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COMMENTARY

Maternal nicotine exposure and fetal programming of vascular oxidative stress in adult offspring

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Despite the well-known harmful effects, many women continue to smoke throughout pregnancy. Consequently, nicotine replacement therapy (NRT) – which has been developed as a pharmacotherapy for smoking cessation – has been used as an alternative to smoking during pregnancy. However, like cigarette smoking, NRT results in biologically significant levels of nicotine crossing the placenta, leading to both fetal and neonatal exposure to nicotine, and yet, NRT safety during pregnancy has not been extensively evaluated. There is now evidence from studies in rats that maternal nicotine exposure throughout gestation results in fetal programming of vascular oxidative stress in the offspring during adulthood. This phenomenon involves vascular dysfunction mediated by reactive oxygen species in association with decreased superoxide dismutase activity and increased Nox2-NADPH oxidase expression in the vascular wall. If this phenomenon also occurs in humans, either smoking or NRT use during pregnancy may represent a novel risk factor for the unborn that results in accelerated cardiovascular disease in their adulthood.

LINKED ARTICLE

This article is a commentary on Xiao *et al.*, pp. 1400–1409 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2011.01437.x

Abbreviations

NADPH, nicotinamide adenine dinucleotide phosphate; NRT, nicotine replacement therapy

Despite readily available literature on the harmful effects of smoking during pregnancy, as many as 20% of women continue to smoke throughout pregnancy (Andres and Day, 2000). Obstetrical and fetal complications associated with cigarette smoking include stillbirth (Hogberg and Cnattingius, 2007), placental abruption (Ananth *et al.*, 1999), spontaneous abortion (George *et al.*, 2006) and sudden infant death syndrome (Mitchell and Milerad, 2006). Consequently, nicotine replacement therapy (NRT) has been developed as a pharmacotherapy for smoking cessation and may be used during pregnancy. However, the clinical safety of NRT use during pregnancy has only been evaluated in a small number of short-term human trials. Data from animal studies suggest that nicotine may be a crucial component of cigarette smoke responsible for many long-term effects associated with maternal cigarette smoking on the offspring, such as impaired fertility, type 2 diabetes, obesity, hypertension, neurobehavioural defects and respiratory dysfunction. This subject was recently reviewed in detail by Bruin *et al.* (2007).

Experimental and, ultimately, clinical research into developmental origins of disease could provide parents with new information to assist in lifestyle choices that have significant impact on their offspring. For example, a study of milk quality in lactating rats found that exposure to tobacco smoke altered glucose homeostasis and hormonal profiles in feeding pups. Thus, serum from pups born to smoke-exposed mothers had lower blood glucose levels, as well as lower adrenal catecholamine and serum corticosterone (Santos-Silva *et al.*, 2011). An earlier study of *in utero* and neonatal rat exposure to second-hand tobacco smoke demonstrated reduced endothelium-dependent relaxation in aortas of 4-week-old offspring (Hutchison *et al.*, 1998). In non-human

primates, perinatal exposure to second-hand smoke (from day 40 of gestation to 1 year of age) increased aortic levels of 3-nitrotyrosine and 2,4-dinitrophenylahydrazine, accompanied by reduced aortic superoxide dismutase protein expression and activity, as well as increased mitochondrial DNA lesions, as seen in human smokers (Westbrook *et al.*, 2010). Smoking during pregnancy results in biologically significant levels of nicotine crossing the placenta (range 3.3–28 $ng \cdot g^{-1}$) in amniotic fluid (range 1.5–23 $ng \cdot mL^{-1}$) and in fetal serum (range 0.5–25 $ng \cdot mL^{-1}$) (Luck *et al.*, 1985). Nicotine concentrates in fetal blood and amniotic fluid and is detectable in breast milk (Luck and Nau, 1985; Jordanov, 1990; Lambers and Clark, 1996). As such, like smoking, maternal use of NRT results in both fetal and neonatal exposure to nicotine.

In this issue, Xiao and colleagues report the first evidence of an impact of maternal nicotine exposure on fetal programming of vascular oxidative stress in adult offspring (Xiao *et al.*, 2011). Remarkably, administration of nicotine to pregnant rats throughout gestation resulted in augmented angiotensin II-induced vasoconstriction and impaired endothelium-dependent NO-mediated vasodilatation in their 5-month-old male offspring. These functional abnormalities could be abrogated by acute treatment of the vessels with the NADPH oxidase inhibitor, apocynin, or the superoxide dismutase mimetic, tempol, consistent with a detrimental effect of reactive oxygen species generated acutely in the vascular wall. Furthermore, the changes in vascular function were associated with decreased superoxide dismutase activity and increased Nox2, malondialdehyde, superoxide and nitrotyrosine levels in the vascular wall. The authors have previously reported that prenatal nicotine exposure leads to altered vascular reactivity in male adult offspring (Xiao *et al.*, 2007) associated with increased AT_1 angiotensin II receptors but decreased AT_2 receptor levels (Xiao *et al.*, 2008). Together with the current findings of enhanced vascular oxidative stress, it would therefore be anticipated that antenatal nicotine exposure increases the risk of hypertension and vascular disease, at least in male adult offspring. An important goal of future studies will thus be to carefully test this hypothesis, and if ultimately proven in humans, this important work will have revealed a novel cardiovascular risk factor that can only be modified before birth.

While these present findings have major implications for cardiovascular health, the fundamental processes that underlie oxidative stress and the resulting cellular dysfunction are likely to exist in other organ systems, and thus should also be carefully evaluated. Indeed, maternal nicotine exposure during pregnancy and lactation in Wistar rats has been reported to exert a direct effect on the nicotinic acetylcholine receptor in the developing pancreas to induce oxidative stress and subsequent beta cell loss (Bruin *et al.*, 2008), a scenario that is associated with increased risk of developing type 2 diabetes later in life (Leahy, 2005; Rhodes, 2005).

There is some information available regarding the ontogeny of chromatin remodelling to the onset of adult metabolic syndrome; however, the epigenetic changes during fetal development that result in adult vascular oxidative stress and dysfunction remain unknown. Fetal epigenetic changes following maternal nicotine exposure are an important aspect of fetal programming that needs to be studied in detail as DNA methylation is greatest during fetal life. Glucocorticoids have a demethylating action (Zhavoronkova and Vaniushin, 1987), which might modulate expression of genes involved in vascular structure and functional development, while reactive oxygen species can modify methylation, leading to changes in gene transcription and protein expression (Cerda and Weitzman, 1997; Valinluck *et al.*, 2004). Furthermore, modifications of histones H3 and H4 have been described in experimental intrauterine growth retardation associated with impaired development of pancreatic beta cells and insulin resistance, as a result of progressive epigenetic silencing of Pdx1 (Park *et al.*, 2008).

A reduction in the cost of health care will rely heavily on the birth of healthy children who are less likely to develop cardiovascular disease and metabolic syndromes later in life. Xiao *et al.* (2011) have here provided a further glimpse into a mechanism by which NRT-mediated maternal exposure to nicotine may programme the fetus to increased cardiovascular risk. Future epigenetic studies in experimental mouse models, and especially in humans, are needed to bolster our understanding of the complex fundamental biological processes of fetal programming affected by the prenatal and perinatal exposure to nicotine, received either through smoking or from the use of NRT.

Conflicts of interest

None.

References

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

Andres RL, Day MC (2000). Perinatal complications associated with maternal tobacco use. Semin Neonatol 5: 231–241.

Bruin JE, Gerstein HC, Holloway AC (2007). Long-term consequences of fetal and neonatal nicotine exposure: a critical review. Toxicol Sci 116: 364–374.

Bruin JE, Petre MA, Lehman MA, Raha S, Gerstein HC, Morrison KM *et al.* (2008). Maternal nicotine exposure increases oxidative stress in the offspring. Free Radic Biol Med 44: 1919–1925.

Cerda S, Weitzman SA (1997). Influence of oxygen radical injury on DNA methylation. Mutat Res 386: 141–152.

George L, Granath F, Johansson AL, Anneren G, Cnattingius S (2006). Environmental tobacco smoke and risk of spontaneous abortion. Epidemiology 17: 500–505.

Hogberg L, Cnattingius S (2007). The influence of maternal smoking habits on the risk of subsequent stillbirth: is there a causal relation? BJOG 114: 699–704.

Hutchison SJ, Glantz SA, Zhu BQ, Sun YP, Chou TM, Chatterjee K *et al.* (1998). In-utero and neonatal exposure to secondhand smoke causes vascular dysfunction in newborn rats. J Am Coll Cardiol 32: 1463–1467.

Jordanov JS (1990). 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 149: 734–737.

Lambers DS, Clark KE (1996). The maternal and fetal physiologic effects of nicotine. Semin Perinatol 20: 115–126.

Leahy JL (2005). Pathogenesis of type 2 diabetes mellitus. Arch Med Res 36: 197–209.

Luck W, Nau H (1985). Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. J Pediatr 107: 816–820.

Luck W, Nau H, Hansen R, Steldinger R (1985). Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. Dev Pharmacol Ther 8: 384–395.

Mitchell EA, Milerad J (2006). Smoking and the sudden infant death syndrome. Rev Environ Health 21: 81–103.

Park JH, Stoffers DA, Nicholls RD, Simmons RA (2008). Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest 118: 2316–2324.

Rhodes CJ (2005). Type 2 diabetes – a matter of beta-cell life and death? Science 307: 380–384.

Santos-Silva AP, Oliveira E, Pinheiro CR, Nunes-Freitas AL, Abreu-Villaca Y, Santana AC *et al*. (2011). Effects of tobacco smoke exposure during lactation on nutritional and hormonal profiles in mothers and offspring. J Endocrinol 209: 75–84.

Valinluck V, Tsai HH, Rogstad DK, Burdzy A, Bird A, Sowers LC (2004). Oxidative damage to methyl-CpG sequences inhibits the binding of the methyl-CpG binding domain (MBD) of methyl-CpG binding protein 2 (MeCP2). Nucleic Acids Res 32: 4100–4108.

Westbrook DG, Anderson PG, Pinkerton KE, Ballinger SW (2010). Perinatal tobacco smoke exposure increases vascular oxidative stress and mitochondrial damage in non-human primates. Cardiovasc Toxicol 10: 216–226.

Xiao D, Huang X, Lawrence J, Yang S, Zhang L (2007). Fetal and neonatal nicotine exposure differentially regulates vascular contractility in adult male and female offspring. J Pharmacol Exp Ther 320: 654–661.

Xiao D, Xu Z, Huang X, Longo LD, Yang S, Zhang L (2008). Prenatal gender-related nicotine exposure increases blood pressure response to angiotensin II in adult offspring. Hypertension 51: 1239–1247.

Xiao D, Huang X, Yang S, Zhang L (2011). Antenatal nicotine induces heightened oxidative stress and vascular dysfunction in rat offspring. Br J Pharmacol 164: 1400–1409.

Zhavoronkova EN, Vaniushin BF (1987). [DNA methylation and interaction with glucocorticoid receptor complexes in the rat liver]. Biokhimiia 52: 870–877.