

Special Article - Nicotine Addiction and Withdrawal

Maternal Smoking and Perinatal Outcomes

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Abstract

Nicotine is one of the major components in tobacco smoke, and it can cross the placenta. It enters the fetal circulation and accumulates in the fetal compartments from as early as seven weeks of gestation, even with passive smoking. Elevated fetal carbon monoxide levels may result in hypoxia due to reduced availability of hemoglobin for oxygen transport. Exposure to hazardous substances in cigarette smoke could lead to adverse pregnancy and birth outcomes. In particular, maternal nicotine exposure is associated with many adverse fetal, placental, and postnatal health outcomes, including both short-term and long-term complications. Despite increased awareness of the harmful effects of smoking during pregnancy, approximately 20% of women continue to smoke throughout pregnancy in the world. Reducing smoking in pregnancy is a global public-health priority. We recommend clinical and public-health strategies aimed at the primary and secondary prevention of tobacco exposure for fetuses and children.

Keywords: Maternal Smoking; Perinatal Outcomes

Introduction

Cigarette smoke is estimated to contain 4,000 chemicals, including nicotine, tar, arsenic, lead, and hydrogen cyanide [1,2]. Exposure to hazardous substances in cigarette smoke could lead to adverse pregnancy and birth outcomes. In particular, maternal nicotine exposure is associated with many adverse fetal, placental and postnatal health outcomes, including both short-term and long-term complications. Epidemiological studies have provided indirect but compelling evidence that maternal cigarette smoking has serious consequences on all aspects of human reproduction. Many reports have linked maternal smoking with increased risk of fertility problems, spontaneous abortion, placenta abruption, fetal growth restriction, stillbirth, preterm birth, low birth weight, obesity, and type 2 diabetes mellitus in human and animal studies [3-5]. Despite increased awareness of the harmful effects of smoking during pregnancy, 10-23% of women continue to smoke throughout pregnancy in the US and Europe [6,7] and 5.1% of women in Japan [8]. Smoking is strongly associated with socioeconomic conditions, being more prevalent among less-educated women and those in the lowest income group [9,10]. Reducing smoking in pregnancy is a global public-health priority. This review focused on the effects of maternal nicotine exposure during pregnancy on birth outcomes.

Prevalence of Maternal Smoking Rates

The World Health Organization (WHO) estimates that the prevalence of smoking is approximately 22% of women in developed countries and 9% of women in underdeveloped countries [11]. The 2011 Pregnancy Risk Assessment Monitoring System (PRAMS) polled women from 24 states in the US. The self-reported data showed that about 23% of reproductive-aged women smoked during the three months before pregnancy, and about 10% of women smoked during the last three months of pregnancy. About 55% of women who smoked before pregnancy reported they had quit smoking by the last three months of pregnancy. The highest prevalence of those smoking

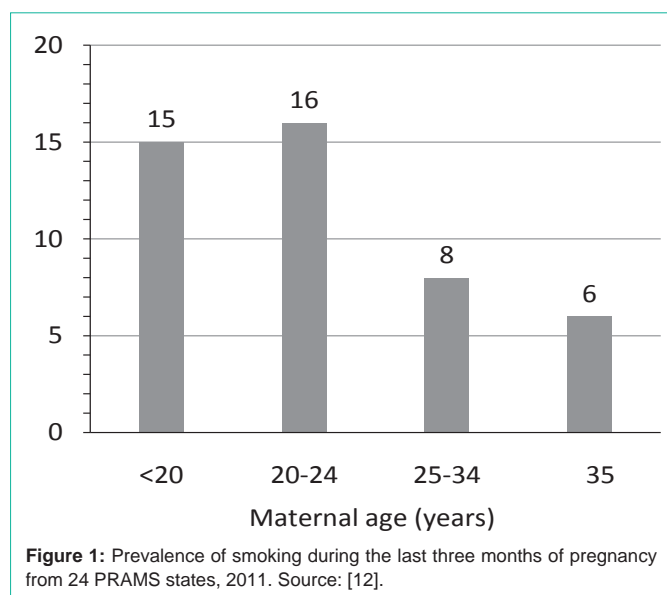
during the last three months of pregnancy (15-16%) was in the age groups of 24 years and younger (Figure 1) [12]. A strong correlation has been seen between maternal smoking during pregnancy and young age, unmarried status, and being from a low socioeconomic status [13].

The Centers for Disease Control and Prevention's (CDC) PRAMS showed the trends of smoking three months before pregnancy, during, and after pregnancy data from 40 states in the US from 2000 to 2010. During this decade, the prevalence of smoking in the three months before pregnancy remained unchanged at about one in four women. However, the prevalence of smoking declined in the last three months of pregnancy from 13.2% to 11.6% and after delivery from 17.8% to 16.6%. The data showed that 40% of women who quit smoking during pregnancy relapsed within six months after delivery (Figure 2) [14].

Other parts of the world had a greater decrease in smoking for women. Dias-Dame et al., conducted population-based survey in Brazil, data of 7,572 women showed that the prevalence of smoking before pregnancy decreased from 28% in 2007 to 22% in 2013, and the prevalence of smoking during pregnancy decreased from 22% in 2007 to 18% in 2013 [15]. In Australia, the prevalence of smoking in pregnancy in New South Wales declined from 22.1% in 1994 to 13.5% in 2007. The largest decrease in smoking in pregnancy rates was among the highest socioeconomic group, and smaller declines were observed among teenage and remote rural mothers [16].

Maternal and Newborn Cord Plasma Cotinine Concentration

Nicotine is one of the major components in tobacco smoke, and it can cross the placenta. From the placenta, it enters the fetal circulation and accumulates in the fetal compartments from as early as seven weeks of gestation, even with passive smoking [17]. Cotinine, nicotine's metabolite measured in plasma, saliva, or urine, is a reliable marker of recent smoking status [18]. Maternal and newborn plasma cotinine levels are strongly associated, as the placenta does not bar



plasma cotinine from moving between pregnant mother and her fetus.

Umbilical cord plasma cotinine correlates with the self-reported daily number of cigarettes at the end of pregnancy [19]. Berlin et al., [20] collected the data from 11 mothers who smoked cigarettes (average 95.1, SD±96, range 10-420) the week preceding delivery. Maternal blood was drawn on average 6h earlier than the umbilical cord blood. The mothers' and newborns' plasma cotinine concentrations were highly correlated ($r=0.97$, $p<0.001$). Similar results were reported in Hukkanen et al., study [21].

Nicotine also accumulates in breast milk. Studies have indicated that the amount of nicotine found in breast milk is 2.9 times greater than that found in maternal blood plasma [17] and that the amount of cotinine, the major metabolite of nicotine, present in the urine of infants breastfed by smoking mothers is, on average, 10 times higher than that found in bottle-fed children whose mothers smoke [22]. Urinary cotinine levels in infants breastfed by smoking mothers are similar to those found in adult smokers [23].

Maternal Smoking Exposure and Perinatal Outcomes

Placentation is an explosive process that occurs before embryonic development, which ultimately depends on placental function. The progenitor population of embryonic Cytotrophoblasts (CTBs) forms a polarized epithelium attached to a basement membrane that forms around the stromal cores containing the intrinsic vasculature of the placenta. Chronic exposure to tobacco constituents in early pregnancy likely affects placental development directly or indirectly by reducing blood flow, which creates a pathologically hypoxic environment. Nicotine depresses active amino-acid uptake by human placental villi and trophoblast invasion, and cadmium decreases the expression and activity of 11 beta-hydroxysteroid dehydrogenase type 2, which is causally linked to fetal growth restriction [24]. Smoking decreases the flow of uterine blood to the placenta through mechanisms that include vasoconstriction. Evidence has shown that smoking is a causal factor in intrauterine growth restriction and may precipitate a preterm delivery.

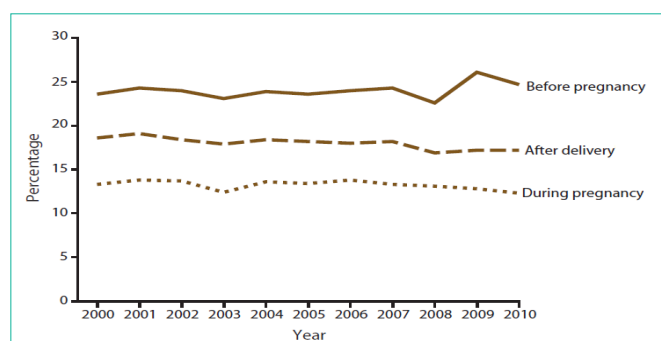


Figure 2: Trends of smoking before, during, and after pregnancy from nine states in the US, 2000-2010. Source: [14].

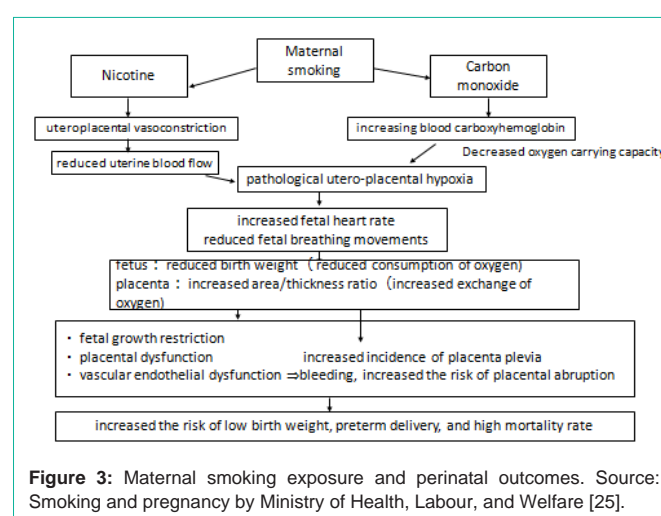


Figure 3 shows the effects of maternal smoking exposure and the perinatal outcomes [25]. Maternal smoking results in high levels of carbon monoxide in the circulation, which approximates the levels found in cord blood samples. Elevated fetal carbon monoxide levels may result in hypoxia due to reduced availability of hemoglobin for oxygen transport. This fetal hypoxia may be the cause of growth retardation, although it has also been suggested that nicotine-induced placental vasoconstriction may impede the transfer of oxygen and nutrients. Smoking may increase the risk of intrauterine infection, and it may also stimulate the production of prostaglandin E₂, which causes contractions in myometrial tissue, and leading to premature labor. In addition, smoking reduces the level of type III collagen, which may increase the risk of preterm rupture of the membranes [26].

Smoking mothers have newborns with dramatically lower birth weight, on average 200 g less than gestation-matched controls, than nonsmoking mothers [27]; a more recent study reported a 377-g decrease in average birth weight for infants of mothers who smoked during pregnancy [28]. Reductions in birth weight have serious consequences, as they are strongly associated with infant morbidity and mortality [29]. Varner et al., analyzed 137,297 singleton births and their linked birth certificate data from the 2004 to 2010 PRAMS. The study's multiple logistic regression analysis revealed that women who had a previous poor birth outcome were 22% more likely to smoke during a subsequent pregnancy. Women who had a previous low birth weight and preterm birth were 30% and 13%, respectively,

more likely to smoke during pregnancy than were mothers with routine previous births [30].

Ion et al., [31] reviewed 13,359 deliveries from 2012 to 2014 in UK, with complete data for 5,066 and 4,793 women in the self-reported and measured, respectively, groups for exhaled carbon monoxide. Self-reported exposure was associated with earlier delivery (-0.19 weeks, 95% confidence interval (CI): -0.32 to -0.05) and reduced birth weight (-56 g, 95% CI: -97 to -16 g) but not associated with an increase in the risk of preterm birth or small-for-gestational age (SGA). Similarly, in a study of 3,661 Japanese women who gave birth to single full-term infants (37-42 weeks), Watanabe et al., reported woman who smoked 10 cigarettes a day during pregnancy were associated with a 110.5-g decrease in birth weight. Women who smoked more than 10 cigarettes per day had a 2.5 times (CI: 1.8-3.5) higher chance of having an SGA infant than did nonsmokers, but no such effect was observed among women who smoked fewer than 10 cigarettes per day [32].

Environmental Tobacco Exposure

Environmental Tobacco Smoke (ETS) consists of almost all the constituents of inhaled cigarette smoke, including tar, nicotine, carbon monoxide, and carbon dioxide. ETS exposure can also cause harmful effects to the fetus, such as low birth weight and preterm delivery [33,34]. The World Health Organization has estimated that 40% of children and 35% of female nonsmokers were exposed to secondhand smoke in 2004 [35], and tobacco kills nearly 6 million people each year and, among them, 10 % were due to second hand smoke [36]. According to the 2010 Global Adult Tobacco Survey in China, 65.1% of nonsmoking women from 15-49 years of age were exposed to ETS at home and 52.6% were exposed in the workplace [37].

Some studies indicated that ETS exposure of nonsmoking, pregnant women decreased mean birth weight. Infants born to women exposed to passive smoking during pregnancy were 40-50 g lighter than were those born to unexposed mothers, primarily due to growth restriction [38]. Leonardi-Bee et al., meta-analysis indicated that nonsmoking, pregnant women exposed to secondhand smoke are estimated to be 23% more likely to experience stillbirth and 13% more likely to give birth to a child with a congenital malformation, but no significant change was seen for perinatal or neonatal death [39]. However, Pineles et al., meta-analysis showed that ETS exposure was not significantly associated with miscarriage [40].

Health Problems for Offspring

ETS harms children's respiratory health, and it has been linked to a higher risk of middle ear infections, bronchitis and pneumonia, coughing and wheezing, decreased lung function, and asthma development [41]. Smaller size at birth is generally associated with a reduced risk for being overweight later in life; however, recent research suggests that mothers who smoke during pregnancy have children at increased risk for later obesity. The combination of small size at birth and becoming overweight in later life is not only characteristic of the epidemiologic transition from acute to chronic disease, but it also confers a high risk of cardiovascular outcomes in adulthood. In a meta-analysis by Oken et al., children whose mothers smoked during pregnancy were at an elevated risk for becoming overweight (pooled

adjusted odds ratio (OR) = 1.50, 95% CI: 1.36, 1.65) compared with children whose mothers did not smoke during pregnancy [42].

Child obesity is a major public-health problem in the world. Behl et al., [6] reviewed 42 human studies investigating the relationship between childhood overweight/obesity and exposure to maternal smoking during pregnancy. The studies included cross-sectional, prospective, or retrospective designs. Ethnic groups were also different, including Asian, Hispanic, American, and European subjects. In 14 of the observational studies, maternal smoking during pregnancy was associated with being overweight at 3-33 years of age (adjusted OR = 1.50, 95% CI: 1.36, 1.65).

However, a large retrospective study by Sharma et al., [43] reported a significant association between maternal smoking and child obesity only in white and black children, but not in Hispanic, American Indian, or Asian/Pacific Islander children. In addition, a meta-analysis conducted by Weng et al., [44] suggests that children with mothers who smoke regularly during pregnancy are 47% more likely to be overweight at 3-8 years of age compared with same age children of mothers who do not smoke during pregnancy (adjusted OR = 1.47, 95% CI: 1.26 to 1.73). Based on these human epidemiological studies, current evidence supports an association between maternal smoking and childhood obesity.

Nicotine Replacement Therapy

Nicotine Replacement Therapy (NRT) is considered a good smoking-cessation tool in the nonpregnant population. It was introduced to help with smoking cessation, because the administration of nicotine in the form of NRT was thought to be less harmful than exposure to nicotine through smoking. Kepaya et al., analyzed the data of 2009-2010 PRAMS, and one in five pregnant smokers was offered NRT for smoking cessation [45]. The FDA has classified nicotine as a "pregnancy category D drug," meaning there is evidence of risk to the human fetus. Therefore, NRT should be reserved for women unable to quit using nonpharmacological methods.

Leung et al., [46] reviewed the efficacy and safety of smoking-cessation strategies in pregnancy. NRT administered as gum may be better than using transdermal forms to avoid high levels of nicotine in the fetal circulation. A small trial demonstrated that bupropion is an effective aid for smoking cessation and it does not appear to be associated with an increased risk of major congenital malformations.

However, in a prospective cohort study of 1,217 women in India, Gupta et al., reported that smokeless-tobacco use was associated with an average reduction of 105 g in birth weight and a reduction in gestational age of 6.2 days. The adjusted OR was 1.4 for preterm delivery (< 37 weeks) and 1.6 for low birth weight [33]. In addition, a meta-analysis of NRT clinical trials for prenatal smoking cessation by Coleman et al., reported that NRT had no significant effect on quit rates [47]. Currently, insufficient evidence has been found on the safety of NRT during pregnancy and on adverse NRT effects on perinatal outcomes and both short and long-term consequences for the child. Cochrane's review on pharmacological interventions for smoking cessation during pregnancy concluded that insufficient evidence was available to demonstrate NRT improved smoking cessation in pregnant women [47].

Conclusion

Tobacco smoke toxins readily cross the placental membrane, and even nonsmoking mothers have a risk of exposure to ETS, either from the home or workplace, during pregnancy. Quitting smoking as soon as pregnancy is known positively affects fetal growth and development, in both short-term and long-term consequences. Reducing smoking in pregnancy is a global health priority. Educational anti-tobacco campaigns and quit-smoking initiatives should target both mothers and fathers to ensure smoke-free living conditions and a healthy environment for all family members. We recommend clinical and public-health strategies aimed at the primary and secondary prevention of tobacco exposure for fetuses and children.

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