

## Mini Review

# Results of Smoking in Pregnancy: The Genotoxic Effect of Nicotine or why Cigarette should not be Smoked in Pregnancy?

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Submitted: 23 March 2017

Accepted: 10 April 2017

Published: 14 April 2017

ISSN: 2333-665X

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## Keywords

- Smoking
- Pregnancy

## Abstract

Smoking in women is a rapidly growing and serious public health problem worldwide. All tobacco products contain toxicants, so smoking increases risk for disease. Tobacco smoking is a risk factor for numerous disorders, including cancers affecting organs outside the respiratory tract. Nicotine readily crosses the placenta and the fetuses of mothers who smoke are exposed to relatively higher nicotine concentrations than their mothers. Cigarette abuse during pregnancy increases maternal health risks as well as mental and physical problems for the fetus, contributing to multiple adverse outcomes such as preterm delivery and stillbirth. Recent studies have suggested a direct contribution of nicotine the addictive component of tobacco and tobacco smoke to human carcinogenesis, and it remains the most common harmful substance to which pregnant women are exposed. Also, it has deleterious effects on the fetus. The newborns of smoking mothers have elevated frequencies of chromosome translocations and DNA strand breaks. It is known that cigarette smoking has genotoxic effects and causes mutations. The toxic substances from cigarette smoke induce structural and numerical chromosomal aberrations in vitro and could potentially increase levels of aneuploidy in the fetus. Moreover, increased levels of aneuploidy in fetus are correlated with low implantation rates, spontaneous abortions and fetal losses. Due to the harmful effects of cigarette, pregnancy is one of the ideal times to quit smoking. Because, mothers should repeatedly be aware about the harmful effects of cigarette on their baby health and that the pregnancy period is perfect time to quit smoking for having a healthy baby. It is up to you.

## INTRODUCTION

The number of cigarette smokers is increasing worldwide, and many people are exposed to environmental tobacco smoking. Moreover, many people exposed the mutagenic and carcinogenic effects of genotoxic agents in their daily life or work environment. In this respect, our recent study confirmed that the combined use of nicotine and cell phones might lead to detrimental effects on the health of users [1]. The acute toxicity of nicotine and the longer-term exposure has adverse effects on reproductive health, lung growth and development, neurocognitive function and cognitive decline, psychiatric morbidity, immune function, cancer risk, and cardiovascular disease.

According to the World Health Organization (WHO) report on Global Tobacco Epidemic, smoking is a major world health problem that kills more than 5 million people each year, substantiating harmful effects of nicotine and in 2014, the proportions of men and women who consume cigarette is 40% and 13%, respectively [2]. In 2002, about 11.4% of all pregnant women in the USA were using cigarettes [3]. Also in Turkey, smoking habit rate has been increased in recent years, particularly among young people, and now 14.8 million person (27.1%) are using tobacco. According to a report prepared by Turkish Statistical Institute in 2012, smoking rate is 41.4% for

males and 13.1% for females. At the same time, 11% of pregnant women and 17% of breastfeeding mothers are smoking cigarette [4]. In 2002, about 11.4% of all pregnant women in the USA were using cigarettes [5]. The high consumption of cigarette in a female population leads to an increased risk of pregnancy related problems. Smoking or being exposed to smoke, the most extreme example of a systemic human mutagen, is the most important preventable cause of diseases or deaths.

Nicotine as the major chemical component responsible for addiction in tobacco products is known for causing strong addiction. Metabolism of nicotine to cotinine *in vivo* occurs within minutes after nicotine absorption. The smoke of combusted tobacco is estimated to contain over 4000 chemicals of which over half are considered potential toxins or carcinogens. 24 to 81 of those chemicals are classified as carcinogens by The International Agency for Research on Cancer (IARC) [6]. There are numerous studies that focus on lung cells and cells from other organs relating to nicotine exposure. Smoking is known to cause cancer, e.g., of the lung, oral cavity, pharynx, larynx, esophagus, pancreas and urinary bladder cancers as reviewed by IARC [7]. A wide range of effects has been reported in cellular systems, including at doses similar to those in the blood of smokers [8]. It has been shown that nicotine inhibits apoptosis including apoptosis induced by chemotherapy in lung cells [8,9]. At the

same time, the exposure to tobacco increases the potential for chromosome breakage at three cancer sites in the genome. In another study we conducted, we showed that smokers had a higher frequency of total CA expression compared with non-smokers. Active tobacco exposure increases chromosomal damages, in particular, at three critical chromosome-sites in smokers. These three regions have been previously identified as potential susceptibility loci for several cancers. It is interesting that the tobacco compounds were particularly interactive with cancer loci but not with the other loci [10].

Substance or cigarette use in women is a rapidly growing and serious public health problem worldwide. Normally, nicotine passes to fetus, placenta, amniotic fluid (during pregnancy) and milk of smoking mothers. Maternal smoking during pregnancy causes reduction of fetal breathing movements, an effect attributed to nicotine in fetal blood. Nicotine is metabolized to cotinine, which has a long plasma half-life and exhibits slow clearance across membrane barriers [11]. Nicotine affects the cell development of fetus. In the study we conducted, I personally observed the fetal-cell development of women who smoke during pregnancy in cultures. The growth of fetal cells in pregnant smokers is later than non-smokers in amniocentesis cultures. This shows that the nicotine passed from mother to fetus it decelerates the development of the baby's cells. Although, information on the *in vivo* genotoxicity of nicotine is limited, in our study it was confirmed that the nicotine leads to significant direct genotoxic effects on human fetal cells *in vitro* [12]. The metabolism of nicotine is known to produce reactive intermediates capable of binding to proteins and DNA [13]. The DNA damage induced by cigarette smoking has been extensively studied. Most reports indicate that cigarette smoking causes DNA damage as assessed by several tests including DNA adducts, micronuclei assay, SCEs, 8-hydroxyguanosine [14,15]. Also, high DNA damage is known to influence apoptosis and cell cycle [16]. Most cells have the ability to perform DNA repair. However, if DNA lesions are mis-repaired and the physiological pathway of apoptosis is interrupted, DNA lesions can cause CAs or other changes with the potential of inducing mutagenesis in a multistep mechanism [17]. Certain studies have shown that nicotine induces aneuploidy and polyploidy [18], SCE and CAs in bone-marrow cells of mice [19].

According to our findings, there is a significant difference of CAs between nicotine containing medium grown cells and control medium grown cells. Tetraploidy and aneuploidy were found to be the most frequent abnormalities in our study. These findings may explain the increased aneuploidy rates in fetal cells, and were in agreement with other cytogenetic studies among smokers [20,21]. The prenatal exposure to nicotine increases the frequencies of premature centromere separation and premature anaphase, in agreement with the results of our study which suggested that nicotine elevates aneuploidy levels in human fetal cells. This data indicates that nicotine expresses significant direct genotoxic effects on human fetal-cells *in vitro* [12]. This possibility is consistent with the genotoxic effects in fetal cells from smoking during pregnancy are most likely caused by cigarette constituents, providing a potential mechanism for polyploidies and aneuploidies in fetal cells or embryo. Accordingly, in a few *in vivo* studies measuring CAs, nicotine has been reported to

interfere with oocyte maturation and chromosome disjunction [22], and to induce aneuploidy and polyploidy in mouse bone-marrow cells [23]. The origin of autosomal trisomies has also been investigated, and several studies showed that smoking can be a confounding factor when assessing aneuploidy and DNA damage in epidemiological studies [24]. In utero exposure to tobacco smoke also increases CAs frequencies in the newborns [25]. Various studies have found that smoking caused a 10–20% increase in CAs frequency [26]. All chromosome groups are represented in aneuploidies, but non-disjunction is not a random event in female meiosis. In particular, there is a significant excess of nondisjunction in the acrocentric D (13,14,15. chromosomes) and G (21,22 chromosomes) groups chromosomes [27] or in the G group chromosomes only [28]. This fact has been reported in studies conducted on spontaneously aborted fetuses and live-born infants. In our work on the genotoxic effects of nicotine in smoking mothers; we provide the evidence that nicotine exposure *in vitro* has detrimental effects on fetal cells, and the most common numerical aberrations were chromosome 21 aneuploidies, followed by monosomies and trisomies 22, X, 8, 10, 15 and 20, respectively. In particular, there is a significant excess of nondisjunction in G group chromosomes, and G group chromosomes are more sensitive to nicotine in terms of non-disjunction events. Our findings indicate that smoking can be a confounding factor when assessing aneuploidy and tetraploidy in human fetal cells [12].

Despite the damages explained above of nikotin it is estimated that about 20–25% of women still smoke during pregnancy [29]. For example, women who smoke during pregnancy are more likely to be depressed, anxious, or to have other mental health problems that could affect parent-child interactions and/or impose a genetic influence on the development of the child. An important issue regarding the effect of maternal smoke on fetal development and subsequent health condition is determining the sensitivity of the fetus to the detrimental effects of smoke. From a public health perspective, it is vital to know whether smoking is harmful to the fetus in the first trimester when women smoke and do not know that they are pregnant, will be unintentionally exposing their fetuses to the harmful effects of smoke. Smoking during pregnancy is well known to cause adverse effects on the development of the fetus and the newborn. It is therefore excessively important to help pregnant women and their doctors become aware of the toxic effects of active or passive smoking in pregnancy. The mother's smoking during pregnancy leads to perinatal or postnatal problems. In most studies it is expressed that smoking or being exposed to smoke causes the fetus to have low birth weight, failure in intrauterine growth, and congenital abnormalities. It may also cause sudden infant death syndrome, insufficient breastfeeding, and problems with respiratory system. It may also lead to failure in the development of cognitive and behavioural functions of the baby in the future [16,30-32]. Thus, smoking during pregnancy is well known to cause adverse effects on the development of the fetus and the newborn. It is therefore excessively important to help pregnant women and their doctors become aware of the toxic effects of active or passive smoking in pregnancy.

It is known that nicotine passes to milk of smoking mothers. The chemicals from the tobacco smoke enter the mother's breast

milk and will therefore be passed into the baby upon feeding. Breast milk will normally contain whatever is in the mother's body. Without a doubt, the more cigarettes the mother exposed to environmental tobacco smoking, the higher concentration of harmful substances is passed onto the child. As regards body composition, smoking appears to reduce fat mass. The prevention of smoking and being exposed to smoke during pregnancy is therefore extremely important as intrauterine growth seems to be negatively influenced not only by active smoking but also by passively being exposed to smoke. Evidence also shows that exposure to cigarette smoke and to nicotine has adverse effects on fetal and adolescent brain development, which could result in lasting deficits in cognitive function. Experimental research documents that nicotine plays a key role in several adverse consequences of maternal smoking for the fetus, including altered lung development, and has effects on the developing brain.

## CONCLUSION

All studies have shown that fetal exposure to nicotine has numerous consequences to the detriment of the health of the fetus and that these effects may last well into adulthood. Our results strongly suggest that nicotine is hazardous to chromosomes of human fetal cells. There is a positive correlation between the frequency of aneuploidy and the effect of nicotine to induce chromosome damage. Smoking in women may increase aneuploidy rates, providing a potential mechanism for aneuploidy in fetal cells and their resulting embryos. It is well understood that the fetal environment is of tremendous importance during the developmental period in determining health throughout the life of the individual. In any case, women who are planning a pregnancy now have additional reasons to stop smoking in addition to the health benefits that they will receive from nicotine abstinence. Therefore, the pregnancy period should be considered to be the ideal time for stimulating women to quit smoking. From a public health perspective, it is essential that pregnant women should be advised to give up smoking from conception and avoid exposure to environmental tobacco smoke during pregnancy. Likewise, healthcare units and maternity wards should hold lectures and explain the harm of tobacco to health and the environment.

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#### Cite this article

Demirhan O (2017) Results of Smoking in Pregnancy: The Genotoxic Effect of Nicotine or why Cigarette should not be Smoked in Pregnancy? *J Addict Med Ther* 5(1): 1026.