Maternal Smoking during Pregnancy and Regional Brain Volumes in Preterm Infants

Mikael Ekblad, BM, Jyrki Korkeila, MD, PhD, Riitta Parkkola, MD, PhD, Helena Lapinleimu, MD, PhD, Leena Haataja, MD, PhD, Liisa Lehtonen, MD, PhD and The PIPARI Study Group*

Objective To evaluate the association between maternal smoking during pregnancy and both brain volumes and head circumference in very-low-birth-weight/very-low-gestational-age infants.

Study design The PIPARI Study is a prospective follow-up study of infants with a birth weight ≤1500 g or a gestational age <32 weeks born in 2001 to 2006 (n = 232) at Turku University Hospital. The brain was imaged by serial brain ultrasound examinations until discharge and magnetic resonance imaging at term age. The head circumference was measured at birth, term, and 2 years corrected age. These measures were correlated to maternal smoking during pregnancy as reported by the mothers.

Results The prevalence of maternal smoking was 18%. The frontal lobe (P = .01) and the cerebellar (P = .03) volumes were significantly smaller in the exposed than in the unexposed infants. The volumes of the other parts of the brain did not differ. There was no association between prenatal smoking exposure and head growth or structural brain disease.

Conclusions Prenatal smoking exposure was associated with significantly smaller frontal lobe and cerebellar volumes in the brains of preterm infants. This is consistent with reports showing an association between prenatal smoking exposure and impairments in frontal lobe and cerebellar functions such as emotion, impulse control, and attention. *(J Pediatr 2010;156:185-90)*.

See editorial, p 175

Smoking during pregnancy affects the growing fetus in a number of ways. Women who smoke during pregnancy are more prone to prenatal complications,[1] including prematurity,[2,3] than nonsmokers. Smoking during pregnancy also causes intrauterine growth restriction.[4-6] The fetal lungs also mature faster if exposed to smoking, but prenatal smoking may also contribute to impaired pulmonary function and increased respiratory illnesses later on.[7,8] Newborns may have withdrawal symptoms after birth if they have been exposed to heavy smoking.[9]

Animal studies have shown that nicotine has a modifying and damaging effect on brain development.[10-12] Nicotine modulates the development of axons and synapses of the neural cell,[13] which may subsequently affect the development of the brain.[14] The maturation process of white matter is a prerequisite for normal neurologic development.[15] The effects of the other potentially toxic ingredients of tobacco smoke on the development of the fetal brain are less well known. Although fetal growth during pregnancy may be impaired because of maternal smoking, there are no solid data on its influence on the growing human fetal brain. There is evidence of increased serious long-term behavioral consequences for the offspring of smokers during pregnancy. Conditions that have behavioral manifestations such as attention-deficit hyperactivity disorder (ADHD) and neuropsychological deficits may be related to an impaired development of the brain. The effects on the individual trajectories may be robust, but the mediating factors are largely unknown. Recent evidence implies that prenatal exposure to maternal smoking modulates the development of the white matter microstructure in, for example, the frontal cortical regions and their respective neurocognitive functions.[16]

The aim of this study was to evaluate the association between smoking during pregnancy and the brain volumes at term in very-low-birth-weight (VLBW)/very-low-gestational-age (VLGA) infants. The hypothesis was that maternal smoking during pregnancy is associated with smaller brain volumes and head circumference in VLBW/VLGA infants.

ADHD	Attention deficit and hyperactivity disorder
ICC	Intraclass correlation coefficients
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
VLBW	Very-low-birth-weight
VLGA	Very-low-gestational-age

From the Department of Pediatrics (M.E., H.L. and L.L), Radiology (R.P.), and Pediatric Neurology (L.H.), Turku University Hospital and University of Turku, the Department of Psychiatry (J.K.) and the Turku PET Center (R.P), University of Turku, and the Department of Psychiatry, Satakunta Hospital District (J.K.), Harjavalta, Finland

*List of additional members of the PIPARI Study Group available at www.jpeds.com (Appendix).

Funded by the Emil Aaltonen's Foundation, the Finnish Academy of Science, the South-West Finnish Fund of Neonatal Research, the Päivikki and Sakari Sohlberg Foundation, the Finnish Foundation for Alcohol Studies, and the Turku University Hospital Research Foundation. The funding sources had no role in study design, the collection, analysis, or interpretation of data, the writing of the article, or the decision to submit it for publication. The authors declare no conflicts of interest.

 10.1016/j.jpeds.2009.07.061

Methods

This study is a part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants). The PIPARI Study consists of VLBW/VLGA infants born in 2001 through 2006 at Turku University Hospital. Inclusion criteria included birth weight ≤ 1500 g in a preterm infant (born below 37 gestational weeks) from 2001 to the end of 2003. From the beginning of year 2004 the inclusion criteria were expanded to include all infants below the gestational age of 32 weeks at birth even if the birth weight exceeded 1500 g. In addition, at least 1 of the parents had to speak Finnish or Swedish. A total of 293 VLBW/VLGA infants were born, and 40 (13.7%) of them died before discharge. Six infants were excluded because the language criteria were not fulfilled. Two hundred forty-seven infants were invited into the study. Eleven families refused to participate, and 4 infants moved outside the catchment area of the hospital. Altogether 232 (93.9%) eligible preterm infants participated in the study. Written consent was obtained from all parents. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland.

The background information and the information about smoking and alcohol consumption of the mothers during pregnancy were collected from maternal antenatal follow-up and hospital records. The question of maternal smoking is part of neonatal follow-up. It is recorded and reported nationally along with other prenatal data. In addition, before discharge, the mothers completed a questionnaire about their prenatal smoking, use of alcohol, and use of illicit drugs. Neonatal inflammatory diseases including chronic lung disease, necrotizing enterocolitis, and septicemia, were defined according to the Vermont Oxford Network definitions.[17]

Head Circumference and Brain Imaging

Head circumference was measured by use of tape-measurement of the maximal occipitofrontal circumference at birth, at term, and at 2 years of age corrected for prematurity. Serial brain ultrasound examinations were performed by the attending neonatologist, trained to do brain ultrasound examinations, in the neonatal intensive care unit at 3 to 5 days, at 7 to 10 days, at 1 month of age, and then monthly until discharge from the hospital.

Magnetic resonance imaging (MRI) was performed at term of corrected age. The imaging took place during postprandial sleep without pharmacologic sedation or anesthesia. The MRI equipment was either an open 0.23 Tesla Outlook GP (Philips Medical Inc., Vantaa, Finland) for the first 126 investigations or 1.5 Tesla Philips Gyroscan Intera (Philips Medical Systems, Best, The Netherlands) for the remaining 106 infants. A total of 209 of 232 magnetic resonance investigations were successfully performed. For volume measurements, at 0.23 T we obtained a T_1-weighted field echo sequence with a time repetition of 30 msec, a time echo of 10 msec, a flip angle of 45 degrees, a slice thickness of 5 mm, a field of view of 220 × 220 mm^2, and a matrix of 256 × 256 was obtained in the coronal plane. At 1.5 T we obtained a coronal T_1-weighted inversion recovery sequence with a time repetition of 3500 msec, a time echo of 400 msec, a time inversion of 15 msec, a flip angle of 90 degrees, a slice thickness of 4.8 mm, a field of view of 180 × 180 mm^2, and a matrix of 256 × 256. The sequences were optimized relative to the field strength of the equipment used.

The postacquisition volume measurements were performed on a GE workstation (GE AW1.0, GE Medical Imaging Systems, Milwaukee, Wisconsin). The coronal T_1-weighted images were loaded into Functool 1.0 post-processing software (GE Medical Systems). Volume measurement was manually performed separating cerebrospinal fluid and the skull from brain tissue. Anatomic differentiation of the brain areas was based on both the anatomic landmarks and on signal intensity differences of the brain structures. In addition to the total brain volume (total brain volume excluding ventricle volumes), the regional brain volumes measured were the cerebral volume, the cerebellar volume, the frontal lobe volume, the combined volume of the medulla oblongata and the pons, and the combined volume of the basal ganglia and the thalami. The cerebellar volume included the cerebellar hemispheres, the vermis, and the cerebellar pedunculi. The frontal volume included the frontal lobes anterior to the central sulcus, excluding basal ganglia and lateral ventricles. The pons and medulla oblongata area were delineated together, with the upper border being the lower border of the mesencephalon and the lower border being the junction between the medulla oblongata and the cervical spinal cord. The basal ganglia and thalami were measured as a block, and the anatomic border between these basal grey matter nuclei and unmyelinated deep white matter on both field strength images was easily delineated by visual inspection. The medial border of the basal ganglia and the thalami was formed by the third ventricle, the lateral border was formed by the external capsule, and the inferior border was formed by the upper border of the mesencephalon. The classification of intraventricular hemorrhage (IVH) was done as described by Papile et al.[18] Structural brain disease was categorized into normal, minor, and major pathology group (definitive brain pathology) according to the most pathologic brain finding either with ultrasonography or MRI.[19]

The brain volume measurements of all the infants in this study were performed by 1 neuroradiologist (R.P.) blinded to the clinical data. The reproducibility of the brain volume measurements was assessed by repeated brain volume measurement of 20 infants, performed by another neuroradiologist who was blinded to the clinical data and the results of the first volume measurement. The intraclass correlation coefficients (ICC [2,1])[20] were calculated to describe the reliability of the brain volume measurements. The ICC ranged from 0.93 to 0.99, except for the volume of brainstem for which the ICC was 0.78. The ICC was 0.95 for the volume of the cerebellum and 0.99 for the frontal lobe. In addition, we calculated the ICC of the volume of the frontal lobe and the cerebellum separately for the 0.23 T and 1.5 T MRI