Tobacco Smoke and Pregnancy Outcome: Literature Review

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Abstract

Pregnant women have a risk for tobacco smoke both actively and passively. Various effects of tobacco smoke on pregnancy have been investigated. Pregnant women are usually exposed to enviromental tobacco smoke (ETS) in various places with different duration of time. Cigarette smoke has a severe effect not only on pregnant women but also on the fetus. This is a literature review. Various references were collected from online database including reports, journals, mostly in the last 10 years. The journals were mostly from the scholarly journals. The articles were screened according to the research objectives. The keywords used are tobacco smoke, environmental tobacco smoke and pregnancy outcome. Tobacco smoke can effect the immunity, hormonal and metabolic system of the pregnant woman, therefore disturbing the growth of the fetus. Tobacco smoke also known to increase the risk of premature birth and reduce gestational age. Tobacco smoke cause several problems in newborn such as respiration distress, low birth weight (LBW), neural disorder, sudden infant death syndrome (SIDS) and congenital anomaly.

The effect of tobacco smoke, actively of passively, have worse outcome for the pregnant women and their babies.

Keyword: *Pregnancy Outcome, tobacco smoke, ETS, LBW, preterm birth.*

Introduction

Smoking pregnant women have an increased risk of having an ectopic pregnancy, spontaneous abortion and other complications leading to pregnancy complications as well as the placenta. The fetus also has the risk of exposure to tobacco smoke, more than thousands of types of hazardous chemicals, especially nicotine, tar and carbon monoxide can have an effect on the fetus and cause unwanted disorders or abnormalities[1].

Environmental tobacco smoke (ETS) is a complex mixture consisting of most of the smoke emitted from the smoker's body, the smoke produced by burning cigarettes and the surrounding air[2].Exposure of ETS in pregnant women causes increased levels of carbon monoxyde(CO), nicotine and cotinin in maternal serum or urine, in the fetus and in amniotic fluid. The effect of ETS on pregnant women can occur from the first semester to the third semester. Pregnant women are usually exposed to ETS in various places with different duration of time. Places that have the potential to become ETS exposure locations include at home, at work and the outside environment [3.]

The effect of exposure to cigarette smoke on secondary smokers has not been widely studied in developing countries even though the prevalence of smokers is higher in developing countries than in developed countries. The increasing number of smokers in the world causes ETS exposure to secondary smokers become a concern for the global health. Environmental conditions such as population density make the ETS effect on health increased. Research in developing countries has found that ETS exposure in pregnant women is associated with poor pregnancy outcomes[3].

Tobacco smoke and pregnancy: One effect of the cigarette smoke exposure on pregnant women is its effect on the mother's immune system. In pregnancy changes occur in the mother's immune system to prevent rejection of the fetus. Exposure to ETS can cause changes in the immune system of pregnant women. Changes include an increase in activated leukocytes and a decrease in the percentage of regulator T lymphocyte cells (Treg cells). Smoking during pregnancy also affects the function balance between Th1 cells (T helper lymphocytes) and Th2 cells, causing an increase in the production of cytokines, proinflammatory chemokines and Th1 growth factors. In addition, the percentage of macrophages and NK cell residues is higher in smokers in the first semester [4]

Smoking is also associated with physiological changes in hormones during pregnancy. In smoking mothers there are a decrease of estrogen, globulin bindingsex hormone and human chorionic gonadotropin (hCG) compared to non-smokers. Nicotine as the main component of cigarettes has a substantial impact on the hormones of pregnant women, nicotine causes excessive stimulation of the acetylcholine receptors, releasing vasoactive catecholamines. The activation of nicotine receptors causes the release of acetylcholine, dopamine, serotonin, growth hormones and adrenocorticotropic hormones and glutamate, these hormones significantly influence fetal growth. Smoking is also associated with changes in metabolism during pregnancy. Some reports say that there is a strong relationship between smoking and the incidence of diabetes mellitus and disruption of insulin sensitivity, which can also have an effect on fetal metabolism[4].

Tobacco smoke exposure can also effect the fetus. Exposure to nicotine in pregnant women can cause vascular placental vasoconstriction, decrease placental blood flow and reduce trophoblast invasion which results in inhibition of good placental circularization leading to placental hypoxia causes disruption of placental invasion. Placenta previa is a form of placental invasion disorder[4]. Nicotine can cause a significant decrease in the mitotic potential of cytotrophoblast tissue in vitro. This effect is also found in smoker women. This effect can explain the mechanism of impaired placental development during the early phases of pregnancy due to placental ischemia which can cause fetal death[5.] Low placental weight strongly related with LBW [6].

Beside nicotine and cotinin, CO levels are also the found highest in smokers. The presence of CO in the body causes oxygen binding to hemoglobin decrease due to the higher affinity of hemoglobin for CO. CO Exposure tothe fetus prevents the release of oxygen and then converted to carboxyhemoglobin. The result is a decrease in tissue oxygenation through competitive inhibition with oxyhemoglobin. Prolonged CO exposure in pregnant women can cause significant permanent damage to the brain of a fetus which sensitive to hypoxia. Nicotine is also considered to have a bad effect due to the stimulation of nicotine cholinergic receptors and their neuroteratogenicity effects.[4,7,8]Kadmiun, the other components found in cigarettes are embryotoxic and tetarogenic in animals. Increased cadmium levels in maternal and placental blood are inversely correlate to zinc levels in placental cord blood, suggesting that cadmium interferes with zinc transfer to the fetus and causes impaired fetal growth.[4]Nicotine also interferes with the micro RNA which is important for the maturation of fetal stem cells.[9]

The effects of tobacco smok on the fetus are considered to be multifactorial, including indirect effects such as poor nutritional status associated with anorexiagenic effects of nicotine exposure and CO. Placental blood flow decrease is associated with the vasoconstrictive effect of catecholamines released from adrenals and nerve cells after nicotine exposure. The direct effects of nicotine on the nicotinic acetylcholine receptors that occur during the formation of the fetal brain are also factors that may contribute.[10]

Tobacco Smoke and Preterm Birth: The rate of preterm birth is quite high around the world.In Europe rates of preterm births are reported between 5 - 9%, while in developing countries and the United States the rate of preterm births reaches 12%. The cause of preterm birth is often difficult to determine. Some risk factors associated with preterm birth include excessive distension of the uterus, low economic status and smoking[11].

Smoking is known as a risk of spontaneous and elective preterm birth, but has a stronger relationship with spontaneous preterm birth. Passive smoking in pregnancy also has a risk of preterm birth both spontaneous and elective 5. Elective preterm birth may be associated with cigarette-related obstetric complications such as placenta previa, placental abruption and impaired fetal growth. Research shows that smoking during pregnancy

increases the risk of preterm birth by 25% [11]. The exposure of ETS also specifically has an influence on preterm birth[12,13].

Active smoker mothers have been accepted as a risk for preterm birth, for around 14% of preterm births. One mechanism that links cigarette exposure with preterm birth is the CYP1A1 genotype and GST (glutathione S-transferase). Abnormalities in these genes make mothers more vulnerable to exposure to hazardous substances such as cigarette smoke.[14] Cotinin levels as anindicator of cigarette exposure are also strongly related to preterm birth.[4] The danger of non-smoking tobacco is also seen in the research of Munmun et al. Which shows that non-smoking tobacco (chewed and swallowed) increases the risk of preterm birth.[15]

There are four mechanisms proposed by Goldstein et al in 1964 to explain the relationship between smoking and preterm birth: (1) Decreased maternal appetite caused by smoking leading to a decrease in nutrition for the fetus, (2) vasoconstriction caused by smoking results in decreased blood supply to the fetus, reduced fetal nutritional supply and slowing the release of catabolism results, 3) cigarettes may have a direct effect of toxins on the fetus and 4) an increase in fetal CO levels causes reduced oxygen transport capacity and teratogenic properties.[11,16]

The mechanism of smoking effect on preterm birth is currently believed to be likely caused by various effects that play a simultaneous role. CO levels in cigarettes are about 4% of the volume, after dilution of air in elveoli CO levels in smokers are 400-500 ppm. A room filled with cigarette smoke, CO levels can reach 100 ppm, causing the risk of CO exposure to non-smokers in the room. In blood CO is bound to hemoglobin and forms carboxyhemoglobin, because its affinity is about 200 times of oxygen, hemoglobin binds stronger with CO than oxygen. The binding of CO to hemoglobin causes the oxygen affinity of hemoglobin to increase, so that the remaining oxygen bound to hemoglobin is difficult to release. Carbon monoxide can cross the placental blood barrier. Carboxyhemoglobin levels in the fetus are usually higher than the levels in the mother. Increased levels of carboxyhemoglobin in the fetus cause fetal hypoxia. With decreased oxygen delivery to cells, CO also has an effect on the intercellular process by interfering with the work of cytochrome enzymes.[11]

Research on rhesus monkeys shows that nicotine administration does not cause changes in oxygen partial pressure so that the fetus also does not experience changes in oxygen pressure. Fetal hypoxia in this study was caused by decreased placental blood flow. Other studies on sheep have also shown that nicotine causes an increase in catecholamines and decreases uterine blood flow. Although data from studies in monkeys and sheep show that nicotine decreases uterine blood flow, research data in humans are very limited.[11]

Tobacco smoke can also increase the risk of preterm rupture of placental membranes through several mechanisms, 1) tobacco smoking decreases immunity and becomes a predisposing factor for infection, 2) tobacco smoking decreases copper levels and ascorbic acid in the blood,leading to a decrease in the elasticity of the placental membranes and increase the risk of rupture. Both of these mechanisms have the potential to cause preterm birth[11]

Prostagladin has been known to trigger labor. Prostaglandin levels such as F2-isoprostane as a marker of oxidative stress are found in the amniotic membrane and amniotic fluid in smokers. F2-isoprostane levels increased 3 times compared to non-smokers. Increased F2-isoprostane levels is considered asa mechanism that associated smoking and preterm birth. Smoking is also considered to increase the sensitivity of the uterus to the contractile hormone. Research by Egawa et al in mice shows that inhalation of cigarette smoke increases the contractile activity and sensitivity of myometrium to oxytosis.[11,17]Cadmium found in tobacco smoke interacts with calcium and effects myometrial activity. Cadmium may modulate the function of the oxytocin receptors in the myometrium. Increased levels of cadmium in pregnant women are found to be associated with an increased risk of preterm birth.[11,18]Another condition associated with preterm birth is necrotizing-enterocolitis (NEC). The study of Ding et al in smoking pregnant women showed an increased risk of infant death by NEC in the preterm newborn. Death in neonates by NEC is difficult to prevent with a mortality rate of 15-20%.[19]

Spontanious Abortion: Spontaneous abortion or miscarriage is one of the most common pregnancy complications, about 12-26% of known pregnancies. Generally the literature on the relationship between smoking and abortion does not show any consistency although some studies have concluded that smoking can cause abortion. A meta-analysis study by Pineles et al. Showed the relative risk of abortion during pregnancy

is 1.32. The risk of abortion increases with the number of cigarettes. One cigarette per day increases the risk of abortion by 1%. Secondary smokers have an 11% increased risk of abortion.[20]

Tobacco Smoke Effect on Newborn: Various studies provide an overview of the effects of cigarette smoke on fetal growth and development during pregnancy and infant growth and development after birth

Respiratory Disorder: Based on several studies children who are exposed to cigarette smoke can experience lung growth disorders and are more prone to lung infections and asthma. Exposure to cigarette smoke in pregnant women can also affect the newborn.[1]Smoking during pregnancy can cause the newborn's lungs failed to reach maximum function and continues with decreased lung function. Preterm births in most smokers also cause disruption of lung maturation. Diseases caused by these infants include wheezing, bronchitis, hospitalization due to lung infections and asthma in children.[21]

Generally, children who are exposed to nicotine during pregnancy also experience exposure to cigarette smoke in childhood. This raises the question whether the increased risk of asthma is caused by exposure to prenatal or post natal cigarette smoke. Research by Pattenden et al showed that exposure to cigarette smoke during pregnancy without post natal exposure still shows an association with an increased risk of asthma.[22,23]

Immune factors are also considered to play a role in impaired lung development in fetuses exposed to cigarette smoke. In animal models, there is a change in immune cell phenotype after exposure to cigarette smoke/nicotine. Wang's study et al showed a decrease in Th1 cytokine production after pre-natal and post-natal cigarette smoke exposure associated with increased Th1 immune cell recruitment to the lung parenchyma. By adjusting for risk factors for infection, secondary smokers have an immune system which tends to Th2 leading to an allergic phenotype, small airway inflammation and asthma-like symptoms. Exposure to cigarette smoke pre natal and post natal also shows an imbalance of Th1/Th2 causes susceptibility of airway reactivation.[24]

The mechanism of exposure to nicotine causes various pathological conditions in the lungs is not yet fully understood, but based on some data it was found that nicotine causes various anomalies in the lungs. Histological studies in animals show goblet cell hypertrophy after nicotine exposure and it is associated with asthma in the community.[22,25,26]

Low Birth Weight: Low birth weight babies are the variables most widely studied the effect of smoking mothers during pregnancy or exposure to cigarette smoke in pregnant women on pregnancy outcomes. Data shows that LBW is more common in smokers (12.4%) compared to nonsmokers (7.7%). Women who smoke have a 1.5 to 3.5 times greater risk of giving birth to LBW and the risk increases along with the cigarette consumption.[1]

The physical environment has an important role in determining the weight of babies born and their health in the future. Research in Jordan shows that exposure to ETS in non-smokers pregnant women causes an increase in LBW. Increased ETS exposure increases the risk of LBW infants. All ETS exposure in the home, office and outside environment has the potential to reduce the weight of newborn. It was also found that second and third semester exposures were the most vulnerable time of exposure causing LBW. LBW infants tend to be more at risk for neurological problems including cerebral palsy, seizures, severe mental retardation, respiratory diseases and other morbidity.[3]

It has been ascertained which component of cigarettes affects the flow of uterine blood and primarily affects the birth weight of the baby.[4] Lee et al study showed that exposure to ETS in pregnant women also has the potential to cause LBW and the effect of smoking on LBW from active smokers has the same mechanism as the effect of smoking on LBW in secondary smokers. The risk of small infants according to pregnancy is also increased in the group of mothers with high ETS exposure compared with mothers with low ETS exposure[27]

Behaviour and Neural Disorder: Nicotine exposure to the fetus can affect fetal brain development [10]. A study in Finland shows that heavy nicotine exposure causedthe infant born with attention deficit/ hyperactivity disorder (AHDH5 or attention deficit/ hyperactive disorders.[28]Fetuses exposed to tobacco smoke during pregnancy ware found to have a risk of cardiac autonomic abnormalities during sleep especially in preterm babies. Changes in autonomic activity are at risk of causing neurological and cardiological complications[29]

Research on nicotine exposure to lung development in the fetus is mostly done in animals. Perinatal nicotine exposure in mice causes an increase of airway reactivity.

Nicotine also causes an increase in smooth muscle volume in the distal bronchi and hyperreactive airway in sheep.[21]

Sudden infant death syndrome (SIDS): One of the most severe complications of nicotine exposure in pregnancy is sudden infant death syndrome or SIDS. The cause of SIDS is not clearly known in infants less than one year old suddenly die without definite explanation even after a thorough investigation. Exposure to nicotine is known to be a risk factor for SIDS, but the mechanism of nicotine exposure that causes infant death is unclear and is still being debated. But some animal studies provide some clues.[22,30,31]

Research by Cohen et al in rats shows that nicotine exposure causes disruption of catecholamine synthesis in newborn mice. The study also showed that the mice exposed to prenatal nicotine had impaired response to induced hypoxia. Other studies have shown that mice exposed to nicotine during pregnancy have a risk of death after exposed to hypoxic conditions and have disruption of catecholamine release from adrenal medulla. Human and mouse responses to hypoxia include the release of catecholamines from the adrenal medulla to maintain cardiovascular function. Disorders of catecholamine release in neonates exposed to nicotine during pregnancy may cause an increased risk of SIDS.[22,32]

Congenital Anomaly: The effects of tobacco smoke on infanstcongenital anomalies have been investigated. Exposure to tobacco smoke is known to be associated with fetal heart defects including atrial septal defects, atrioventricular septal defects, transposition of large arteries, craniosynostotic cleft palate and gastroschisis.[4,33,34] Exposure to ETS in pregnancy could also affects the abnormalities of the fetus. Research by Hoyt et al. shows that exposure to mothers as secondary smokers is associated with anencephaly and craniorachischisis, spina bifida, palatoschisis (cleft palate), labioschisis (cleft lip) with and without palatoschisis, agenesis or bilateral renal hypoplasia.[35]

Other studies have also shown an association of ETS exposure in pregnancy with anorectal atresia,[36]neural tube defect,[37]and limb abnormalities [38]Meta-analysis study by Salmasi et al on ETS exposed mothers showed a slight increase risk to have a smaller babies, have a congenital anomaly and tends to have smaller head[39]

Conclusion

Tobacco smoke effect the immunity, hormonal and metabolic system in pregnant women. The substance found in tobacco smoke were found to be the cause of some pregnancy complication leading to poor pregnancy outcome such as preterm birth, spontaneous abortion and adverse effect on tha infants. The infants could suffer respiratory disorder, behavior and neural disorder, SIDS and another congenital anomaly. The effect of tobacco smoke, actively of passively, associated with poor outcome for the pregnant women and their babies.

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