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Smoking: An Important Environmental Risk Factor in Pregnancy

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Abstract

It is generally recognized that smoking has been one of the most public health disorders around the world. Nowadays, more and more studies have proved that smoking during pregnancy is responsible for both maternal and fetal health disorders along with several general health effects. It may lead to various kinds of pregnancy illness and cause risk to the fetus during perinatal stage. After birth, this behavior can also have harmful influences on neonates, and even on children. However, smoking during pregnancy has several adverse effects, the molecular mechanism of it remains unclear. Recently, some studies have proved that it is associated with aberrant epigenetic modifications. All of these remind us that more attention should be paid to maternal cigarette smoking, and more studies should be carried out to confirm the effects and investigate the molecular mechanisms. In this chapter, a brief review is given on the perinatal effects and long-term influences of maternal and passive smoking. We also briefly clarify the epigenetic mechanisms underlying the adverse effects of passive smoking during pregnancy.

Keywords: smoking, passive smoking, pregnancy, perinatal effects, effects on neonates

1. Introduction

It is generally recognized that smoking has been one of the most public health problems around the world because it is widespread and harmful. According to the statistics, there are over 1.2 billion smokers all over the world, and nearly 4.9 million people are dying from smoking [1].

As an invisible cause of death, smoking during pregnancy is responsible for both maternal and fetal health disorders including miscarriage and congenital abnormalities along with several general health effects (e.g., cardiovascular disease, respiratory disease, cancer) [2, 3].

The substances contained in cigarettes may cause harm to the fetus. Among those substances, two compounds are especially harmful: nicotine and carbon monoxide. Nicotine is highly addictive. It is well studied that nicotine is a carcinogen and extremely toxic in tobacco leaves, which results in many responses such as increasing heart rate and blood pressure. Meanwhile, carbon monoxide can also lead to fetal hypoxia. Thus, the infant whose mother smokes has a higher perinatal morbidity and mortality. Also, there are many other harmful compounds such as arsenic, formaldehyde, lead, uranium, and ammonia.

This chapter introduces the great harm done to the developing fetus resulting from maternal smoking and passive smoking, which creates problems that will prevail not only during the pregnancy but also long after parturition.

2. Perinatal effects

2.1. Preterm birth

It has been a significant global problem with more than 10% of babies suffering from it. Preterm birth or other relevant disorders lead to death of a million children each year worldwide [4]. Several factors can lead to premature birth, for example, underlying infection or some anatomical considerations. Besides, smoking during pregnancy is also an important factor that may cause preterm birth. Since nicotine exposure leads to several complications of pregnancy and birth, the risk for preterm birth is higher among women who smoke during pregnancy. It is shown that the probability of preterm birth is over 1% higher for women who smoke during pregnancy than others [5]. There are several elements contributing to the alteration of steroid hormone production and changes of the responses to oxytocin such as hypoxia resulting from carbon monoxide and vasoconstriction resulting from nicotine [6].

Using Taiwan Birth Cohort to explore the effects of maternal smoking on birth outcomes, Ko et al. [7] found that maternal smoking is associated with preterm delivery. The incidences of preterm birth of mothers who smoked during the different pregnancy stages increased with the number of cigarettes smoked daily, which was especially significant among those who smoked more than 20 cigarettes/day.

Unlike other unavoidable factors for preterm birth, tobacco smoking is an environmental exposure which can be easily eliminated, and even short behavioral interventions can be effective.

2.2. Ectopic pregnancy

Transport of the fertilized egg through the fallopian tube is controlled by ciliary beating and smooth muscle contractility [8]. Ectopic pregnancy (tubal pregnancy), or ectopic pregnancy, is a complication of pregnancy in which the embryo attached outside the uterus [9]. Ectopic pregnancy in the fallopian tubes are more common among smoking women as nicotine or other substances of cigarettes may lead to the turnover of altered epithelial cell in the fallopian tube and result

in the dysfunction of fallopian tube. Several risk factors of damaging or killing cilia can result from smoking, thus increasing the time for the embryo to reach the uterus. The embryo, which cannot reach the uterus in time, will implant itself inside the fallopian tube, causing the ectopic pregnancy [10]. Besides ectopic pregnancy, cigarette smoking during pregnancy also leads to other human reproduction disorders such as spontaneous abortion and infertility [11].

2.3. Premature rupture of membranes (PROM)

PROM, also known as rupture of membranes occurring in pregnancy, refers to breakage of the amniotic sac. Commonly, it is called breaking of the mother's water [12]. There is amniotic fluid surrounding and protecting the fetus in the uterus contained in the sac (including two membranes, the chorion and the amnion). When rupture occurs, the fluid leaks out of the uterus through the vagina. Fetal membranes will be likely to be broken because they become weak and fragile. This change is usually a normal process that happens along with the body preparing for labor or delivery. However, this will become a problem when premature birth occurs. Cigarette smoking during pregnancy leads to the abnormal weakness of fetal membranes by the factors of cell death and poor assembly of collagen, and even breakdown of collagen [13].

2.4. Pregnancy-induced hypertension and preeclampsia

Similar with overweight, smoking during pregnancy is shown as an inverse risk factor for hypertensive disorders of pregnancy such as pregnancy-induced hypertension and preeclampsia. Studies demonstrate that, compared with women of normal weight, pregnancy-induced hypertension and gestational hypertension are more common among overweight women, especially in overweight women who smoke. The risk for hypertensive disorders increases 2–3 times among overweight and obese women [14, 15], which reflects an independent effects of obesity or smoking habits on the hypertensive disorders.

On the contrary, there is an inverse association that smoking in women of normal weight has potential effect of decreasing the risk of pregnancy-induced hypertensive disorders. Barquiel et al. [16] found that prepregnancy overweight or obesity and excess gestational weight gain are all associated with pregnancy-induced hypertensive disorders. However, there is no clinical proof of the potentially positive effect of nicotine exposure on hypertensive disorders. It is hypothesized that the combustion of tobacco products circulating angiogenic proteins, which could be released through carbon monoxide [6, 17].

2.5. Fetal growth restriction

Several studies have demonstrated that fetuses with prenatal nicotine exposure have lower birth weight than their peers [18, 19], and the findings are consistent with intrauterine growth restriction [20, 21]. Imaging examination shows that this growth restriction affects brain, kidney, lung, and other lean and fatty tissues. Overall fetal volume and placental volume are also decreased, which may result in embryo damage and miscarriages, thus increasing the infant mortality [22, 23]. This effect is found to be dose-dependent. There is a decreased birth weight by an average of 2.8 g for each additional pack of cigarette smoked during pregnancy [23].

According to a large nationwide birth cohort study in Japan, Suzuki et al. [24] found that maternal smoking during pregnancy can lead to lower birth weight by 125–136 g.

The mechanism of fetal growth restriction is under debate. Several initial studies demonstrated that fetal hypoxia is induced by the carbon monoxide or other combustion products [6, 25]. However, it is observed that using electronic cigarettes also results in fetal growth restriction, making this view seems less likely [22]. Numerous researchers agree that smoking during pregnancy significantly increases the resistance of placental blood flow, which is associated with fetal growth restriction [26, 27]. It may be seen that fetal growth restriction results from nicotine, which leads to the vasoconstriction. While there is another theory proposing that decreased supply of amino acids contributes to fetal growth restriction. Nicotine exposure blocks the cholinergic receptor and impairs amino acid transport [28], while the hypoxia resulting from carbon monoxide also limits the transport of amino acids.

3. Effects on neonates

3.1. Sudden infant death syndrome (SIDS)

SIDS is one of the main reasons for death among healthy infants [29]. It is defined as the sudden death of 1-year-old neonates. SIDS usually occurs with no struggle, no noise produced, and always happens between 00:00 and 09:00 during children's sleep [30]. SIDS seems to occur when a neonate has an underlying biological vulnerability, such as premature infants or low-birth-weight infants, or has problems in the part of the brain [31]. Studies show that SIDS rates are higher in infants with fetal growth restriction resulting from prenatal nicotine exposure [32]. The study of Zhang and Wang [33] also suggested that maternal smoking could increase the risk of SIDS, and it was dose-dependent. Mitchell and Milerad [34] discovered that the exposure of the fetus to tobacco is associated with SIDS. They also suggested that if maternal smoking is avoided, about one-third of SIDS deaths might have been hold back. However, until now, no one knows the exact cause of SIDS, and the mechanism that how prenatal nicotine exposure leads to SIDS remains unclear.

3.2. Future obesity and endocrine imbalance

Similar to fetal restriction, studies proved that prenatal smoking could affect growth patterns over the long term, with height deficits documented in childhood through to adulthood [35]. Disproportionate weight gain opposite to fetal growth restriction is considered to be associated with the infant's self-regulation of food intake after birth, as small-for-date babies take more milk than large-for-date babies, suggested by Ounsted's study [36]. A recent study has proposed that despite birthing with lower weights, children of mothers who smoke during pregnancy tend to be overweight [37, 38], and such an effect will last for a lifetime [39, 40]. It is noted that alterations in ghrelin concentrations are likely to be involved [41]. Thus, the offspring of smoking mothers takes more risk of suffering from type 2 diabetes [42, 43].

Alternatively, endocrine imbalances could occur at critical developmental periods. Studies point out negative effects of prenatal smoking on reproductive system. The menarche may be earlier in females exposed to nicotine prenatally [25]. In males, analysis of semen samples points out that prenatal nicotine exposure results in poor semen quality and decreased sperm count [44, 45]. This indicates that such long-term health consequences are not confined to one generation, but also continued to impair the health of a future generation.

3.3. Respiratory tract infections and compromised lung function

Maternal smoking can also influence fetal lung development and lung function. The embryonic immune function will have over reaction to certain substances, thus producing antibodies, which are easy to cause allergic diseases after the baby was born. Pulmonary function testing demonstrates that the impaired lung function of children is associated with the exposure to nicotine prenatally [46, 47]. Compared with their peers, the incidents of respiratory tract infections and compromised lung function (e.g., asthma or wheezing) increased [48, 49], as a result of developmental anomalies in the lung caused by nicotine. These changes will impair the gas-exchange ability of the pulmonary parenchyma, leading to a directly increased amount of work for respiration [50]. In addition, Hayatbakhsh et al. [51] proved that the bad effects on the growth and development of the respiratory tract may continue into adulthood.

3.4. Congenital heart defects and hypertension

As is shown that nicotine increases placental vascular resistance [52, 53], children with maternal nicotine exposures tend to have a greater risk of hypertension throughout the whole life [54, 55]. Further studies show that women who smoke during pregnancy put their fetus at a higher risk of birth defects, especially congenital heart defects than their peers [56, 57]. Using an epidemiological case-control study, Kuciene and Dulskiene [58] collected the information on potential risk factors of newborns' health. They chose 261 newborns with congenital heart septal defects and 1122 randomly selected newborns without any defects. They found that smoking during pregnancy can increase the risk of congenital heart septal defects in infants.

However, the effect of smoking during pregnancy on the progeny of hypertension is not clear. De Jonge et al. [59] found that the association between smoking during pregnancy and the risk of hypertension in the offspring are largely determined by weight, and the mechanisms in utero remain unknown.

3.5. Brain function

Since there are many toxic chemicals in tobacco, smoking during pregnancy can restrict the head growth, change the structure and function of the brain, and have lifelong bad effects on the fetal brains. In addition to the direct impact of the chemical composition, evidence suggests that smokers are more susceptible to depression and refuse to take health promoting actions. To be specific, smokers will not receive prenatal care timely and recognize their pregnancies later [60]. Along with the adverse effects of nicotine on the fetal brain, children of smokers are more likely to have learning disorders or behavioral problems. El Marroun

et al. [60] proved that smoking during pregnancy is associated with brain dysfunction of children. They found that maternal cigarette smoking can lead to smaller brain volumes, smaller cortical gray and white matter volumes of children, and these children will also have thinner superior frontal, superior parietal, lateral occipital, and precentral cortices, and show more behavioral and emotional problems.

In conclusion, smoking during pregnancy can cause bad effects on the growth of the fetal head and influence the normal brain function [61]. However, the mechanisms of how these bad effects happen on the fetus need more research.

4. Effects of passive smoking

We all know that maternal active smoking is harmful to pregnant women and the fetus; however, more and more studies have showed that passive smoking is also a hidden threat [62]. Ohida et al. [63] demonstrated that passive smoking could make pregnant women suffer from sleep disturbance, because nicotine affected the central nervous system, kept people awake, and increased the sleep latency, reduced both total sleep time and REM sleep. Qiu et al. [64] have found that passive smoking can lead to preterm birth. However, when they stratified the data by gestational age, they also found that passive smoking was strongly associated with very preterm birth (<32 weeks of gestation) but not with moderate preterm birth (32–36 weeks of gestation), and the risk of very preterm birth is increased when the time of the exposure to tobacco is increased.

In recent years, many anti-smoking activities have been carried out in public places to prevent nonsmoking women and children who suffer from passive smoking. However, bad effects of passive smoking on pregnant women have not been widely publicized because they are less clear, and many people are still not aware of them. So more studies should be carried out to ensure bad outcomes of pregnant women associated with passive smoking.

5. The epigenetic mechanism of adverse effect of smoking during pregnancy

Several studies have demonstrated that smoking during pregnancy takes effects through epigenetic mechanisms, just like other environmental factors. Knopik et al. [65] proved that smoking during pregnancy can change the process of DNA methylation and disrupt miRNA expression. They deemed that maternal cigarette smoking was associated with incorrect DNA methylation patterns, which were important for the health of the embryo, and it could also lead to the aberrant expression of miRNA. Therefore, many biological processes would be disturbed. Suter et al. found that smoking during pregnancy is associated with aberrant placental epigenome-wide DNA methylation and gene expression, including changes in promoter methylation of placental *CYP1A1*, which are related to *CYP1A1* gene expression and

fetal growth restriction. They also suggested that smoking during pregnancy is concerned with altered site-specific CpG methylation which is necessary for important changes in gene expression, which ensure proper growth and development [66]. Lee et al. [67] demonstrated that smoking during pregnancy may change the DNA methylation of the offspring reproducibly, which may last for many years, even into adolescence.

Although many facts show that smoking during pregnancy has many bad effects in terms of epigenetics, we still cannot figure out the specific process of it. Therefore, more studies should be done to increase the understanding of mechanisms involved.

6. Anti-smoking measures

Since smoking during pregnancy can lead to many bad effects on pregnant women, the fetus, and newborns, increasing awareness of the consequences of smoking during pregnancy among women is obviously very important. However, participants were not fully aware of the bad outcomes of smoking during pregnancy [68]. Koren [69] showed that about 25–30% of women smoke at the beginning of the pregnancy. Many pregnant women had given up smoking for the health of the fetus; however, some of them remained smoking during pregnancy. The study indicated that except those psychosocial factors, nicotine addiction is widely acknowledged as the main reason of smoking cessation failures. So, they put forward a smoking cessation therapy called nicotine replacement therapy. It used nicotine patches, gum, or intranasal preparations to help people quit smoking, and was superior to placebo.

For pregnant women who are already smoking, smoking cessation is necessary because smoking during pregnancy can damage the health of the fetus. The adverse effects of smoking may be attenuated if mothers quit or reduce the cigarette consumption during pregnancy, because cigarette quitting can increase the use of multivitamin and decrease the consumption of caffeine. However, smoking cessation in early pregnancy may have negative impacts, because it can increase high caloric intake, and high caloric intake in the first trimester may have bad effects on maternal and child health [70]. In general, behavioral therapies and patient education should be recommended as first-line therapy for smoking cessation. However, if someone fails to quit smoking, nicotine replacement therapy can be attempted as an adjuvant treatment [71].

7. Conclusion

As one of the most important environmental factors that influence the health of human, smoking can lead to a series of health problems, and smoking during pregnancy will have a great impact on the fetus (**Figure 1**). Prenatal nicotine exposure affects the mother and fetus in many ways, such as respiratory tract, lung, cardiovascular, brain, and leads to many chronic

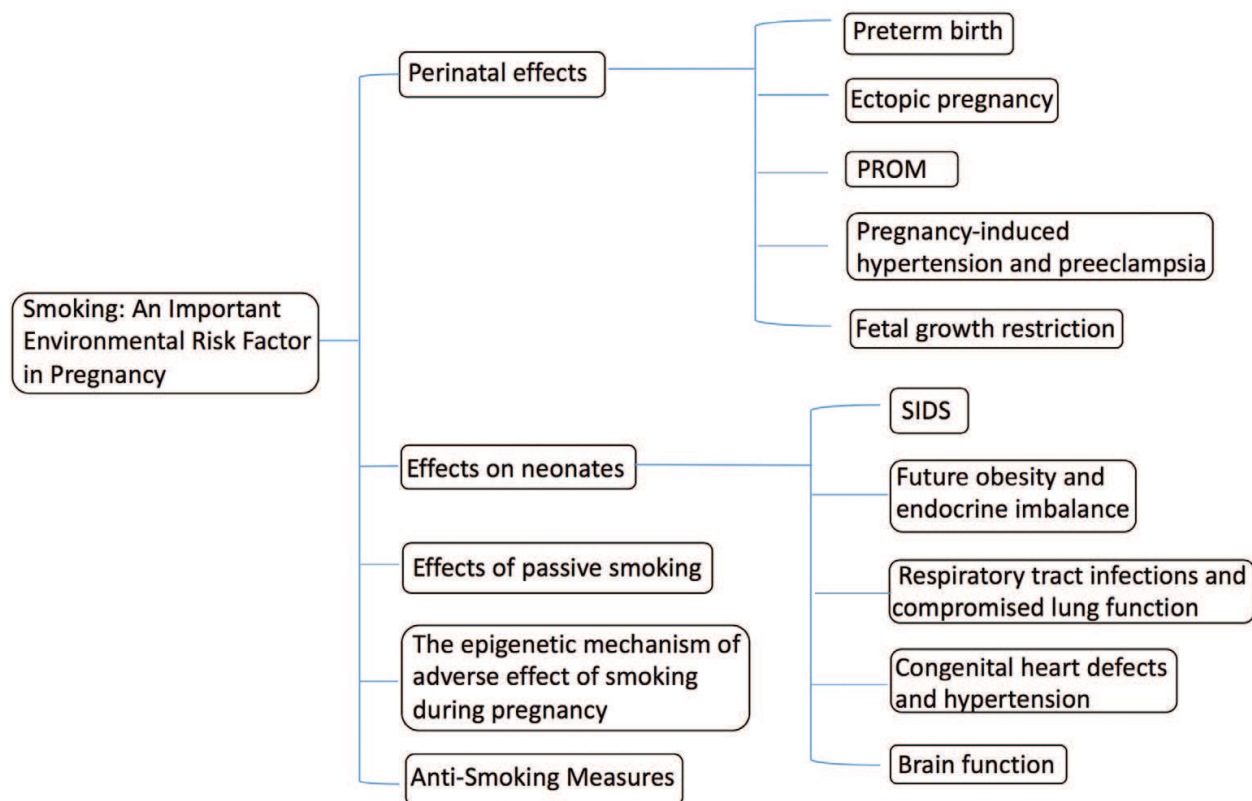


Figure 1. Schematic representation of smoking as an important environmental risk factor in pregnancy.

diseases. Longitudinal studies have shown that the vast majority of these effects (e.g., health effects, learning disorders, or behavioral problems) will last for the whole life, and have profound influences on the growth of children. Moreover, not only the active smoking but also the passive smoking can affect the health of the fetus greatly (**Figure 1**).

Studies have pointed out that nicotine exposure has the most harmful effects during the third trimester. This provides a remedial opportunity for these smoking mothers to improve the status of the pregnancy and their children's health for life. In view of the widespread use of tobacco and the harmful effects of nicotine, more anti-measures should be carried out to create a smoke-free environment for pregnant women, and the education related to the harmful effects of cigarette smoking during pregnancy should be carried on and the expectant mothers should be advised to quit smoking at least during their pregnancy. Also, more effective therapies should be explored to help pregnant women quit smoking. Nowadays, more and more people pay attention to the environmental factors that can affect the health of pregnant women and the fetus. We believe further studies will provide more details of the effects of nicotine, carbon monoxide, and other substances of the cigarette, which may contribute to creating a greater sense of urgency about smoking cessation in patients. Also, we should explore more accurate epigenetic mechanisms to help us better understand how those chemicals affect offspring, so that we can find better treatments for the affected children.

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