Tobacco Addiction: Effect on Human Health

Chapter 4

Maternal Cigarette Smoking and Fetal Programming of Cardiovascular Dysfunction Late in Life

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Abstract

Maternal tobacco smoking during pregnancy and lactation remains a major public health concern and is associated with a higher risk of poor pregnancy outcomes. It is well known that the adverse environmental exposure within the critical window of gestation period can initiate aberrant fetal development that leads to cardiovascular diseases in adulthood, a phenomenon called programming. Here, we summarize several epidemiological and experimental studies that demonstrate the association between maternal nicotine or tobacco exposure during pregnancy and the development of cardiovascular dysfunction. This chapter also presents some novel epigenetic molecular mechanisms underlying the maternal smoking/nicotine-induced fetal programming of the adult cardiovascular disease. Taken together, a smoke-free environment during pregnancy is essential to improving health outcomes and reducing the risk for future cardiovascular diseases. A better understanding of the epigenetic molecular mechanism underlying the effects of perinatal smoking exposure on programming could provide novel insights into the therapeutic strategies for cardiovascular diseases.

Key words: smoking; nicotine; offspring; cardiovascular dysfunction

1. Introduction

In the last half-century, great attention has been focused on the adverse effects of tobacco smoking on human health, especially on fetal development [1]. Although an increasing number of women realize the critical health issues of smoking during pregnancy and make decisions to cease smoking, the prevalence is still unsatisfactory [2]. There are about 6.8% to 12.3% of women who smoke during pregnancy in the United States and more than 10% of women in Europe [2,3]. In Asian countries, such as China, 2.4% of the women also smoke [4].

Tobacco smoke contains numerous chemicals which are not only harmful to smokers, but also to secondhand non-smokers and the fetus while in utero [5]. This toxic smoke consists of tar, heavy metals (such as lead, cadmium, and chromium), hydrogen cyanide and gaseous phases such as carbon monoxide (CO), carbon dioxide, nitric oxide, and the notorious nicotine [6-8]. Nicotine, one of the most hazardous substances and carcinogens in tobacco smoke, can easily cross the placenta entering the circulation of the fetus, and penetrate into the mother's milk [9]. In fact, the fetus tends to be more prone to injury because nicotine is concentrated in the fetus at levels at 15% higher than maternal levels [10]. To investigate the adverse effects of tobacco smoke in the fetal cardiovascular system, the relationship between maternal smoking during pregnancy and the increased risk of cardiovascular disease has been extensively studied [11,12]. Furthermore, previous studies have demonstrated that nicotine exposure in the fetal period could lead to fetal programming of cardiovascular dysfunction later in life [13-16].

2. Maternal Cigarette Smoking and Development of Congenital Heart Defect (CHD)

2.1. Maternal cigarette smoking increases the risk of CHD in offspring

CHD is one of the leading causes of perinatal and infant morbidity and mortality which involves the structural abnormalities of the heart and large arteries [17,18]. CHD has a high incidence of 6 to 12 per 1000 live births around the world [18]. There have been substantial studies about the genetic and chromosomal risk factors for CHDs; however, the etiology of CHDs is still an enigmatic [19,20]. Growing evidence suggest that maternal smoking is one of the important risk factors for the development of CHDs [12]. In the 1970s, investigators from London and UCLA reported that, across all races, offspring of tobacco smoking mothers had a higher incidence of CHDs from 7.3% to 8.1%, respectively [21,22]. In addition, epidemiologi-cal studies have further confirmed that maternal tobacco smoking acts as a significant risk factor for CHD [23,24]. For example, meta-analysis evidence shows that smoking exposure (odds ratio (OR) =2.766, 95% confidence interval (CI): 1.982-3.859) during maternal pregnancy is the main risk factor of neonatal CHDs [25]. Furthermore, there is approximately a 10% relative increase in the incidence of CHDs which appears in infants whose mothers were addicted

to tobacco smoking during pregnancy [12].

2.2. The effect of maternal cigarette smoking on CHD is dependent on the pregnancy period and exposed dosage

The first trimester of pregnancy, especially at 11-13 weeksgestationjs one of the most important periods for changes in the maternal serum levels of the placental growth factor and other factors. These factors could induce CHDs in the fetus [26]. There are 3 subtypes of CHDs associated with maternal tobacco smoking during this period: pulmonary valve (PV) anomalies, pulmonary artery anomalies and the isolated atrial septal defect (ASD) (the secundum type) [11]. Coincidentally, in the Baltimore-Washington study, first-trimester maternal cigarette smoking contributed to the right ventricular outflow tract (RVOT) defect (OR=1.32, 95% CI: 1.06-1.65), PV stenosis (OR=1.35, 95% CI:1.05-1.74), secundum ASD (OR=1.36, 95% CI: 1.04-1.78), L-transposition of the great arteries (L-TGA) (OR=1.79, 95% CI: 1.04-3.10) and truncus arteriosus (TA) (OR=1.90, 95% CI: 1.04-3.45) [27]. In a population based case control study in the USA, mothers who were addicted to tobacco smoke before pregnancy and/or during the first trimester of pregnancy had a higher risk of having the congenital septal defect in their infants [28].

The risk of increased CHD is not only dependent on the maternal smoking exposure time but is also dependent on the smoking dosage. Mothers who were heavier smokers were significantly increased by the incidence of congenital septal defect in their infants [28]. In another population-based study among 14,128 non-patent ductus arteriosus cases with CHDs, the maternal first trimester of tobacco smoking shows a dose dependent increase in the risk of CHDs in their offspring [29]. In this study, the adjusted odds ratio (aOR) for the anomalies of pulmonary vein and pulmonary artery are increased as the dose of maternal tobacco smoking increased. The dose response was especially strong among offspring with a septal defect and left ventricular outflow tract obstruction with a four-fold and six-fold rise from medium maternal smoking to heavy maternal smoking, respectively [12,30,31].

2.3. The effect of maternal cigarette smoking on CHD may be dependent on the genetic and epigenetic background

In mothers with a functional gene defect, maternal smoking exposure could put off-spring closer to the threshold of CHDs as compared with normal genetic mothers [30]. It was reported that mothers with the GSTM1 and GST1 deletion tend to have increased chances for development of CHDs in their children, if they have a higher hair nicotine concentration [30]. Previous studies have shown that Gata4 and Tbx5 are two cardiac transcription factors which play an important role in the development of CHDs [32, 33]. Maternal nicotine exposure could promote DNA hypermethylation, resulting in an inhibition of the Gata4 and Tbx5 gene expression in both differentiating embryonic bodies and their offspring hearts [34]. This suggests that

epigenetics may play a key role in the maternal cigarette smoking-mediated development of CHDs.

3. Maternal Cigarette Smoking and Fetal Programming of Adult Cardiovascular Dysfunction

Fetal hemodynamic changes in response to maternal tobacco smoking during pregnancy, and such changes may be associated with either cardiovascular adaptation or maladaptation in their offspring [35]. Previous studies have suggested that cardiovascular dysfunction in adult-hood may be programmed from its onset early in the prenatal period [36,37]. Therefore, we provide some key evidence to show that maternal smoking may predispose fetal programming to adult cardiovascular dysfunction.

3.1. Fetal programming of atherosclerosis of aorta late in life

Atherosclerosis of the aorta is one of the inducing factors of heart disease causing cardiovascular dysfunction [38]. One of the earliest signs of atherosclerosis of the aorta is increased aortic intima–media thickness (aIMT) [39]. In animal models, nicotine administration (3 and 6 mg/kg/day) in female rats during gestation had significantly increased aIMT in their offspring [40]. Another similar study showed that rat pups had twice the thickness of the intima in the maternal nicotine exposure period during pregnancy as well as in the lactation period as compared with the saline control group [38]. In a human study located in a Turkey hospital, it was reported that increased mean and weight-adjusted aIMT was detected among neonates whose mother had smoked [41].

3.2. Fetal programming of adult hypertension

Hypertension is a worldwide cardiovascular disease with a prevalence among 30% of the world's population that damages multiple organs such as the heart, lung, brain, and kidney [42]. Extensive studies demonstrate that hypertension is considerable when associated with maternal tobacco smoking exposure in utero which is characterized by a higher systolic and/or diastolic blood pressure in childhood [2,43]. Epidemiologic studies have shown that maternal tobacco smoking increases blood pressure not only in newborns [44,45], and children [46,47], but also in adults [48]. Maternal smoking-induced hypertension is most likely associated with the action of nicotine. Nicotine is a ganglionic agonist which could stimulate neurotransmitter (such as norepinephrine) release. Indeed, direct treatment with nicotine during pregnancy has been shown to increase risk of hypertension in adulthood among different animal models [14, 15,49,50].

The effect of maternal smoking/nicotine exposure on the development of hypertension in offspring is complex, with many underlying mechanisms. Previous studies have demon-

strated that the functional changes of endotheliocytes, perivascular adipose tissue and kidneys may contribute to the maternal smoking/nicotine exposure-induced hypertension [43]. It's well known that the renin-angiotensin system plays a key role in the regulation of blood pressure. Recent studies suggest that alterations of the renin-angiotensin system may be one of the important mechanisms contributing to the fetal programming of hypertension [51,52]. In the kidneys, the angiotensin receptor type 1 (AT1R) gene is downregulated in offspring rats of maternal rats exposed to cigarette smoking [53]. On the other hand, AT1R expression and the ratio of AT1R/ AT2R in vasculatures were increased in adult offspring whose mothers had been treated with nicotine [54]. The overexpression of AT1R results in the enhanced capability of Angiotensin II-induced vasoconstriction, and the consequent development of hypertension in adult offspring. In addition, it has been shown that prenatal nicotine exposure can inhibit baroreflex sensitivity which maintains blood pressure steadily by a rapid negative feedback loop [55]. Further more, nicotine exposure during pregnancy could increase arterial reactive oxygen species (ROS) production, which enhances vascular reactivity, resulting in the development of hypertension in offspring. Inhibition of ROS could block maternal nicotine-induced hypertension [56], suggesting that heightened ROS production may be one of the molecular mechanic linkers between maternal nicotine exposure and the fetal programming of adult hypertension.

3.3. Fetal programming of arrhythmia

In addition to the development of hypertension in offspring, previous studies have also found an irregular fetal pulse and permanent development of arrhythmia in adulthood following exposure to nicotine during pregnancy [57]. It has been reported that maternal cigarette smoking acutely increases the fetal heart rate, which may be due to an increase in sympathetic activity [58]. However, the chronic long-term effects of fetal nicotine exposure on the heart are some what different and may result from alterations in heart development. Fetal nicotine exposure during pregnancy has been shown to alter the types of nicotinic receptors that facilitate excitatory inputs to cardiac vagal neurons, which may be responsible for the bradycardia observed in offspring [59]. Moreover, cardiac cycle irregularity and single/multiple dropped cardiac cycles have been detected in fetal sheep prenatally exposed to nicotine [57]. This cardiac conduction dysfunction and malignant arrhythmia may be one of the major causes for sudden infant death and cardiac dysfunction-induced by maternal cigarette smoking [57,58]. Studies in rats and sheep models have suggested that uterine hypoxia may be considered as one of the potential mechanisms underlying prenatal nicotine-induced arrhythmia in offspring [57]. In adult offspring rats, maternal nicotine exposure caused myocardial fibrosis and cardiac remodeling. Given the fact that myocardial fibrosis and cardiac remodeling are the major factors for the development and progression of atrial fibrillation, these factors may be other potential mechanisms underlying nicotine-mediated arrhythmia in offspring [50,55,60]. Previ-

ous studies have demonstrated that in the three month-old offspring rats prenatally exposed to nicotine, heart rates are significantly increased, with loose, confused myofibril arrangement and excessive ECM accumulation. Mean while, the cardiac eject function was impaired and diastolic LV posterior wall thickness had thickened [55]. The TGF-β1 geneplays a key role in the development of myocardial hypertrophy and fibrosis [61]. Previous findings have shown that the expression of TGF-β1 was increased with the β-myosin heavy chain in offspring born to prenatal and postnatal nicotine-treated dams.This suggests that the TGF-β1 genes may be one of the important mechanisms in perinatal nicotine-induced cardiac hypertrophy and arrhythmia [62].

3.4. Fetal programming ofpulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension is another cause of cardiac dysfunction [62]. Pulmonary fibrosis is one of the key factors in the pathology of PAHwithan excessive accumulation of the extracellular matrix protein (ECM) which contributes to vascular stiffness through a decrease in tissue and vessel compliance [63]. It has been reported that maternal nicotine exposure adversely affects lung development and function in fetuses and neonates [64,65]. In pregnant rats treated with nicotine, male adult offspring showed higher collagen content and expressions of collagen 1 and 3 in the lungs, associated with an increase in the expressions of AT1R and the ratio of AT1R/AT2R in the lung tissues [66]. In addition, the expressions of TGF-β1, CTGF and Smad3 were also increased in the lung tissues [66]. This evidence suggest that maternal cigarette smoking could induce the occurrence and development of pulmonary fibrosis in adult offspring and increase susceptibility to PAH [66].

Epithelial-mesenchymal transition (EMT) is one of the key factors in the pathogenesis of pulmonary fibrosis. Recentstudies have shownthat prenatal nicotine exposure can directly regulate EMT-related protein expression [67,68]. EMT related protein expressions were significantly higher as early as postnatal day 7 in the maternal nicotine exposed group [68]. The maternal smoking/nicotine-mediated enhanced the EMT-related protein expression which may contribute to the development of pulmonary fibrosis and pulmonary arterial hypertension in offspring [68,69].

3.5. Fetal programming of heart ischemia-sensitive phenotype

Human epidemiological studies suggest a link between adverse intrauterine environments and an increased risk of ischemic heart disease in adulthood [70]. Our previous studies in a pregnant animal model have demonstrated that fetal nicotine exposure reprogrammed cardiovascular function and induced the development of a heart ischemia-sensitive phenotype in adult offspring [16,71]. Nicotine exposure in pregnancy significantly enhanced Ischemia/Reperfusion (I/R) injury in the left ventricle (LV) and led to poor outcomes of LV function with a lower coronary flowrate in the adult offspring [16,71]. Furthermore, the development

of heart ischemia-sensitive phenotype is associated with a significant decrease in protein kinas Cε(PKCε) in the hearts [16]. PKCε plays a pivotal role in cardioprotection from heart ischemia and reperfusion [72]. This evidence suggest that prenatal nicotine exposure-induced fetal programming of the PKCε gene expression pattern in the developing heart. This may be one of the key molecular mechanisms underlying why the nicotine-mediated increased its'heart susceptibility to ischemia/reperfusion injury in adult offspring.

Another vital mechanism that contributes to myocardial ischemia/reperfusion injury and heart dysfunction is oxidative stress. Maternal smoking is associated with the increased levels of reactive oxygen species (ROS) in offspring [73]. Furthermore, fetal nicotine exposure leads to increasing levels of ROS in fetal, neonatal and adult tissues [74,75]. Our recent studies in the pregnant rat model have demonstrated that fetal nicotine exposure increases cardiac ROS production, which leads to an epigenetic downregulation of the cardioprotective protein, PKCε gene expression and an upregulation of cardiac GSK3 βphosphorylation. This results in an increase in the heart I/R injury and dysfunction [76].

Protein disulfide isomerase (PDI)acts as a cardioprotector and a survival factor during ischemia [77]. In the perinatal nicotine exposed rat adult offspring, PDI levels were significantly decreased in the heart tissues, associated with decreased levels of superoxide dismutase enzymes, mitochondrial complex proteins, and the tissue inhibitor of metalloproteinase-4 [78]. These findings suggest that fetal nicotine exposure could program cardiac PDI expression, leading to promote oxidative stress and mitochondrial damage, consequently increasing heart ischemic injury in adulthood.

4. Conclusion

Maternal cigarette smoking is one of the most perinatal insults. Maternal smoking during pregnancy not only induces fetus growth restriction, but also affects fetal organ development. Epidemiological human and animal studies have shown that fetal cigarette smoking exposure is a major risk factor for the development of CHD and other cardiovascular diseases later in life. As the prevalence and incident use of tobacco cigarette or e-cigarettes continues to increase worldwide, an understanding of their risks during pregnancy becomes a pressing need in areas of public health. Although we begin to understand that fetal smoking exposure could affect fetal cardiovascular development and consequently lead to cardiovascular disease in adulthood, the epigenetic molecular mechanisms are still not fully understood. A better un-derstanding of those mechanisms is critical and could help professionals to identify early bio-markers and provide new leads in the development of the preventive diagnosis and therapeutic strategies of maternal smoking-mediated fetal programming of cardiovascular disease.

6. Reference

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