Brief Review

Smoking and pregnancy

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SUMMARY. Maternal smoking during pregnancy is considered to be one of the most significant causes of complications in pregnancy and is associated with an unfavourable outcome in childbirth compared with pregnancy in non-smokers. Specifically, smoking during pregnancy increases the likelihood of placenta praevia, abruptio placentae, ectopic gestation and premature rupture of the membranes (PRM). In addition, research has established that smoking during pregnancy increases the rates of low birth weight (LBW), perinatal mortality, premature birth and sudden infant death syndrome (SIDS). As these children grow up they present a variety of health problems, including respiratory illness, behaviour disturbances, attention deficit hyperactivity disorder (ADHD) and high arterial blood pressure. LBW is also associated with an increased incidence of health problems in the neonatal period. Effects have been documented of maternal smoking during pregnancy on the future fertility of male infants and the occurrence of congenital abnormalities, and a connection has been reported between daily maternal smoking in early pregnancy and infantile autism. *Pneumon 2010, 23(2):160-167.*

INTRODUCTION

In Greece, the number of women who smoke has steadily increased throughout the past decade, and World Health Organization (WHO) 2007 statistics indicate that highest tobacco consumption in the world among female smokers is recorded in Greece, where 31.3% of women smoke.[1] In this context, some pregnant women continue to smoke. Pregnant women may not realise that smoking during pregnancy is another form of passive smoking for their child, and that they forcibly expose the foetuses they are carrying to the risks of smoking. As a result, the foetus will suffer all the harmful consequences of smoking, which can in the most extreme cases lead to death, as there is no level of foetal exposure to passive smoking that could be considered safe.[2]

The prevalence of smoking during pregnancy varies from country to country. In Europe, South Africa and Australia a percentage of 20-40% of

pregnant women continue to smoke during pregnancy, while the incidence of smoking in South America and Canada is relatively lower at almost 20%.[3-9] In Sweden, a country that has carried out ongoing campaigns on smoking reduction during pregnancy, the reported reduction of smoking among pregnant women, based on systematic inventories, was impressive: while in 1994 29% of pregnant women smoked daily, by 1997 the smoking prevalence had decreased to 15%.[10]

THE EFFECTS OF SMOKING ON PREGNANCY AND THE FOETUS

The two major products of tobacco smoke responsible for unfavourable consequences in the mother and foetus are nicotine and carbon monoxide (CO).[11] Due to the placental communication between the mother and the foetus, nicotine has been detected in the foetal circulation at levels that exceed those levels detected in mothers by a factor of 1.12 ± 0.30. Nicotine has also been detected in the amniotic fluid at levels 1.54 times higher than in the maternal plasma.[12] As a result, nicotine reduces the supply of oxygen of the foetus, contributing to non physiological gas exchange in the placenta. Nicotine is also associated with an increase in foetal mean arterial blood pressure.[13]

CO also crosses the placental barrier and has been detected in the foetal circulation at levels 15% higher than in the mothers,[14] and this results in a decrease in the amount of oxygen available to foetal tissues.[15] As a result of oxygen deprivation, infants are born with lower birth weight (BW) and smaller length and facial dimensions, and they present more health problems during the neonatal period.[16]

Smoking during pregnancy has been shown to be associated with premature labour and perinatal mortality[17]: the perinatal mortality rate is 150% greater when the mother is a smoker,[18] and smoking is responsible for 15% of all cases of premature labour.[19] Perinatal mortality is increased in the foetuses of pregnant smokers regardless of the number of cigarettes smoked daily. The main causes of perinatal mortality in infants of mothers who smoke are anoxia and premature birth resulting from frequent bleeding from placental detachment or placenta praevia or premature rupture of the foetal membranes (PRM). Perinatal mortality is decreased to a significant degree when pregnant women stop smoking in the last trimester of pregnancy.[20] In addition, tobacco consumption causes premature ageing of the placenta, which justifies the inclusion of pregnant smokers in a programme of High Risk Pregnancy.[21]

Placental abnormalities

Research into the effects of maternal smoking during pregnancy on placental morphology, based on histological examination of placentas, has indicated that histological changes take place in the placenta, including a reduction in the capillary surface of the embryonic trichoids and reduction in the size of the intervillous spaces. These changes reduce oxygen diffusion through placenta, and as a result the foetus can develop a condition of hypoxic stress.[22]

This effect of smoking on the placental morphology is also confirmed by other studies which have identified a change in the balance between proliferation and differentiation of the cytotrophoblast caused by maternal smoking, which can compromise placental growth. The exposure of pregnant woman to passive smoking has been shown to produce the same effects on placental development as active smoking.[23]

Ectopic pregnancy

When pregnancy implants outside the uterine cavity, this is named ectopic pregnancy.[24] In a research project that lasted from 1983 until 1987, women who reported that they smoked were 2.5 times more likely to experience ectopic pregnancy than women who had never smoked. Women who smoked less than 10 cigarettes daily were 1.4 times more likely, and those who smoked more than 1½ packs of cigarettes daily were 5 times more likely, to develop ectopic pregnancy than those who had never smoked.[25]

The study of Saraiya et al. showed that smoking constitutes an independent and dose-related risk factor for ectopic pregnancy: the increased risk of ectopic pregnancy was proportional to the increase in the number of cigarettes smoked by the pregnant woman. Specifically, the relative risk of ectopic pregnancy increased to 1.6 times that of non-smoking women for those who smoked from 1-5 cigarettes daily, and to 2.3 times for women who smoked 11-20 cigarettes daily.[26]

Abruptio placentae

The premature detachment of the normally situated placenta from the uterus before the birth of the foetus is named abruptio placentae. This term is used after the 20th week of gestation and mainly in the third trimester, although detachment can occur at any time during preg-

nancy.[27] The increased frequency of abruptio placentae in pregnant smokers was first identified by Meyer et al. in 1976, who showed that the frequency of abruptio placentae increased by 23% in pregnant smokers who smoked less than one pack of cigarettes daily, and by 86% in pregnant women who smoked more than one pack daily. These researchers concluded that the relation between smoking and increased bleeding during the third trimester was responsible for almost 50% of the increase in perinatal mortality caused by smoking during pregnancy. [28] Meta-analysis of eight studies indicated that abruptio placentae is greatly increased in pregnant smokers, with an odds ratio (OR) of 1.62%.[29]

A nationwide research project was recently carried out in Sweden, with the participation of 526,690 women who had given birth following singleton gestation to their two first children between 1983 and 2001. This study confirmed the cross-correlation of smoking with the increased risk of abruptio placentae in the second gestation: when woman smoked during both gestations, the risk was almost 11 times greater. The large sample size not only increases the statistical significance of the results, but also allows generalisation of the results to other countries. [30]

Placenta praevia

When the placenta is implanted and develops in the lower part of the uterus, overlapping the outlet, this is termed placenta praevia.[20] The occurrence of placenta praevia has been shown to be associated with cigarette smoking during pregnancy, and specifically in a research project including 28,358 births, the incidence of placenta praevia generally was shown to be increased in smokers by 6.4 per 1,000 childbirths. Pregnant women who smoked less than one pack of cigarettes daily had an incidence of placenta previa that was 8.2 per 1,000 births, while for the group of pregnant women who smoked one pack per day or more the incidence was 13.1 per 1,000 births. [28]

This correlation between placenta praevia and smoking during pregnancy was strengthened by the findings of later studies. A research review by Castes et al. of six studies indicated that smoking in pregnancy was positively correlated with placenta praevia, with an odds ratio of 1.58%.[29] The data from the Swedish medical record of births, which represents almost 2,000,000 births over more than 18 years, included 2,345 cases of placenta praevia. The overall OR for placenta praevia among pregnant smokers was 1.53. A dose-related association was observed, with an OR of 1.40 for women who smoked less than 10 cigarettes daily, and 1.72 for those who smoked more than 10 cigarettes daily.[31]

The US Cohort study, which was based on the data from the United States of America (USA) medical records of births from 1989 to 1998, included 37,956,020 singleton gestations and 961,578 twin gestations. According to this study, the number of cigarettes smoked on a daily basis displayed a dose-related association with the occurrence of placenta praevia in both groups; the relative risk for placenta praevia associated with smoking was 4.4% for singleton births and 2.7% for twin births.[32]

Premature rupture of the foetal membranes

Premature rupture of the membranes (PRM) is the term for the automatic rupture of the membranes prior to the onset of labour.[29] Preterm PRM prior to 37 weeks gestation constitutes the most frequent cause of preterm birth [33], representing almost 30% of all preterm deliveries.[34] Smoking is considered by most researchers to be one of the most important causes of PRM, with an OR of 1.81 in six research projects.[29]

Williams et al. found that women who smoked during the entire pregnancy had 2.2 times greater risk of PRM and 2.1 times greater risk of preterm automatic birth throughout the pregnancy, compared with non smokers. Notably, when smoking was stopped during pregnancy the relative risk for PRM decreased. When the mother stopped smoking before conception, the risk was almost the same as that of non smokers. [33]

THE EFFECTS OF MATERNAL SMOKING DURING PREGNANCY ON THE INFANT

When a pregnant woman smokes, the foetus is obliged to become a passive smoker, which has adverse effects on his/her health and growth.[35] Since the first study on smoking in pregnancy was reported in 1957, differences have been deetected not only in the BW of the babies of smokers, but also in their body size characteristics, such as length, head circumference (HC) and the circumference of the thorax and shoulders.[36] The involuntary *in utero* exposure of the foetus to smoking affects the growth of the lungs and brain,[37] placing a burden on the child's health for the rest of his/her life.[38]

Maternal smoking and low infant birth weight

BW not only reflects foetal growth, but it is also one of the main indicators for determination of infant sickness.[39]

In the USA it has been calculated that maternal smoking during pregnancy accounts for 20-30% of LBW infants.[40] There is a positive correlation between the number of cigarettes smoked by pregnant women and the rates of premature birth and LBW.[41] Women who smoke during pregnancy give birth to infants who are on average 150-250 gr lighter than those of non smokers.[42]

The vulnerability of moderately LBW infants, compared with those of normal BW, to a wide range of health, learning and behavioural problems was examined in a recent study by Stein and colleagues in a nationally representative sample of children in the USA.[43] The findings indicate that, compared to infants of normal BW, LBW infants have greater health care needs, suffer more often from chronic diseases, and have higher rates of learning disabilities and attention deficit hyperactivity disorders (ADHD). [43] Particularly striking is the relative increase in the rate of illness of very LBW (VLBW), infants particularly in the post-neonatal period. These children face a variety of health problems, including respiratory problems [44] and raised blood pressure, from their first hour of life until their second year of life.[45]

Sudden infant death syndrome

The infants of mothers who smoke during pregnancy are at increased risk of sudden infant death syndrome (SIDS), which is defined as the sudden death of healthy infants in the first year of life, when the cause of death cannot be determined either from the medical history or from the autopsy.[46] Infants whose mothers smoked during pregnancy have been shown to be at a 2.3 times greater risk of SIDS than those whose mothers did not smoke. This probability is increased threefold in infants whose mothers continued to smoke after gestation.[47,48] Higher concentrations of nicotine and cotinine were found in the lungs of infants who died from SIDS compared with infants who died from other causes.[49]

Maternal smoking and the respiratory system of the child

Maternal smoking during pregnancy decreases the respiratory function of the infant.[50,51,52] These effects on respiratory function, such as diminished maximal forced expiratory flow at functional residual capacity (Vmax (FRC), and the ratio of time to reach peak expiratory flow to total expiratory time (TPTEF:TE), are obvious even seven weeks before the expected gestation date, indicating that negative effects of prenatal exposure to smoking are not limited to the last weeks of gestation, but start earlier. [52]

Recent epidemiological research indicates that maternal smoking is a basic risk factor for asthma in childhood.[53,54] Jaakkola et al surveyed a sample of 5,951 children aged 8-12 years from nine Russian cities and concluded that prenatal exposure to cigarette smoking, through maternal smoking, was associated with an increased risk of diagnosed asthma among the children.[54] In a study in Australia, girls whose mothers had smoked more than 20 cigarettes a day during pregnancy had an increased risk of asthma symptoms at an even later age (14 years) than that observed in the earlier Russian research.[53] Maternal smoking during pregnancy is also considered to be a significant factor in "asthmatic bronchitis" during the first year of life.[55]

Recent epidemiological data gathered from a representative sample of 2,374 children of preschool age from the whole of Greece confirmed that the smoking habit of a pregnant woman is a significant risk factor for the occurrence of bronchial asthma symptoms and for the diagnosis of asthma in preschool children. These effects were dose-related: for each cigarette that a pregnant woman smoked during pregnancy the probability of wheezing or the diagnosis of bronchial asthma increased by 1%. Of particular interest are the findings related to the exposure of pregnant women to passive smoking, mainly during the third trimester, which was also associated with asthma and symptoms related to allergy in childhood.[56]

Apart from childhood asthma, the findings from a recent cohort study conducted by Skorge and his colleagues in Norway suggest that asthma in adolescence and adult life may also be associated with maternal smoking in pregnancy. The study lasted eleven years (1985-1997) and examined the incidence of asthma and respiratory symptoms in 3,786 individuals aged from 15 to 70 years.[57]

The limited data about the respiratory function of premature infants in adulthood led Narang et al. (2008) to conduct a longitudinal study to evaluate airway function 21 years after premature birth. Preterm infants who had participated in a research study from birth and who had been found to have increased respiratory symptoms and airway obstruction in mid-childhood were re-examined. Even though there was no evidence of persistent airway obstruction or airway hyper-responsiveness, these individuals continued to have still excess respiratory symptoms 21 years after a premature birth.[58]

Behaviour disturbances and attention deficit hyperactivity disorder

Various epidemiological studies provide evidence that exposure to cigarette smoking during pregnancy can affect the foetal nervous system, leading to behavioural disturbances in infancy, childhood, and even in early adult life.[59,60] It is evident that smoking in pregnancy is associated with ADHD in children[61] and with a higher risk of hyperactivity, specific learning difficulties[30] and distractibility.[62]

There is a strong association between maternal smoking during pregnancy and sub-standard academic achievement of children at the age of 15 years.[63] It is not clear whether the reported relationship between smoking in pregnancy and cognitive function is causal, or whether a role is played by passive smoking after gestation, or the socio-economic or other characteristics of smoking mothers, as maternal smoking may be related to a less advantageous family environment.[64,65] This association may reflect the effect of the differences that characterize the family environment of smokers and non smokers across all social strata, such as variations in parenting skills such as the time and the attention dedicated to children.[66]

Daily maternal smoking and autism

Even though the relative risk of autism is low, with a rate of around 1/1,000 births,[67] it has been shown to be associated with maternal daily smoking in early pregnancy according to a recent epidemiologic study at a national level in Sweden.[68] Based on a subsample of 408 children born between 1974 and 1993 and officially diagnosed with infantile autism, the researchers suggested that there is a possibility that a subgroup of children develops infantile autism following intrauterine growth restriction and exposure to prenatal and neonatal asphyxia. This observation is consistent with hypotheses concerning the non-genetic environmental mediation of risks that lead to autism in susceptible individuals.[54]

The effect of maternal smoking on male fertility

According to research carried out in Denmark, maternal smoking during pregnancy can influence the future fertility of male infants. The first stage of this study was conducted between 1984 and 1987, as a study on smoking during pregnancy and the effects of smoking on the foetus. In the second stage, in 2005-2006, samples of sperm were gathered from 347 men who, with their mothers, had participated in the earlier stage. Analysis of the samples showed that the more the mother smoked during pregnancy, the greater the adverse effects on the volume and concentration of the son's sperm. Specifically, men whose mothers had smoked more than 19 cigarettes daily during pregnancy demonstrated reduction in sperm volume of almost 19%, a 17% lower sperm concentration, and an overall reduction of 38% in sperm levels. [69]

Congenital abnormalities and maternal smoking

The correlation between smoking during pregnancy and the appearance of congenital abnormalities has been doubted, because it was believed that smoking during pregnancy could not lead to teratogenesis. However, various researchers have claimed that when the mother smokes during pregnancy, the occurrence rate of congenital abnormalities increases, particularly of cleft palate and cleft lip.[70]

The largest survey of the association between maternal smoking in pregnancy and elevated risk of birth of a child with polydactyly, adactyly or syndactyly was carried out in the USA, using the US natality databases from 2001 and 2002.[71] Specifically the files of 6,839,854 births were examined, among which 5,171 infants were found to have isolated polydactyly, adactyly or syndactyly. These children were then compared with 10,342 infants without congenital abnormalities, leading to the conclusion that smoking 1 to 10 cigarettes daily during pregnancy was associated with a 29% increase in relative risk, 11 to 20 cigarettes daily with a 38% increase, and more than 21 cigarettes daily with a 78% increase of relative risk of birth of a child with individual polydactyly, adactyly or syndactyly. The results of this survey are statistically significant because of the large sample size: the sample represented 84% of births in the USA, which is not considered an excessive size, but is well suited for the epidemiological study of rare diseases. However, even if the relative risk is highly increased, the number of children at risk of being born with these conditions remains very small, since the rate of such genetic abnormalities is particularly rare, with a rate of 1 per 2,000 – 2,500 births.[71]

Maternal smoking and increased hospitalization of children

According to an observational study of 1,974 children by Wisborg et al., investigating the relationship between smoking during pregnancy and the hospitalization of infants before the age of 8 months, 8% of children were hospitalised during the first 8 months of life. Specifically,

children of mothers who smoked 15 or more cigarettes daily had twice the risk of hospitalization than those whose mothers had not smoked. The report concluded that smoking 15 or more cigarettes daily influences the health of the unborn child to such a degree that if all pregnant women who smoke 15 or more cigarettes daily stopped smoking, 5% of hospitalizations of children aged under 8 months could be avoided.[72]

CONCLUSION

The most dramatic adverse effects of smoking are those affecting the health of children whose mothers smoke during pregnancy, because they are exposed to smoking involuntarily, through the choice of their mothers. This involuntary foetal exposure to passive smoking has serious consequences for children's health that will follow them into adult life.[38]

Recognition of the health hazards for the foetus of maternal smoking during pregnancy, and of the right of each and every child to enjoy the highest possible level of health, emphasizes the need for cessation of smoking during pregnancy, which is more imperative than ever before in Greece. This could be achieved with the introduction and promotion of effective targeted programmes for smoking cessation during pregnancy. It is also necessary to introduce well organized health education programmes in schools, in order to discourage young girls, who constitute the new target group of the advertising campaigns of the tobacco industries, from taking up smoking.

REFERENCES

1. Organization for Economic Co-Operation and Development. Health at a Glance 2007: OECD Indicators, 2007. http://puk.surceoecd.org/vl=3932594/d=13nw=/rpsv/health 2007/index.htm
2. European Network for smoking Prevention, Annual Report. Bruxelles; 2007. http://www.ensp.org
3. Schuz J, Kaatsch P, Kaletsch U, et al. Association of childhood cancer with factors related to pregnancy and birth. Int J Epidemiol 1999;28:631–9.
4. Chatenoud L, Chiaffarino F, Parazzini F, et al. Prevalence of smoking among pregnant women is lower in Italy than England.BMJ1999; 318:1012.
5. DeFarias AragaoVM, Barbieri MA, MouraDaSilva AA, et al. Risk factors for intrauterine growth restriction: a comparison between two Brazilian cities. Pediatr Res 2005;57:674–9.
6. Grange G, Vayssiere C, Borgne A, et al. Description of tobacco addiction in pregnant women. Eur J Obstet Gynecol Reprod Biol 2005;120:146–51.
7. Viljoen JE, Odendaal HJ. Smoking in pregnancy—what does my patient know? S.Afr Med J 2005;95: 308–10.
8. Hoyert DL, Mathews TJ, Menacker F, et al. Annual summary of vital statistics: 2004. Pediatrics 2006;117:168–83.
9. Pichini S, Garcia-Algar O. In utero exposure to smoking and newborn neurobehavior: how to assess neonatal withdrawal syndrome? Ther Drug Monit 2006;28:288–90.
10. Cnattingius S, Haglund B. Decreasing smoking prevalence during pregnancy in Sweden: the effect on small-for-gestational-age births. Am J Public Health 1997;87:410-413
11. Pitsiou GG, Argyropoulou-Pataka P. Woman and smoking Pneumon 2007;20:1:27-42
12. Luck W, Nau H, Hanesen R, et al. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. Dev Pharmacol Ther1985;8:384–395.
13. Lambers D, Clark K. The maternal and fetal physiologic effects of nicotine. Semin Perinatol 1996;20:115–126.
14. Hill E, Hill J, Power G, et al. Carbon monoxide exchanges between the human fetus and mother: a mathematical model. Am J Physiol 1977;232:H311–323.
15. Benowitz N. Nicotine replacement therapy during pregnancy. JAMA 1991;266:3174–3177.
16. Perry CL, Silvis GL. Smoking Prevention: Behavioural prescriptions for the pediatrician. Pediatrics 1987;79:790-99.
17. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bulletin of the World Health Organisation 1987;65:663-737.
18. Kleinman J, Pierre MJ, Madans J, et al. The effects of maternal smoking on fetal and infantmortality. Am J Epidemiol 1988;127:274–282.
19. Ventura SJ, Martin JA, Taffel SM, et al. Advance report of final natality statistics, 1993. Monthly Vital Stat Rep 1995;44 (suppl):1-88.
20. Creatsas G. Modern obstetrics and gynecology. Obstetrics. Paschalidis PH, Athens, 1998, pp. 162,280.
21. Chasman AH. The effect of tobacco and coffee in the placenta ultrasound depiction. PhD Thesis. Department of Medicine, University of Patras, 1990.
22. Bush PG, Mayhew TM, Abramovich DR, et al. A quantative study on the effects of maternal smoking on placental morphology and cadmium concentration. Placenta 2000;21:247-56.
23. Genbacev O, McMaster MT, Zdravkovic T, et al. Disruption of oxygen-regulated responses underlies pathological changes in the placentas of women who smoke or who are passively exposed to smoke during pregnancy Reproductive Toxicology 2003;17:509–518.
24. Creatsas G. Modern obstetrics and gynecology. Gynecology. Paschalidis PH, Athens, 1998, p.313.
25. Handler A, Davis F, Ferre C, et al. The Relationship of Smoking and Ectopic Pregnancy AJPH September 1989;79:1239-1242.
26. Saraiya M, Berg C, Kendrick J, et al. Cigarette smoking as a risk factor for ectopic pregnancy. Am J Obstet Gynecol 1998;178: 493-498.
27. Salamalekis E. Special Topics in Fetal Medicine. Publications of

the 3rdDepartment of Obstetrics and Gynaecology. General University Hospital 'ATTIKON', Athens, 2003 p. 107.
28. Meyer M, Tonascia J. Perinatal events associated with maternal smoking during pregnancy. Am J Epidemiol 1976; 1103:464–476.
29. Castles A, Adams K, Melvin CL, et al. Effects of smoking during Pregnancy: five meta-analyses. Am J Prev Med 1999;16;3:208-215.
30. Avanth CV, Cnattigious S. Influence of maternal smoking on placental abruption in successive pregnancies: A population –based prospective cohort study in Sweden. Am J Epidemiol 2007:1-7.
31. Monica G, Lilja C. Placenta previa, maternal smoking and recurrence risk. Acta Obstet Gynecol Scand 1995;74:341–345.
32. Ananth CV, Demissie K, Smulian JC, et al. Placenta previa in singleton and twin births in the United States,1989 through 1998:A comparison of risk factor profiles and associated conditions. Am J Obstet Gynecol 2003;188:275-281.
33. Williams M, Mittendorf A, Stubblefield P, et al. Cigarettes, coffee and preterm premature rupture of the membranes. Am J Epidemiol 1992;135;8:895-903.
34. Hadley C, Main D, Gabbe, S. Risk factors for preterm premature rupture of the fetal membranes. Am J Perinatol 1990;7: 374–379.
35. United Nations. Framework Convention on Tobacco Control of World Health organisation, New York, 2003.
36. Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. Am J Obstet Gynecol 1957;73: 4: 808.
37. Hofhuis W, de Jongste JC, Merkus PJF. Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child 2003;88:1086-1090.
38. United Nations. Convention of United Nations on the Rights of Child, New York, 1989.
39. Barker D, Osmond C, Simmonds SJ, et al. The relation of head size and thinness at birth to death from cardiovascular disease in adult life. BMJ 1993;306:422-426.
40. U.S. Department of Health and Human Services. Women and Smoking: A Report of the Surgeon General. Rockville; 2001.
41. Labropoulos L. Smoking and Pregnancy. Medicine 1992;62: 237-241.
42. Yu S, Park C, Schwalberg R. Factors associated with smoking cessation among U.S. pregnant women. Matern Child Health J 2002;6:89–97.
43. Stein R, Siegel MJ, Bauman LJ. Are Children of Moderately Low Birth Weight at Increased Risk for Poor Health? A New Look at an Old Question Pediatrics 2006;118;1:217-223.
44. Fergusson DM, Horwood LJ. Parental smoking and respiratory illness during early childhood: A six-year longitudinal study. Pediatr Pulmonol1985;1:99–106.
45. Panagoulias D. Arterial Pressure of children of mothers who are smokers at the neonatal age and the first year of life. PhD Thesis. Department of Medicine, University of Patras;1999.
46. Willinger M, James LS, Catz C. Defining the sudden infant death syndrome (SIDS): deliberations of an expert panel convened by the National Institute of Child Health and Human Development. Paediatr Path 1991;11:677-84.
47. Gavin NI, Wiesen C, Layton C. Review and Meta-Analysis of the Evidence On The Impact of Smoking on Perinatal Conditions Bull into SAMMECII, Final Report to the national centre for the chronic Disease Prevention and health promotion, Research Triangle Institute (RTI) RTI Project NO 7171-010, Sept 2001.
48. American Academy of Pediatrics. Task Force on Sudden Infant Death Syndrome. The Changing Concept of Sudden Infant Death Syndrome: Diagnostic Coding Shifts; Controversies Regarding the Sleeping Environment; and New Variables to Consider in Reducing Risk. Pediatrics 2005;116:1245-1255.
49. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, 2006; Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
50. Stick SM, Burton PR, Gurrin L, et al. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 1996;348:1060-1064.
51. Dezateux C, Stocks J. Lung development and early origins of childhood respiratory illness. Brit Med Bul 1997;53:40–57.
52. Hoo A, Henschen M, Dezateux C, et al. Respiratory Function Among Preterm Infants Whose Mothers Smoked During Pregnancy. Am. J. Respir. Crit. Care Med 1998;158;3:700-705.
53. Alati R, Al Mamun A, O'Callaghan M, et al. In utero and postnatal maternal smoking and asthma in adolescence. Epidemiology 2006;17:138-44.
54. Jaakkola JJ, Kosheleva AA, Katsnelson BA, et al. Prenatal and postnatal tobacco smoke exposure and respiratory health in Russian children. Respir Res 2006;7:48.
55. Bisgaard H, Dalgaard P, Nyboe J. Risk factors for wheezing during infancy. Acta Paediatr Scand 1987;76:719-726.
56. Xepapadaki P, Manios Y, Liarigkovinos T, et al. Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. Pediatr Allergy Immunol 2009;20:423–429.
57. Skorge TD, Eagan TM, Eide GE, et al. The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood. Am J Respir Crit Care Med 2005;172:61–6.
58. Narang I, Rosenthal M, Cremonesini D, et al. Longitudinal Evaluation of Airway Function 21 Years after Preterm Birth. Am J Respir Crit Care Med 2008;178:74-80.
59. Browne CA, Colditz PB, Dunster KR. Infant autonomic function is altered by maternal smoking during pregnancy. Early Hum Dev 2000;59:209–218.
60. Dombrowski SC, Martin RP, Huttunen MO. Gestational exposure to cigarette smoke imperils the long-term physical and mental health of offspring. Birth Defects Res A Clin Mol Teratol 2005;73:170–176.
61. Olds D. Tobacco exposure and impaired development: A review of the evidence. Ment Retard Dev Disabil Res Rev 1997; 3:257–269.

62. Brennan P, Grekin E, Mednick S. Maternal smoking during pregnancy and adult male criminal outcomes. Arch Gen Psychiatry 1999;56:215–219.
63. Lambe M, Hultman C, Torrång A, et al. Maternal Smoking During Pregnancy and School Performance at Age 15. Epidemiology. 2006;17;5:524-530.
64. Fergusson D, Lloyd M. Smoking during pregnancy and its effects on child cognitive ability from the ages of 8 to 12 years. Paediatr Perinat Epidemiol 1991;5:189 –200.
65. Baghurst P, Tong S, Woodward A, et al. Effects of maternal smoking upon neuropsychological development in early childhood: importance of taking account of social and environmental factors. Paediatr Perinat Epidemiol 1992; 6:403– 415.
66. Larroque B. Prenatal exposure to tobacco smoke and cognitive development: epidemiology studies. Journal de Gynıcologie Obstıtrique et Biologie de la Reproduction. (Paris). 2003;32: IS23–29.
67. Gillberg C, Wing L. Autism: not an extremely rare disorder Acta Psychiatr Scand 1999;99:399–406.
68. Hultman CM, Sparén P, Cnattingius S. Perinatal Risk Factors for Infantile Autism. Epidemiology 2002;13;4:417-423.
69. Ramlau-Hansen CH, Thulstrup AM, Storgaard L, et al. Is prenatal exposure to tobacco smoking a cause of pure semen quality? A follow-up study. Am J Epidemiol 2007;165;12:13372-9.
70. Himmelberger DU, Brown BW, Cohen EN. Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. Am J Epidemiol 1978;108; 6:470-479.
71. Man LX, Chang B. Maternal Cigarette Smoking during Pregnancy increases the Risk of Having a Child with a Congenital Digital Anomaly. Plast Rreconstr Surg 2006;117;1:301-308.
72. Wisborg K, Henriksen TB, Obel C, et al. Smoking during pregnancy and hospitalization of the child. Pediatrics 1999;104:4: e46.