toxicol. 2002;43:121–126. [PubMed] [Google Scholar]

[166] Zenzes MT, Krishnan S, Krishnan B, Zhang H, Casper RF. Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. Fertil. Steril. 1995;64:599–603. [PubMed] [Google Scholar]

[167] Zheng Y, Ritzenthaler JD, Roman J, Han S. Nicotine stimulates human lung cancer cell growth by inducing fibronectin expression. Am. J. Respir. Cell Mol. Biol. 2007;37:681–690. [PubMed] [Google Scholar].