



Review Article

<http://wjpn.ssu.ac.ir>**Effects of Smoking on the Health of Children from Embryonic Period to Adulthood: A Review Article**Haniye Alihoseini^{1*}¹ Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

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ARTICLE INFO**Corresponding author:**

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Email:haniye.ali93@gmail.com**Keywords:**Smoking,
Congenital Abnormalities,
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Cigarettes contain many toxic and harmful compounds. There are approximately 600 substances in cigarette that produce more than 7,000 chemicals when burned. In general, these compounds are hazardous either for smokers or both smokers and passive smokers. Today, due to the increasing number of female smokers, especially mothers who smoke during pregnancy, fetuses and children are faced with serious and irreparable consequences. Nicotine (the addictive substance in cigarettes), carbon monoxide, and numerous other poisons inhaled from cigarettes are transported through the bloodstream, which can be harmful to health of the fetus and the development of its organs, such as the fetal brain. Smoking has consequences not only during pregnancy but also during breastfeeding. In addition to the aforementioned, smoking is considered as one of the most concerning teratogens which can cause structural or functional abnormality, growth restriction, birth defects, and so on. These consequences can have dramatic and significant effects on infancy, childhood, and adulthood. According to the contents, in this review we try to discuss influences of smoking on the development of the fetus, growth of children, and eventually its effects on the development of congenital disorders.

Introduction

Cigarette smoke contains several complex, dynamic, and reactive chemicals. Also, tobacco smoke is considered as a significant source of exogenous pro-oxidants containing a complex mixture of numerous chemicals with carcinogenic, toxic, and mutagenic potentials.

^{1,2} Thus, smoking induces oxidative stress that causes many effects on the body and can potentially be very harmful to the fetus. Many studies have proven that smoking during pregnancy brings about considerable risks regarding adverse pregnancy outcomes.^{1,2} Smoking results in severe short- and long-term negative effects on the fetus, children,

and so forth.^{1,2} These effects contain cognitive disabilities in the newborn, slower fetal growth, abortion and premature birth, several birth defects, and so on¹. The aim of this study was to concentrate on some of influences of smoking during pregnancy.^{1,2}

The effects of smoking on the fetus

Many studies support adverse effects of maternal smoking on fetuses, children, and adults. Nicotine and other compounds in cigarettes can cross the placenta and enter the fetal circulation. Therefore, they can affect fetal growth in the womb. Carbon monoxide and oxygen bind at the same active site in hemoglobin.^{1, 3-6} However, carbon monoxide binds more strongly than oxygen. Thus, this change increases carboxyhemoglobin in umbilical arteries, prevents oxygen transfer to the fetus, and leads to hypoxia. CO also binds to other biological molecules such as cytochrome P450 and cytochrome c oxidase (COX) or Complex IV.^{4,7} These bindings can lead to mitochondrial hypoxia, a decrease in phosphorylation system, an increase in apoptosis caused by mitochondrial dysfunction, increased production of reactive oxygen species (ROS), and so on through the COX dysfunction caused by a CO-mediated inhibition.^{3,4,7} Thus, it has been hypothesized that mitochondrial dysfunction and CO may be two of the key factors for reduced birth weight in female smokers. Docosahexaenoic acid is necessary for fetal growth.^{3,4,8} Significant amounts of ω -3 docosahexaenoic acid (DHA) are transferred from maternal to fetal blood.^{4,8,9} However, smoking during pregnancy can impair DHA synthesis or maternal transfer.^{3,4,8} Another possible etiology of the growth restriction is epigenetic changes caused by smoking which may mediate some of consequences of prenatal exposure to maternal cigarette smoking through changes in DNA methylation of genes associated with growth restriction, such as CYP1A1 promoter.^{4,10} The other mechanism associated with low birth weight is impaired amino acid transport due to

blockage of the cholinergic receptor or hypoxia. Hence, smoking has a significant effect on fetal growth, reduces fetal weight, and results in low birth weight (< 2500 gr LBW).⁴ Studies show the neonatal body mass will reduce by 2.8 gr through smoking each extra pack of cigarettes during pregnancy^{3,4,6,8} (0.7 gr reduction in fat mass and 2.1 gr reduction in fat-free mass).⁴

The effects of different cigarette components on the fetus

Studies have suggested that exposure to polycyclic aromatic hydrocarbons (PAH) during pregnancy may have serious effect on birth weight, premature birth, intrauterine growth retardation, gestational length, small for gestational age (SGA), increased risks of morbidity, and mortality and early pregnancy fetal death.¹¹ Studies have revealed that being exposed to cadmium during pregnancy brings about consequences such as low birth weight, and shorter length of babies.¹²

Cigarette smoking and brain growth

The brain is one of the most important organs affected by smoking. Maternal smoking has several adverse effects on the brain, such as impairments in normal brain function and activities especially in the basal ganglia, as well as total brain size and volume.^{4,13} Analyses have found a relationship between the number of cigarettes smoked by mothers and the increased risk of smaller head circumference (HC) at birth.^{4,14} Moreover, they have demonstrated that the average head circumference of fetuses exposed to nicotine is 5 mm smaller.⁸ Studies have shown that when a fetus is exposed to nicotine, the head circumference reduces by 0.13 mm/week of maternal smoking, biparietal diameter (BPD) decreases by 0.04 mm/week of smoking, width of the ventricular atrium reduces by 0.12 mm/week of maternal smoking, and transcerebellar diameter (TCD) decreases by 0.08 mm/week of maternal smoking.⁸ Reasons mentioned for the influences of prenatal smoking on fetal brain development

are fetal hypoxia, epigenetic alterations in the brain-derived neurogenic factor (BDNF) gene that is involved in normal brain development, and so on.⁸ It has been suggested that prenatal exposure to cigarette smoke may have effects on BDNF gene expression through enhancing DNA methylation in its promoter region.^{4,14} Besides, fetuses exposed to nicotine are susceptible to abnormalities in cell proliferation and differentiation, and neuronal dysfunction.^{4,8,14}

SIDS

The sudden and unpredictable death of a seemingly healthy baby under the age of one, having no clinical symptoms on its body, which can only be detected by autopsy, is called SIDS that usually occurs during sleep.^{8,15,16} There are several reasons for this, including genetics, low birth weight, smoking, alcohol use, and so on.^{8,15} Maternal smoking increases the risk of SIDS by up to five times. Smoking can lead to increased fetal SIDS by reducing infant weight.^{8,15,16} Besides, studies have shown that prenatal exposure to cigarette smoke can increase a baby's risk of SIDS through the effects of nicotine on nicotinic receptors. Nicotinic acetylcholine receptors (nAChRs) are expressed in the brain from as early as 4-5 weeks of gestation.^{8,15,17} Nicotine binds to the nicotinic acetylcholine receptors by crossing the placenta and being present in the fetal circulation.^{8,15-17} This change may cause inappropriate stimulation of the nAChRs function and alter some of critical autonomic reflexes. Thus, nicotine may elevate the risk of sudden death through dysfunction in these key reflexes, which may destabilize breathing, heart rate, and blood pressure.^{8,15,16} Smoking raises infant vulnerability to SIDS by decreasing lung capacity and consequently causing chronic hypoxia and increasing the risk of respiratory tract infections.^{8,15} Catecholamines include neurotransmitters such as dopamine, epinephrine, and norepinephrine, which are released from the adrenal glands during the body's physiological stress response

(including hypoxic events).^{8,15,16} Release of catecholamines during hypoxia is essential for the maintenance of cardiac conduction characteristics.^{8,15,16} Nicotine may increase the risk of SIDS through impairing catecholamines release and response to hypoxia induced by smoking.^{15,16} Besides, the analyses of human autopsy specimens from unexplained intrauterine fetal demises or postnatal death have found that exposure to cigarette smoke in utero can affect the maturation and migration of cerebellar Purkinje cells, which may lead to an increase in the risk of SIDS.^{8,15,18} In addition to the aforementioned, studies have shown negative effects of prenatal exposure to nicotine on the development of the autonomic nervous system, particularly in the fourth ventricle choroid plexus. This change can result in the baby's susceptibility to SIDS.^{4,8,15,16,18}

Necrotizing enterocolitis (NEC)

Necrotizing enterocolitis (NEC) is the most common, serious, and dangerous gastrointestinal emergency in premature babies.^{8,19} Many factors contribute to this disease, including hypotension, gestational diabetes, high BMI, congenital heart disease, intrauterine growth retardation, PROM, maternal smoking, and so on.^{8,19,20} Analyses have shown that there is a relationship between maternal cigarette smoking during pregnancy and increased risk factors for the development of NEC in premature neonates. Infants often require surgical intervention in order to respect the necrotic bowel. Untreated NEC can lead to the death of the baby and threaten his or her life.^{8,19,20}

Smoking and Obesity

There is growing concern regarding smoking and obesity in children and adolescents who are prenatally exposed to smoking.^{4,21-23} A meta-analysis has shown that children whose mothers smoke are at risk of getting overweight two times more than others.^{4,21-23} There are many reasons showing the relationship between smoking and obesity, such as:

1) Smoking during pregnancy leads to oxidative stress and hypoxia which may result in lower fetal growth and rapid postnatal weight gain. Moreover, studies have shown that smoking during pregnancy may be associated with low levels of cord blood leptin. Low concentration of this hormone correlates with smaller size at birth and more rapid growth or catch-up growth in early life. Many studies have demonstrated that rapid infant weight gain is a major risk factor for later obesity in adulthood.^{4, 23, 24}

2) Nicotine leads to alterations in the hypothalamic regulatory mechanisms of energy intake and consumption.^{4, 21, 23}

3) It seems that fetal exposure to nicotine can result in abnormalities of cell proliferation and differentiation in the brain through targeting specific neurotransmitter receptors. Ultimately, these changes can alter synaptic activity in the brain and peripheral autonomic pathways. Therefore, this phenomenon can suggest a possible mechanism to explain the development of obesity in offspring whose mothers smoke.^{4, 21, 23}

4) Cigarette smoke can lead to immune deficiencies and make babies susceptible to obesity.^{21, 23} Studies have also shown that mean BMI and prevalence of overweight and obesity among adolescents whose mothers smoke before and after pregnancy but do not smoke during pregnancy are similar to those who do not smoke at all.^{4, 21, 23} Obesity is a cause of high blood pressure, diabetes, and cardiovascular disease.^{4, 21, 23}

Lactation

Breastfeeding is one of the most essential and susceptible postpartum periods. It may have deleterious effects due to the presence of nicotine in breast milk.⁴ It has been suggested that the amount of nicotine in breast milk depends on the number of cigarettes smoked by the mother and the interval between the last cigarette smoked and the start of breastfeeding.^{4, 9}

Some studies have suggested that smoking during and after pregnancy causes a decrease

in the amount of n-3 long-chain polyunsaturated fatty acid in milk through inhibiting $\Delta 5$ -desaturase enzyme or affecting the $\Delta 5$ -desaturation step.^{4, 9} This change can have structural and functional consequences because adequate amounts of LC-PUFA are necessary for the maturation of the developing brain, retina and other organs in newborn infants.⁴ Other effects of smoking during breastfeeding include insufficient levels of milk, excessive fatigue, paleness and colic early in infancy, excessive crying, neurobehavioral disorders, sudden death syndrome, respiratory problems, nervous behavior in infants, metabolic consequences, and disruption of newborns' sleep-wake patterns. Nicotine also leads to changes in the functions of liver and lung tissues.⁴

The effects of nicotine on chromosomes

Various studies have clearly shown that maternal smoking causes higher chromosomal aberration frequencies and increased aneuploidy rates, as well as a positive relationship between the dose of nicotine and chromosome damage.^{25, 26} Nicotine leads to increased DNA fragmentation, interference with oocyte maturation, increased Sister chromatid exchange (SCE), chromosome aberrations, premature centromere division (PCD), and premature anaphase (PA). Studies have shown a dose-response relationship between nicotine and oocyte maturation.^{25, 26} Analyses of spontaneously aborted embryos and live-born infants have shown a significant increase in nondisjunction of acrocentric chromosomes in groups D and G. Also, chromosomes of group E are frequently involved in nondisjunction, whereas, groups B, A, and F are less involved.^{25, 26} The most common numerical chromosomal aberrations are correlated with aneuploidies of chromosome 21, followed by other chromosomes 22, X, 8, 10, 15, and 20. Generally, analyses show that G group chromosomes are highly susceptible to nicotine regarding nondisjunction.^{25, 26} Studies show that for chromosomes 15 and 21,

meiosis I errors are the dominant maternal errors, while for chromosome 18 meiosis II errors are predominant.^{25,26} It has been reported that numerical changes of sex chromosomes have been found in four cells including 45XO, 47XXX, and 47 XXY.^{25,26} Plus, some studies have demonstrated that smoking can cause a noticeable increase in translocation and insertion. In addition to the aforementioned, some studies done on sperm genetic material show that smoking may lead to a higher increase in meiosis II NDJ of sex chromosomes in smokers than others and induce aneuploidy of chromosomes 1,13.^{25,26}

Epigenetic alterations in smokers

Smoking leads to an increase in some diseases such as cardiovascular diseases, asthma, obesity, certain cancers. Various factors contribute to these diseases, one of which is epigenetic alteration caused by exposure to smoking.²⁷⁻²⁹

Many studies support that smoking potentially affects the DNA methylation within the GFI1, MYO1G, and AHRR genes and consequently, causes the incidence of disease in adults.^{27,28} A relationship has been found between maternal smoking during pregnancy and differentially methylated CpGs in some genomic regions in infants. These regions include AHRR (cancer development), FTO (obesity), CNTNAP2 (developmental processes), CYP1A1 (detoxification), MYO1G (cell signaling), GFI1 (low birth weight), FRMD4A (nicotine dependence), and so forth.²⁷⁻²⁹ Moreover, analyses have revealed a relationship between DNA methylation alteration at eight GFI1-linked-CpGs associated with exposure to cigarette smoke either in utero or in adulthood and cardiovascular health.^{27,28,30} Lower DNA methylation at all of GFI1-CpGs is related to adults' own smoking, and some of these GFI1-CpGs are associated with maternal prenatal smoking. So, maternal smoking during pregnancy has long-lasting effects on offspring's epigenome by changing DNA

methylation and having influences on possible epigenetic mechanisms.²⁷⁻³⁰

Congenital disorders

Any structural or functional anomaly present in a baby at birth is called congenital disorder.^{31,32} The pattern and prevalence of these abnormalities may vary over time or in different geographical locations.^{31,32} Such a phenomenon indicates a complex interaction of different genetic and environmental factors.^{31,33} Since organogenesis occurs between the third and eighth week of gestation, smoking has an important effect on birth defect in the first trimester of pregnancy. Some women think if they quit smoking as soon as they figure out, they are pregnant, they can reduce the risk of congenital disorders.³¹⁻³³ Although studies show that not only can smoking before pregnancy, can be detrimental to a developing fetus, but also limiting smoking to the months leading up to pregnancy can have an effect on the fetus.³² Many studies have shown a link between smoking and cleft lip or palate, cardiovascular disease, Club Foot, craniosynostosis, gastroschisis, and so on.^{31,32}

Smoking and congenital cardiovascular diseases

Several pieces of evidence have shown that smoking increases the risk of congenital cardiovascular disease.^{31,32} Smoking causes changes in heart rate, hypertension, ventricular septal defect, and changes in systolic and diastolic pressure. Chronic smoking plays a major role in the pathogenesis of different cardiovascular disorders inducing increased oxidative stress, hypoxia, and disruption of endothelial function in maternal and fetal circulations.³⁴ Some studies have shown that female smokers who have the variant alleles NOS3 (A922G) or NOS3 (glu298asp), can cause a higher risk of congenital heart disease in their babies.³⁴ Besides, genetic abnormalities of several cardiac transcription factors correlate with the development of disease. These

factors include Tbx5, NKx2.5, and Gata4, which are involved in early cardiac development.³⁴ Studies have found that the DNA methylation status of these genes are implicated in CHDs development. Nicotine inhibits the expression of Tbx5 and Gata4 genes through upregulation of promoter DNA methylation.³⁴ These changes show that nicotine can directly inhibit myocardial differentiation.³⁴ So, smoking can cause the development of congenital heart disease and epigenetic dysfunction in cardiovascular disease through altering DNA methylation and attenuating the expression of cardiac transcription factors.³¹⁻³⁴

Gastroschisis

Another congenital disorder which is strongly associated with pre-conception smoking and smoking during the first trimester of pregnancy is gastroschisis.³¹⁻³³ One of the original hypotheses for the development and occurrence of gastroschisis is a vascular incident involving the omphalomesenteric artery. Studies show that smoking during pregnancy may cause gastroschisis through vascular disruption and endothelial dysfunction in both maternal body and fetus.³¹⁻³³

Orofacial clefts

Orofacial cleft is one of the most common congenital disorder.^{35,36} Lip closure occurs from the fourth to seventh week of embryonic development before most women know they are pregnant.³⁵ Besides, the palate closure occurs between the sixth and ninth week of pregnancy. There are several risk factors causing this defect; one of which is maternal smoking.^{32,33,35,36} Studies have shown that there is a link between smoking and cleft lip or cleft palate.³⁵ Smoking increases the risk of orofacial clefts by inducing hypoxia and reducing how the amount of oxygen the fetus requires.^{35,36} Hence, smoking during pregnancy can affect the baby's growth and development.^{31-33,35,36}

Club foot

Another congenital disorder is club foot. Studies show a link between maternal smoking and club foot.^{32,33,37} Analyses have suggested that vascular disruption and induction of hypoxia caused by toxic constituents of cigarettes may contribute to the disease.^{31-33,37}

Cigarette smoking and Neurobehavioral Development Disorders

Smoking leads to neurotic behavior in infancy, childhood, and adulthood. Analyses have shown that maternal smoking during pregnancy can cause changes in biological responses to stress by affecting infant baseline and stress responsive cortisol.³⁸ Infants whose mothers smoke during their pregnancy have been found to have attention deficit and hyperactivity disorder, increased fatigue, poorer attention to stimuli, reduced neonatal attention, increased lethargy, decreased self-regulation, and greater need for care in the first month after birth.^{8,38} Besides, a relationship has been found between smoking and less maternal- fetal dependent attachment, which can have effects on maternal or fetal mental and physical health.^{8,38}

Nicotine has many effects on the smokers, including:

1) Exposure to nicotine can disrupt the nicotinic acetylcholine receptor and lead to changes in the brain's signaling pathways. It also causes neurobehavioral outcomes, altered motor behavior and activity levels, and so on.^{8,38}

2) Nicotine and smoking cause changes in nutrition, and the absorption of essential nutrients, which may adversely affect the growth and development of fetuses and infants. Ultimately, all these changes can have effects on fetal and infant neurobehavioral development, physical growth, and cause neurodevelopmental disorders in children.^{8,38}

3) Nicotine can increase the risk of ADHD by influencing serotonin levels and function.^{8,13,39} Among the behavioral changes in adulthood are externalizing disorders, aggressive and sometimes criminal behaviors, greater likelihood of psychiatric

hospitalization, behavioral control disorder, a tendency to drug- and alcohol-use relapse, greater depressive symptoms, and so on.^{8,38,39}

Smoking and Musculoskeletal Disorders

Musculoskeletal disorders are injuries and disorders that affect muscles, bones, tendons, joints, ligaments, and so on.^{31-33,40} Many studies have shown the adverse effects of smoking on skeletal muscles such as decreased muscle strength and increased muscle weakness. Most of researches about joints focus on rheumatoid arthritis.⁴⁰ There is evidence that smoking in rheumatic patients leads to increased activity of the disease, functional disability, and inadequate response to treatment. Besides, analyses show effects of tobacco on bones contribute to low BMD, delayed fracture healing, and so on.^{31-33,40} Studies on ligaments show a relationship between smoking and poor functional and stability scores after anterior cruciate ligament (ACL) reconstruction.⁴⁰ For tendons, smoking is associated with thinner patellar and achilles tendons, poor postoperative outcomes, and severe rotator cuff tears.⁴⁰

Smoking and Respiratory Diseases

Smoking is associated with an increased incidence of upper respiratory tract infections, bronchitis, lower respiratory tract infections, communicable infections, asthma, wheezing, pulmonary arterial hypertension and more.^{4,8} Research on female smokers reveals a relationship between smoking during pregnancy and increased risk of asthma and wheeze in children and adolescents.^{4,8} Studies have shown that not only are kids who have been exposed to nicotine in the uterus and childhood prone to asthma, but also those who are exposed to nicotine only in utero, without continued postnatal are likely to develop asthma, as well.^{4,8} Asthma is a chronic and complex inflammatory disease of the airways characterized by the presence of diverse collections of activated inflammatory cells and their mediators.⁴ Analyses have shown that nicotine can cause an increase in

the production of cellular mediators, higher allergic inflammatory responses, an increase in the T helper cells (T-h cells) activity, IgE-enhancing activity, enhancement of the cytokine response and impairment of lung function.^{4,8} Thereby, smoking during pregnancy may cause the development of allergic inflammatory responses. Histologic studies in animals have shown that smoking results in the thickening of the alveolar wall and a reduction in the alveolar surface area by stimulating the proliferation of collagen I and III.^{4,8} Ultimately, these changes can impair the function of the pulmonary parenchyma. So, numerous studies have shown a link between smoking and impaired lung function.⁴

Conclusion

In a nutshell, smoking during pregnancy can have effects on the development of the fetus. These effects may include preterm birth, congenital disorders, low birth weight, SIDS, and so on, which have numerous serious and adverse outcomes. Besides, maternal smoking may cause problems for offspring in later lives, some of which include asthma, obesity, neurodevelopmental disorders in childhood, and so forth. In general, due to the different effects of smoking, doctors are supposed to explain these influences to couples who want to have children, so that they can prevent the occurrence of many complications in pregnancy and at birth.

Conflict of Interests

Authors have no conflict of interests.

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