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Maternal Smoking during Pregnancy and Its Impact on Postnatal Neurodevelopment

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Abstract

Background: Nicotine from maternal active smoking or environmental tobacco smoke (ETS) is still the most prevalent substance of abuse during pregnancy in industrialized countries. The negative effects of exposure to tobacco smoke on foetus development have been widely described: impaired foetal growth and increased risks for gestational and perinatal outcomes.

Objective: The aim of this review was to provide an overview on prenatal nicotine exposure and its behavioral and neurodevelopmental deleterious effects in new-borns and children.

Method: We searched MEDLINE and EMBASE for articles catalogued between 1992 and 2015. We identified relevant published studies that assessed the association between maternal smoking and neurodevelopment deleterious effects in offspring. From 33 citations, a total of 17 studies were included.

Results: Literature definitively supports a strong association between exposed new-borns and signs of stress and neonatal withdrawal symptoms. Furthermore, an association between exposure to nicotine and attention-deficit/hyperactivity disorder (ADHD) in children has been reported in many studies, as well as a wide range of externalizing outcomes, especially rule-breaking and aggressive behaviour, with increased risk of conduct disorders and crime.

Conclusions: It is necessary to follow up children with prenatal exposure to ETS in order to detect neurodevelopment effects during childhood. We also recommend the implementation of campaigns to avoid smoking in pregnant women, with structured medical advice and protection of pregnant women and children from ETS.

Keywords: Environmental tobacco smoke (ETS); Pregnancy; Tobacco; Nicotine; Neurodevelopment

Introduction

In the last decades, in industrialized countries, nicotine from active smoking or from environmental tobacco smoke (ETS) has become the most prevalent substance of abuse during pregnancy [1]. In 2012, The European Perinatal Health Report stated that the prevalence of maternal smoking during pregnancy could be above 10% in many countries [2]. According to Ribot et al., 30% to 43% of pregnant women smoke actively at the beginning of pregnancy in Spain [3]. Around 40% of smoking pregnant women quit this habitat early pregnancy, but there are also a significant number of women (between 13% and 25%) who continue smoking throughout all pregnancy, and also about 14% to 26% are passive smokers [3-5]. Puig et al. reported that a 98.4% of the study population was exposed to ETS mainly due to maternal smoking [4]. A recent study performed in 2012 in Spain using cotinine determination in cord blood, reported a rate of smoking in pregnant women of 34.1%, showing a significant difference with self-reporting questionnaires [5].

It is known that pregnant smokers tend to underestimate their consumption. Prevalence data derived from questionnaires are not reliable and it is important to have objective data about prenatal and postnatal nicotine exposure [1]. Nicotine and cotinine, its principal metabolite, are used as biomarkers of tobacco exposure. There are different biological matrices available: conventional (peripheral blood and urine) and alternative (cord blood, saliva, meconium and hair) [1,4-7].

The harmful effects of exposure to tobacco smoke on foetus development have been widely described: increased risk of perinatal mortality, preterm delivery, antepartum haemorrhage and placenta previa, as well as other perinatal complications. During childhood it is also related to cardiovascular and respiratory problems [8-11]. Although there are a lot of studies that describe the deleterious effects in neonatal period and during childhood, neurodevelopment problems derived from nicotine exposure during pregnancy have not been analyzed so widely: withdrawal syndrome, externalizing or conduct problems, hyperactivity disorder and antisocial behaviour [1,9,12].

The aim of our study was to provide an overview on behavioural and neurodevelopmental deleterious effects on new-borns and children following prenatal nicotine exposure.

Materials and Methods

We searched MEDLINE and EMBASE for articles catalogued between 1992 and 2015. We identified relevant published studies that assessed the association between maternal smoking and neurodevelopment deleterious effects in offspring. A narrative review was carried out searching combinations of key words "pregnancy" AND "nicotine" OR "second hand smoke" OR "environmental tobacco smoke" OR "tobacco" AND "neurodevelopment" OR "behavioural problems". The major inclusion criteria were "neurodevelopmental effects of environmental tobacco smoke during pregnancy". The search strategy generated 33 references; from these, 17 studies were included and used in the final analysis.

Results and Discussion

Results are presented in Table 1. The deleterious effects of maternal smoking on new-borns have been deeply described. One of the most detrimental substances in tobacco is nicotine. It can be absorbed chewed by mouth, smoked by the lungs or transcutaneous as a patch [13]. Cotinine, a metabolite of nicotine, enhances the vasoconstrictive action of prostaglandin E2, and the accumulation of cotinine in fetal bloodstream may induce preterm labor and spontaneous miscarriage. When a mother smokes, she exposes her fetus not only to the components contained in cigarette smoke that cross placenta, but also to alterations in oxygen rates, placental metabolism, and in her own metabolism. Carbon monoxide interferes in fetal tissue oxygenation rates in two different ways: by reducing blood oxygen transportation capacity and by altering the oxyhemoglobin saturation curve leftwards, therefore worsening hypoxemia and resulting in growth restriction [11]. It seems that the risk of perinatal and obstetric complications is not only related to the number of cigarettes smoked per day, but also to the pregnancy trimester with the highest exposure. As a consequence, smoking during the second trimester of pregnancy will result in a higher percentage of low-birth-weight children [11]. In addition, tobacco has many other harmful effects during pregnancy, such as an increased risk of miscarriages, higher prevalence of low-birth-weight children (<2,500 g) (with lower lengths and head circumferences), preterm delivery (<37 weeks) and antepartum hemorrhage. Smoking also causes a wide range of perinatal complications as sudden infant death syndrome, abstinence syndrome or major birth defects (cleft lip and palate, heart defects, limb reduction, clubfoot, craniosynostosis, gastroschisis, anal atresia, hernia and cryptorchidism) [8-11,14-17].

Author, year	Reference	Participants/methods; biomarkers/questionnaire	Results
Wakschlag L, et al. (2002)	[28]	MEDLINE and PsychINFO were searched to identify all studies published before June 2001 that examined the association between maternal smoking during pregnancy and severe antisocial behaviour in offspring Biomarkers, questionnaire	The evidence is consistent but not definitive to demonstrate association between maternal smoking during pregnancy and development of oppositional defiant disorder in young children
Linnet KM, et al. (2003)	[23]	73 studies were searched systematically in PubMed, MEDLINE, MBASE and PsyINFO Biomarkers, questionnaire	Exposure to tobacco smoke in uterus is suspected to be associated with ADHD and ADHD symptoms in children
Nakamura MU, et al. (2004)	[11]	758 patients were interviewed regarding smoke inhalation divided in 3 groups: 42 active smokers, 272 passive smokers, 108 mixed and 336 non smokers Questionnaire	High rate of pregnant smokers (55.7%) Active smoking pregnant women were older and had higher parity. Lower education levels, higher rates of spontaneous abortion and newborns with lower weights
Vagnarelli F, et al. (2006)	[21]	50 neonates born between May 2003 and May 2004. Altered behaviour due to prenatal smoke exposure was examined in 25 neonates born from smoking mothers using the BNBAS. Data were compared with 25 non-smoking mothers. Cotinine urinary levels were also measured Biomarkers, questionnaire	COT was the best predictor of infant irritability. Newborns from smoking mothers showed significant lower scores in various BNBAS items
Garzke-Kopp LM, et al. (2007)	[19]	Relation between maternal smoking and child behaviour among 133 women and their 7-15 years old children who were recruited for clinical levels of psychopathology Questionnaire	Smoke exposure during pregnancy predicted conduct disorder symptoms over and above the effects of confounding factors
Puig C, et al. (2008)	[4]	487 infants from Barcelona (Spain) were included and their mothers were asked about smoking habits. Cord serum and children's urinary cotinine were analysed by RIA Biomarkers, questionnaire	COT levels were useful for categorizing children exposed to smoke and showed that a certain increase in ETS exposure during the 4-year follow-up period occurred

Herrmann M, et al. (2008)	[27]	113 papers from scientific literature were examined Biomarkers, questionnaire	There is an association between prenatal and postnatal environmental tobacco exposure and adverse child neurobehavioral development
Salmasi G, et al. (2010)	[8]	76 studies from Medline, EMBASE and reference list were searched and examined Biomarkers, questionnaire	Environmental tobacco exposure increases risk of low-birth-weight, congenital anomalies, higher length and trends towards smaller head circumference
Nomura Y, et al. (2010)	[24]	209 parents (mothers and fathers) of children between 3-4 years were interviewed with ADHD Rating Scale IV and information about pregnancy and smoking was obtained Questionnaire	Maternal smoking during pregnancy is associated with higher inattention hyperactivity and total ADHD scores with and elevated risk for ADHD
Latimer K, et al. (2012)	[25]	1,611 children between birth and 4 years of age with a questionnaire about respiratory problems and tobacco smoke in family. In Barcelona (n=487) cotinine was analysed in several biological matrices Biomarkers, questionnaire	Prenatal exposure is related with higher risk of hospitalization Postnatal exposure is related with sibilance and asthma Higher level of cotinine is related with more wheezing
Delgado YP, et al. (2012)	[10]	1499 pregnant women and their offspring, who were born in Aragón (Spain) during 2009 Questionnaire	Smoking mothers Shorter breastfeeding length, higher prenatal, perinatal and postnatal morbidity
Puig C, et al. (2012)	[5]	3 independent studies with a questionnaire for the mothers at delivery and a cotinine measure in cord blood by RIA 415 in 1996-1998; 283 in 2002-2004 and 207 in 2008 Biomarkers, questionnaire	A significant rate of maternal smoking was found, higher in immigrant women. There was an important decrease in this rate after tobacco laws implementation in 2005 in Spain
Ferrante G, et al. (2014)	[18]	47 papers were reviewed in web-based bibliographic databases Biomarkers, questionnaire	Prenatal smoking and alcohol use among other variables are related with risk of disruptive behaviour disorders in children
Ribot B, et al. (2014)	[3]	282 healthy pregnant women between 2005-2008 Questionnaire	Active and passive tobacco exposure during pregnancy is associated with early delivery and low birth weight
Silva D, et al. (2014)	[10]	12.991 non-Aborigin children and adolescents born in Western Australia, aged < 25 years who were diagnosed with ADHD and prescribed stimulant medication Questionnaire	Smoking during pregnancy increase the risk of ADHD
Joya X, et al. (2014)	[1]	66 clinical studies published in PubMed/Medline databases since 1988 to June 2014 Biomarkers, questionnaire	Active maternal smoking is associated with higher risk of behavioural disorders in children, like ADHD, personality temperament, lowered cognitive development of children at 4 years of age and psychiatric morbidity
Tiesler C, et al. (2014)	[2]	79 studies were searched in web databases Biomarkers, questionnaire	There is no causality between prenatal nicotine exposure and behavioural problems

Table 1: Published articles related to neurodevelopment deleterious effects of prenatal tobacco exposure.

During their development, children from smoking mothers will suffer higher rates of respiratory infections and cardiovascular alterations compared to children from non-smoking mothers [9,18].

Nicotine exposure during pregnancy has been linked to adverse effects on the respiratory system. The increased risk of respiratory complications (probably of viral origen) in children exposed to prenatal passive smoke can be explained by an adverse effect on both the immune system and the structural and functional development of

the lung, and by their decreased ability to neutralize viruses [14,18]. They present a higher rate of hospitalization due to respiratory infection, during the first and second years of life [14]. Also, there is an association between exclusive postnatal exposure and the appearance of late onset wheezing, and the probability of being diagnosed with asthma by four years of age [14].

Smoking during pregnancy has also cardiovascular and metabolic effects in the foetus. It is associated with higher blood pressure during childhood, obesity and increased cardiovascular risk later in life. However, no conclusions about causality for the outcomes of type 2 diabetes and metabolic syndrome can be drawn [2].

The critical period for nicotine-induced damage to central nervous system is during the second and third pregnancy trimester, when the nicotine receptor has the maxim influence in neurodevelopment [19].

Withdrawal syndrome is commonly observed in new-borns whose mothers have heavily smoked during pregnancy. Some symptoms are irritability, tremor, sleep disorders, excitation and hypertonicity. It is characterized by an early onset, because birth interrupts the continuous delivery of the psychoactive substance (nicotine), and a rapid resolution in about 36 hours, unless the mother continues to smoke during breastfeeding [20,21]. The Finnegan score is positively correlated to the number of cigarettes smoked by the mother, and nicotine concentrations in hair and urine are associated with higher scores [12].

Mansi et al. found significantly poorer performances in several items of BNBAS (Brazelton Neonatal Behavioral Assessment Scale) in neonates from mothers who smoked during pregnancy compared with neonates from non-smoking mothers. There was a significant correlation between irritability and poor interaction with the environment and urinary cotinine values [20].

Attention-deficit/hyperactivity disorder (ADHD) is the most common mental disorder in children and adolescents, with a prevalence of 3% to 5% [22,23]. Inheritance rate of ADHD is estimated at 79% and there is a male predominance. However, environmental influence (prenatal, perinatal and postnatal), as well as socioeconomic factors, can interact with genetics. Among these risk factors, prenatal exposure to tobacco smoke is very significant [22-25]. Robust evidence from high-quality large population-based cohort studies, in which potential confounding variables were well controlled, suggested an association between maternal smoking and ADHD [25].

In some studies the ADHD symptoms were observed not only in children from active smoking mothers, but also from mothers passively exposed to environmental tobacco smoke (ETS) [2,24]. An association between gestational exposure to nicotine and hyperactivity or inattention problems in children has been reported in many studies [2,19,22,24,26,27] and the theoretical model has been widely studied: nicotine receptors modulate dopaminergic activity and dysregulation, which can cause ADHD. These children have a dopaminergic midbrain dysfunction at dopaminergic nuclei, decreased cerebral blood flow in parts of the prefrontal cortex, and alterations in prefrontal cortical asymmetry, right frontal-striatal circuitry and cerebellum [19,22,23].

Several authors report a strong association between nicotine exposure during pregnancy and externalising or behaviour problems; although no causal association can be established due to confounding variables and methodological limitations [2]. Carbon monoxide and nicotine are the most important neurobehavioral teratogens in tobacco [28], and an evidence of a direct role of cigarette smoke exposure, direct or second hand smoke has been observed [19]. Externalising problems, especially rule-breaking and aggressive behaviour has been reported, as well as risk of conduct disorder and crime during childhood and adolescence [19,26]. Behavioural effects have been reported to increase proportionally with the number of cigarettes smoked during pregnancy [19]. Maternal smoking has also been associated with oppositional defiant disorder [28]. Conduct disorder is one of the most severe mental disorders in childhood, and a frequent reason for referral to mental health clinics. It is an important public health problem because of its prevalence and related morbidity. The cumulative evidence shows an association between all these disorders and nicotine, although other factors such as social class, parental psychiatric history, quality of the environment must be considered [28,29].

Furthermore, there is one report that shows an increased risk of autism associated with smoking exposure [26]. Although literature shows a diminished intelligence in performance tests, no definitive conclusion can be drawn about the association between prenatal exposure to nicotine and cognitive function in children. It is difficult to control confounding variables such as maternal age, education, intelligence quotient and socioeconomic status [2,28].

On the other hand, postnatal second hand smoke exposures have harmful effects in children during their development. There are many postnatal animal studies that support the presence of learning deficit, hyperactivity, memory and attention impairment in offspring exposed to tobacco [27]. Literature shows that there is a relationship between maternal smoking and behavioural problems; independent of confounders such a maternal personality, maternal mental health, social circumstances or mother´s age [30]. After birth, the period with higher risk of damage seems be the first year of life, because nicotine is transmitted through breast milk [30]. Second hand smoke has an important impact in children and adolescence behaviour. For example, in an interesting study of over 2,000 children between 4 to 11 years old, Weitzman et al. found behaviour problems in children from smoker mothers (despite controlling for multiple confounders) [31].

In addition, some studies suggest that children with socioeconomic problems may be more vulnerable to nicotine adverse effects on neurodevelopment. No sex differences have been proved with reliability [32].

Conclusions

Environmental tobacco smoke exposure during pregnancy has serious deleterious neurodevelopmental effects in new-borns and children. Literature definitively supports a strong association between exposed new-borns and signs of stress and neonatal withdrawal symptoms such as hypertonicity and irritability. Furthermore, an association between gestational exposure to nicotine and attention-deficit/hyperactivity disorder (ADHD) in children has been reported in many studies, as well as a wide range of externalizing outcomes, especially rule-breaking and aggressive behaviour, with increased risk of conduct disorder and crime. No definitive conclusions can be drawn regarding an association with cognitive function in children, due to confounding variables and methodological limitations.

There is enough evidence to recommend avoidance of smoking during pregnancy and protection from ETS to expectant women and children. We recommend implementing campaigns directed to smoking pregnant women, with structured medical advice to cease smoking with nicotine replacement therapy, if necessary, in order to

avoid, not only perinatal and obstetric problems, but also many health problems, including behavioural effects during childhood. Therefore, these children should be included in a special follow up program to detect and treat these health problems as soon they present.

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