The impact of smoking on infertility, pregnancy outcomes and fetal development

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Abstract

Maternal smoking during pregnancy is one of the main causes of pregnancy complications and is correlated with poorer outcomes compared to pregnancy without smoking. Maternal smoking is associated with a statistically significant increase in the risks of placental abruption, placenta praevia, ectopic pregnancy and preterm pre-labor rupture of membranes. In addition, maternal smoking during pregnancy correlated with higher rates of low birth weight, perinatal mortality, and premature birth, as well as complications in respiratory, cardiovascular and nervous systems in childhood. Active and passive smoking of pregnant mothers seems to be one of the causative agents for these and other negative effects on both mothers and their infants. Physicians should clarify these hazardous effects to pregnant women and strongly advise them to quit smoking as soon as possible. Women who continue to smoke during pregnancy should be considered a high-risk pregnancy.

Introduction

Smoking is a worldwide problem and one third of the population are smokers.[1] In addition, it was reported that exposure to the metabolites of tobacco smoke is correlated with cancer in the adult and *in utero* teratogenicity.[2] Also, smoking during pregnancy is recognized as the most important preventable risk factor for an unsuccessful pregnancy outcome.

The report of the World Health Organization (WHO) indicates that smoking rates for women (≥15-years of age) range between 7 and 17% in South Africa, Central and South America, and Asia, while higher rates of female smoking ranging from 24 to 27% were reported in the US, Europe, and Australia.[3]

Many studies revealed that there is an adverse effect of smoking on pregnancy outcomes-[4-6] These negative effects have an influence on the health of both the mothers and their infants. For instance, pregnant women who smoke may suffer from spontaneous abortion,[6] placental abruption,[7] placenta praevia,[4] and ectopic pregnancy.[8] Moreover, the children of mothers who smoke may face prenatal death,[9] premature delivery,[4] and low birth, weight.[9] To summarize, smoking during pregnancy is an important risk factor for maternal and fetal outcomes.

Recent studies showed that smoking during pregnancy is associated with intrauterine fetal growth retardation as well as disturbances in postnatal growth and development.[10-12]

Pregnant women who smoke and their children may face higher levels of oxidative stress than non-smokers.[13-16] A high level of lipid hydroperoxide was detected in both active and passive pregnant smokers.[17-19] Also, an ethane level test of the breath of the newborn infants of smoking women revealed a high level of oxidative stress.[20]

In 2010, Westbrook *et al.* reported that perinatal environmental tobacco smoke (ETS) exposure of primates resulted in significantly increased oxidative stress in which mitochondrial dysfunction and damage were accompanied by a significant decrease in mitochondrial antioxidant capacity and mitochondrial copy number in vascular tissue.[21]

In addition, Chelchowska *et al.*[22] studied the effect of smoking on antioxidant levels in pregnant smokers and their fetuses. They concluded that tobacco smoke enhances lipid peroxidation and depletes antioxidant potential in the plasma of pregnant women and umbilical cord blood. Therefore, smoking during pregnancy may stimulate free radical damage in the mother and her growing fetus.[22]

Furthermore, it was reported that each stage of reproductive function, folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, endometrial angiogenesis, uterine blood flow and uterine myometrium is a target for the components of cigarette smoke.[23]

The aim of this review is to focus on the impact of maternal smoking on fertility, pregnancy outcomes and fetal development.

Constituents of tobacco

Tobacco smoke is known to be toxic to humans. Tobacco smoke contains more than 4800 chemicals; they are either in gaseous or particulate phases. The majority are found in the particulate phase, namely tar.[24] Tar contains 200 chemicals considered to be poisons and 60 as possible carcinogens (*e.g.* benzo[*a*]pyrene, benzene, lead, and chlorinated dioxins and furans).[2,25] Besides this, other components of tobacco smoke, such as arsenic and 1,3-butadiene, negatively affect the reproductive system. Also, hydrogen cyanide and arsenic have adverse effects on the cardiovascular system, acrolein and acetaldehyde affect the respiratory system, and toluene and phenol affect the nervous system.[2,25]

In addition, cigarette smoke contains reactive oxygen species (ROS), such as oxygen oxides, alkyl radicals, peroxyl radicals and peroxynitrite, which may cause diseases.[26] However, tobacco constituents vary according to the plant, the place where they are grown and the manufacturing process.[27-28]

Tobacco smoke is a complex mixture that contains substances such as polycyclic aromatic hydrocarbons (PAHs) and N-nitrosamines. Both are genotoxic and carcinogenic, and their metabolites lead to the formation of DNA adducts[29] (Table 1).

Maternal smoking during pregnancy produces negative effects on both the mother and the fetus through several pathways. These include the adverse effect of cigarette smoke on normal placental function, and the teratogenic effect of some cigarette metabolites. In addition, some metabolites of cigarette smoke act as vasoconstrictors reducing uterine blood flow by up to 38%,[31] seriously compromising the supply of oxygen and nutrients to the fetus, resulting in hypoxia-ischemia and malnutrition, which is the cause of fetal intrauterine growth retardation.[32] Also, carbon monoxide in cigarette smoke binds the hemoglobin creating carboxyhemoglobin, which inhibits release of oxygen to fetal tissues, resulting in tissue hypoxia.[33]

In addition, nicotine, the predominant alkaloid in tobacco smoke, has extensive effects on fetal growth, maternal and fetal cardiovascular systems, the developing cerebral cortex, uter-

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ine vasoconstriction, developing respiratory epithelium, and umbilical and cerebral blood flow. Nicotine can easily cross the placenta and accumulates in the amniotic fluid where its level in the mid-trimester is 54% higher than those in maternal serum. The fetus swallows amniotic fluid, which, therefore, increases fetal intake of nicotine. This can reach levels in the fetal plasma up to 15% higher than those found in the mother.[8] Nicotine causes a vasoconstrictive effect on the uterine and the umbilical artery[8] It can also affect fetal brain development through activating nicotine receptors.[34] Studies conducted on animal models showed that maternal nicotine exposure during pregnancy and lactation can induce transient structural changes in the testis and epididymis of male offspring.[35]

Nicotine has a short half-life, so it is not used as a marker for tobacco smoke exposure. Instead, cotinine and hydroxycotinine (which are the major metabolites of nicotine, the former being the major psychoactive substance found in cigarette smoke,[36] had been used as specific biomarkers of cigarette smoking[37] because they are easily detectable in human body fluids such as urine, saliva,[36] and seminal plasma.[38]

Besides this, carbon monoxide, the second major product of tobacco smoke, can pass through the placenta to the fetus; carbon monoxide levels in fetal blood can reach levels approximately 15% higher than those in the mothers,[39] causing a reduction in fetal oxygen supply resulting in fetal complications and health problems during the neonatal period.[40-41]

Many *in vitro* assay analyses were carried out to study the effect of tobacco smoke and its constituents on the pregnant and non-pregnant female reproductive system.[42] So, generally, there are no recommended *safe* levels of exposure to cigarette smoke.[43]

Adverse pregnancy complications due to smoking

Many studies correlated the cause of adverse pregnancy outcomes to impaired fetal oxygen delivery throughout the pregnancy caused by maternal smoking.

Castles *et al.* conducted a meta-analysis to study the adverse effects of maternal smoking; they reported a statistically significant increase in the risks of placental abruption, placenta praevia, ectopic pregnancy and preterm pre-labor rupture of membranes.[4]

Maternal complications were detected in women aged 40 years and older, including, but not limited to, placental abruption, gestational diabetes, and placenta praevia.[44-46] In addition, the relationship between maternal smoking and pregnancy outcomes is correlated to the age of the mother.[47] However, another study showed that the relationship between maternal smoking and pregnancy outcomes is independent of maternal age.[48]

In order to determine whether women who continue to smoke in pregnancy and develop preeclampsia have a worse outcome than non-smokers, and whether stopping smoking has an impact on outcomes, a cohort study conducted by Pipkin[49] confirmed that pregnant smokers who developed preeclampsia had worse outcomes. However, women who stopped smoking had better outcomes. The relationships between maternal smoking with infertility and pregnancy complications are shown in Table 2.

Infertility and delayed conception

The conception rates in women non-smokers and former smokers appear to be similar,[51] while pregnancy rates are lower in women smokers than non-smokers.[52] Smoking also adversely affects the fecundity of women undergoing *in vitro* fertilization treatment.[53] In addition, a systematic review of 12 studies of infertility showed that the odds ratio (OR) of infertility in women smokers *versus* non-smokers was 1.60 (95% CI~1.34–1.91).[54] Moreover, higher infertility risk in women smokers was reported by de Mouzon and Belaisch-Allart.[55]

Lower levels of serum estradiol in women smokers than in non-smokers[56] suggest that smoking appears to have antiestrogenic effects.[57] Other studies found that the toxic products of cigarettes (especially nicotine) interfere with the maternal formation of corpus luteum, tubal transportation, and implantation.[58]

Another study aimed at determining whether passive and active smoking by women or smoking by men is associated with delayed conception, Hull *et al.*[59] reported that, after adjustment for confounding factors, delayed conception was statistically significantly associated with both active and passive smoking by the woman.

Placental abruption

Placental abruption refers to a premature separation of the placenta from the uterine wall. It occurs in approximately 0.4-2% of all pregnancies and is one of the most common causes of maternal and perinatal death.[60] Perinatal mortality rates due to placental abruption range from approximately 10 to 25%.[60]

Many studies have reported an association between maternal smoking during pregnancy and placental abruption, with odd ratios of 2.07,[61] 2.36,[62] and 2.5.[63] Placental abruption is correlated to smoking during pregnancy, and the risk increases according to the number of cigarettes smoked daily.[64] Pregnant smokers risk placental abruption twice as much as non-smokers.[64-65] Rasmussen *et al.*[66] suggested that smoking during pregnancy may cause degenerative and inflammatory alterations of the

Table 1. Constituents in whole tobacco.[30]

Constituents	Examples	Constituents	Examples
Alkaloids	Nicotine	*Nitrosamines*	NNN
	Nomiocotine		NNK
	Anabasin		NAT
	Anatabine		NAB
Metals	Arsenic	*Others*	Benzo[*a*]pyrene
	Nickel		Triacetine
	Lead		Nitrate
	Cadmium		Ammonia
	Chromium		Glycerol
	Selenium		Propylene
	Mercury		

NNN, N-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, nitrosoanabasine.

Table 2. Smoking-related risks and pregnancy complications.[50]

Complications	Relative risk
Infertility	1.2 – 3.6
Ectopic pregnancy	1.5 – 2.5
Spontaneous abortion	1.0 – 1.8
Placental abruption	1.4 – 2.4
Placenta praevia	1.5 – 3.0
Preeclampsia	0.5 – 0.7

Relative risk: the ratio of the risk of disease or death among smokers to the risk of disease or death among non-smokers.

placenta which will lead to placental abruption. Another study by Faruque *et al.*[67] found a decrease in levels of ascorbic acid in pregnant smokers. In contrast, Sanchez *et al.*[68] reported that smoking did not appear to be a risk factor in smoking Peruvian women.

Placenta praevia

Placenta praevia is defined as a placenta that partly or completely covers the internal cervical opening and is associated with maternal smoking during pregnancy.[69-70] A positive correlation (OR 1.58%) was reported between maternal smoking during pregnancy and placental praevia.[4] In addition, a dose-related response was found between smoking and placenta praevia by which the chance of developing placenta praevia by pregnant women smokers increases in relationship to the increase in the number of cigarettes smoked.[71-72]

Placenta praevia in pregnant women smokers may occur as a result of internal cervical obstruction due to placental enlargement. Increasing levels of carbon monoxide and decreasing levels of oxygen in these women result in hypoxemia. This is thought to cause placental enlargement, which increases the risk of the placenta reaching the cervical opening.

Spontaneous abortion

Studies have shown that smoking increases the risk of spontaneous abortion.[73-74] Estimates show that there is a 25% increased risk of spontaneous abortion in pregnant smokers compared with non-smokers, and this increase was also dose dependent.[75] Consequently, the number of abortions increases with the number of cigarettes smoked.[76]

There was a strong correlation between both maternal and paternal smoking and the rate of spontaneous abortions.[77-78] Tobacco smoke and cocaine use was found to be associated with a significant risk of spontaneous abortion.[79]

Nielsen *et al.*[80] found supportive evidence that pre-pregnancy smoking is associated with spontaneous abortion and the risk of spontaneous abortion increases with the number of cigarettes smoked each day.[80]

In addition, some little support for an association between *in utero* exposure to tobacco smoke and risk of experiencing still birth in later life was provided recently by Cupul-Uicab *et al.*[81]

Generally, in women smokers, spontaneous abortion with normal fetal karyotype is higher than spontaneous abortion with abnormal fetal karyotype.[82] The toxic effects of smoke constituents, such as nicotine, carbon monoxide, and other constituents of tobacco smoke, may increase the risk of spontaneous abortion with normal fetal karyotype.

In contrast, some studies failed to find a significant correlation between maternal smoking and spontaneous abortion.[83-84] These results could be partially explained by the difference in the methodology used in the study, the reduced sample size, and the fact that few women were in the category of high tobacco consumption.

Ectopic pregnancy

Ectopic pregnancy is the term used to describe a pregnancy, which occurs outside the uterine cavity.[85] It usually occurs in the fallopian tube. Ectopic pregnancy is one of the major causes of maternal death in the first trimester of pregnancy[86] and may also affect future maternal fertility. The risk of ectopic pregnancy increases with smoking,[87] and a dose response relationship was found between maternal cigarette smoking during conception and ectopic pregnancy.[88] As the daily number of cigarettes smoked by pregnant woman increased, the chances of those women experiencing an ectopic pregnancy were 5 times higher than for pregnant non-smokers.[89]

Cigarette smoking is correlated with an increased risk of pelvic inflammatory disease (PID), which is one of the most important risk factors for ectopic pregnancy. This partly explains why smoking increases the risk of ectopic pregnancy.[64]

Adverse pregnancy outcomes due to smoking

Cigarette smoking itself is one of the leading contributors to death,[90] whereas maternal smoking during pregnancy has been implicated as a potential risk factor correlated with multiple negative child outcomes, such as low birth weight, conduct disorder, attention deficit hyperactivity disorder, child smoking and cognitive dysfunction.[91]

A recent study by Agrawal *et al.*[92] reported that maternal smoking during pregnancy may influence certain outcomes in offspring via mechanisms that are independent of genetic risk attributable to comorbid conditions.

Pregnant women over the age of 40 and older experienced fetal complications including perinatal mortality, preterm birth, and low birth weight.[44,46,93-94] Salihu *et al.*[47] showed that *in utero* fetal death was highest among older smoking mothers (≥40 years) and declined with decreasing age (trend P<0.0001). This could indicate that the relationship between maternal smoking and pregnancy outcomes is correlated to the age of the mother.

The toxic effects of smoking during pregnancy vary from perinatal complications, such as low birth weight, to changes in adult behavior.[95-99] Table 3 shows the reported results of smoking and risks of adverse pregnancy outcomes from studies.

Fetal growth retardation

Fetal growth retardation is associated to maternal smoking.[50] Active smoking during pregnancy is a well-established cause of fetal growth retardation.[100-102] Infants born to mothers who smoke are three times more likely to have low birth-weight than infants born to mothers who are non-smokers[103] and these infants may die during infancy.[104] In addition, the number of cigarettes smoked by pregnant women each day showed a significant negative correlation with newborn weight, body mass index, length and head circumference.[105] Maternal smoking during pregnancy causes a delay in fetal growth, which is greater in male offspring. Also, intrauterine growth concerning weight, length and head circumference in the offspring of mothers who smoked decreased with parity, whereas they increased in smoking mothers during pregnancy.[48] Several studies reported a greater weight reduction in male than in female offspring of heavy-smoking (>10 cigarettes per day) pregnant women.[105-108] In pregnant smokers, higher arterial resistance indices and lower birth weights were observed. These findings were associated with increasing levels of tobacco smoking exposure. The values were significantly different to those found in non-smoking pregnant women.[109]

Pringle *et al.*[110] reported that smoking during pregnancy resulted in altered placental appearance on ultra-sonography, increased umbilical artery blood flow resistance, and a reduction in longitudinal and intra-abdominal organ growth.

Other factors may interact with the effect of smoking on fetal growth such as; maternal age,[111] genetic factors,[112] and pregnancy

Table 3. Smoking-related risks and adverse pregnancy outcomes.[50]

Complications	Relative risk
Small for gestational age	1.5 – 2.9
Preterm birth	1.2 – 1.6
Stillbirth	1.3 – 1.8
Neonatal mortility	1.2 – 1.4
Congenital malformation (oral cleft)	1.2 – 1.6

Relative risk, the ratio of the risk of disease or death among smokers to the risk of disease or death among non-smokers.

weight.[62] In another study conducted by Cnattingius *et al.*,[113] the effect of maternal age, smoking, and parity as a dichotomous variable on newborn birth weight were studied and they found that the odds ratio for the delivery of low-birth-weight neonates increases with age, smoking and parity, and these parameters are significantly interrelated.[114]

The negative effect of smoking during pregnancy on fetal growth remains unclear.

Maternal hormones and placenta play an important role in fetal growth.[115-117] In addition, fetal hormone concentrations were affected by maternal smoking during pregnancy[118-120] which adversely affect fetal growth and may increase the blood pressure of the neonates and infants of these mothers[121-122] Also, the detection of low concentrations of leptin in the cord blood of both preterm and term newborn infants of smoking mothers could be associated with fetal growth retardation.[114,123]

Preterm birth

Preterm birth refers to the birth that occurs before 37 weeks of conception (4 weeks before estimated date of birth). Two-thirds of all preterm births occur spontaneously, while one-third are electively delivered due to concerns about fetal or maternal health. Smoking is associated with both outcomes and is considered to be one of the major causes of neonatal mortality and morbidity. The risk of preterm birth increased as the number of cigarettes increased.[124-125] Smoking is responsible for 15% of all cases of premature labor.[126] In addition, a relationship between heavy smoking pregnant French women with low obstetric risk and preterm birth was reported.[127]

Moreover, presence of previous adverse pregnancy outcomes is considered to be one of the strongest risk factors for preterm delivery.[128-130] Other researchers showed that other risk factors, such as low socioeconomic status,[131] was associated with preterm delivery among women with a low obstetric risk but not with women with previous adverse pregnancy outcomes. Reports showed that the most frequent reason for preterm birth is preterm premature rupture of membranes (PRM), representing almost 30% of all preterm deliveries, and women who smoked during pregnancy had a 2.1 times greater risk of preterm birth compared to non-smokers.[132-133]

Along with preterm rupture of membranes,[134] smoking increases the risk of preterm birth by increasing the secretion of prostaglandins in fetal membranes.[135] On the other hand, stopping smoking was found to lengthen the gestational period.[136]

In a 2009 prospective cohort study conducted by McCowan *et al.*,[137] an association was reported between both spontaneous preterm birth and infants small for gestational age with women smokers who stop smoking early in pregnancy. In contrast, some studies failed to report a correlation between smoking and preterm birth.[138-140]

Perinatal death

Perinatal death represents both stillbirth and early neonatal death.[141] Smoking was found to be the cause of unexplained stillbirth[142] and one-third of neonatal deaths in the UK.[143] Smoking during pregnancy was associated with a 10% increase in prenatal mortality and an increase in the incidence of premature labor and placental abruption.[144] Other studies also showed that maternal smoking is associated with premature labor and perinatal mortality reaching approximately 150% higher rates in smoking mothers than in non-smoking mothers.[145]

The adverse effect of maternal smoking during pregnancy increased the prenatal and infant mortality rates.[146] Maternal smoking during pregnancy remains an important determinant of a late fatal and infant mortality rate.[61]

The results of many studies support the hypothesis that there is a fundamental relationship between smoking and risk of perinatal death[147-149] which could be correlated to high rates of placental abruption and placenta praevia.[148] In addition, about 40% of the babies of smoking mothers die within the first four weeks of life.[106] Some studies also correlate passive smoking with infant Sudden Death Syndrome.[150-151]

Congenital dysfunction, impaired learning and behavioral problems

Many epidemiological studies showed that maternal cigarette smoking during pregnancy can lead to complications in the fetal nervous system, resulting in behavioral disturbances in infancy, childhood, and even in early adulthood.[152-153] Impaired learning in children prenatally exposed to cigarette smoke was reported by several studies.[154-156]

In 2001, Cornelius *et al.*[157] correlated maternal smoking during pregnancy with deficits in multiple aspects of learning and memory. In addition, Lambe *et al.*[155] reported another correlation between maternal smoking during pregnancy via familial factors and poor school performance.

Law *et al.*[158] conducted a bioassay test of smoking exposure to newborn neurobehavior and reported a dose-response relationship between them. These findings suggest neurotoxic effects of prenatal tobacco exposure on newborn neurobehavior.

This relationship could be linked to the nicotine in cigarette smoke, which was found to be a neuroteratogen factor that interferes with the development of the fetal nervous system.[159] Nicotine binds with nicotinic acetylcholine receptors in the fetal brain affecting cell proliferation and differentiation. Upregulation of nicotinic cholinergic receptor due to nicotine exposure leads to abnormalities in the development of synaptic activity ending with neuronal damage.[160] Low doses of nicotine restrict fetal brain development even if they do not affect the fetal birth weight.[161] Also, smoking during pregnancy correlated with mild neuro-developmental handicaps.[162] Moreover, a 2011 study conducted by Suarez *et al.*[163] suggested that maternal exposure to passive smoke is associated with neural tube defects (NTDs).[163]

Several studies examining the effect of smoking on children's behavior demonstrated an association between maternal smoking and behavioral problems among children.[164] Also, the effect of postnatal tobacco exposure on behavioral development was suggested.[165] A prospective cohort study conducted by Rückinger *et al.*[166] to assess the relative risk of behavioral problems in children who had been subjected to *in utero* and postnatal exposure to tobacco smoke, showed a strong association between *in utero* exposure to smoking and several parameters of abnormal behavioral.[166]

Effects of passive smoking on birth weight

Passive smoking or environmental tobacco smoke (ETS), or *second-hand smoke* or involuntary smoking has been shown to be one of the major causes of health problems.[167,168]

Side-stream smoke represents about 85% of the smoke present in any one place. It contains many toxic gaseous substances in higher concentrations than in the mainstream smoke.[169] Passive smoking during pregnancy is associated with a more than 2-fold higher risk of having a small-for-gestation baby.[170]

A reduction in birth weight was correlated to maternal exposure to passive smoking (to complete the analysis)[171-173] in a systematic review and meta-analysis conducted in 2008 to determine the effects of passive smoking exposure on birth outcomes. The authors reported that the exposure of non-smoking pregnant women to passive smoking reduces mean birth weight by 33% or more, and increases the risk of birth weight below 2500 g by 22%; however, it has no clear effect on gestation or the risk of being small-for-gestation age.[174]

Mutation in newborns due to active and passive smoking

Maternal smoking and secondary exposure to environmental tobacco smoke (ETS) not only have deleterious effects on the developing

fetus, but they may have life-long consequences due to genotoxic damage. Cancer in the adult and *in utero* teratogenicity are associated with exposure to tobacco smoke metabolites.[2]

Both maternal active smoking and passive smoking to ETS cause similar mutational induction in those mothers. The molecular base of mutational induction is chromosome missagregation, resulting in an effective loss of one parental chromosome 4 and duplication of the other.[175]

Grant[176] found the same level of mutation of the *HPRT* gene in both newborns subjected to passive smoking ETS and those subjected to active maternal smoking. Recently, the same author found that similar levels and types of genotoxic damage in the developing fetus were induced by smoking in both active and passive maternal smoking.[177] Also, a combined effect between maternal genetic polymorphisms and smoking during pregnancy was reported by Sasaki *et al.*[178]

Recently, Grazuleviciene *et al.* suggested that even low levels of smoking ought to be considered a potential risk factor for adverse birth outcomes, and that genetic polymorphism may contribute to individual variation in tobacco smoke response.[179]

Maternal smoking in pregnancy and childhood respiratory system complications

Maternal smoking during pregnancy is a well known cause of fetal growth retardation. Moreover, many studies suggested a positive correlation between maternal smoking during pregnancy and fetal respiratory system, which may result in impaired lung function in newborns.[180-185] Smoking may also damage the fetal respiratory system, either to the bronchial tree or to the blood vessels of the fetal lung, the same as has been shown in the umbilical vessels.[186] Cigarette smoking was found to be an immunosuppressive agent both *in vivo* and *in vitro*, which predisposes the infant to respiratory infections.[187] Epidemiological studies indicate that maternal smoking is a risk factor for asthma in childhood.[188-190]

Steffensen *et al.*[191] reported a correlation between low birth weight and subsequent childhood asthma. Similar findings were reported by Jaakkola and Gissler[99] who reported that maternal smoking increased the risk of asthma (adjusted OR=1.35; 95% confidence interval=1.13, 1.62 for high exposure). In addition, low birth weight and preterm delivery were reported to increase the risk of asthma at the age of seven.

Other research groups have also provided evidence that correlated maternal smoking during pregnancy with childhood asthma.[192-198]

Many studies have illustrated the relationship between parental smoking and otitis media in children. Among these, a study by Haberg *et al.*[199] aimed to explore associations between acute otitis media (AOM) in early childhood and prenatal and postnatal tobacco smoke exposure. They concluded that relatively low exposure levels of parental and/or maternal smoking in pregnancy was associated with an increased risk of acute otitis media in early childhood.

Putting together all the data examined in this review, we can recognize that tobacco smoke still has many other negative effects. Among these it was found that prenatal smoke exposure causes alteration in gene expression during the *early* period of hippocampal growth (brain tissue) in mice and may result in abnormal hippocampal morphology, connectivity and function.[200]

Conclusions

Smoking in women of reproductive age can be associated to both fetal and maternal complications in pregnancy. Smoking is well known to have adverse effects on pregnancy. Fetal exposure to passive smoking from the mother may seriously affect childhood health with possible consequences in adult life.

Physicians should clarify these hazardous effects to pregnant women and advise them strongly to stop smoking as soon as possible. If they continue smoking they should be considered a high-risk pregnancy. Governments should cooperate with the World Health Organization to introduce well organized health education programs, encouraging women to stop smoking and discouraging young girls from starting.

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