Early Human Development 87 (2011) 331–334

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Effects of smoking during pregnancy on the optic nerve neurodevelopment

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ARTICLE INFO

Article history:
Received 15 November 2010
Received in revised form 24 January 2011
Accepted 25 January 2011

Keywords:
Retinal nerve fiber layer
Neurodevelopment
Optical coherence tomography
Optic nerve
Pregnancy

ABSTRACT

Background: Tobacco smoking during pregnancy alters neurodevelopment. Optical coherence tomography (OCT) provides precise measurements of the retinal nerve fiber layer (RNFL), which forms part of the central nervous system.
Aims: To assess using the OCT how smoking during pregnancy would affect optic nerve development as detected in human offspring.
Study design: Visual examination and OCT were performed on a group of children (n = 70; 4.15-13.50 years of age), classified as being exposed or not to maternal smoking during gestational period. The association between smoking during pregnancy and RNFL thickness was assessed by a linear regression analysis adjusted for possible confounding factors.
Results: Although visual outcomes did not differ between groups, a significant decrease in the RNFL thickness was found in the group of infants exposed to smoke (105.3 vs 95.6; p = 0.002), even when adjusting for gestational age, birth weight or gender.
Conclusions: OCT measurements show that intrautero exposure to tobacco smoke interferes with the development of the optic nerve.

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1. Introduction

Maternal smoking during pregnancy is the first preventable cause of adverse birth outcomes [1]. However 15-30% of women smoke during pregnancy in developed countries and although this figure has slightly decreased in the last two decades it has increased among young pregnant women [2–4].

It is widely known that changes in the fetal environment during certain periods of neurodevelopment can cause lasting effects on brain structure or function later in life. The effects of prenatal exposure to tobacco smoke can be ascribed to the latter´s toxic constituents, such as CO or lead, and to the nicotine itself being able to cross the placental barrier [5,6]. Reported consequences are low birth weight in newborns [5,7] and several disorders in infants, such as lower cognitive outcomes, reduced skills in language skills, behavioural problems, impaired coordination and attention deficits. [8,9] MRI neuroimaging has been used to study structural changes secondary to exposure to several toxic substances during pregnancy. Maternal cigarette smoking is related to reduced head circumference, lower cortical grey matter and total parenchymal volumes in the offspring [10], as well as lower frontal lobe and cerebellar volumes in preterm infants as measured by MRI [11].

As far as the effects of prenatal exposure to smoking on in vivo human eyes are concerned, only strabismus and poorer stereoacuity have been reported [12,13]. However, no study has been carried out on infants that has focused on structural changes in the ocular anatomy. The anterior part of the optic nerve, the retinal nerve fiber layer (RNFL), as part of the central nervous system, has certain properties that make it unique for the study of neuronal degeneration. Since the RNFL lacks myelin axonal loss can be studied separately from demyelination changes, which turns the RNFL into a good biomarker of axonal damage. It is also the only part of the central nervous system that can be directly visualized. Previous studies in adults with neurodegenerative diseases, such as multiple sclerosis or Alzheimer disease, have shown that there is a direct correlation between the axonal loss observed in the RNFL and either brain atrophy measured by MRI [14] or cognitive dysfunction [15]. This fact has led neuroscientists to propose the retina as a "window to the brain".

Optical coherence tomography (OCT) is a recently developed technology, which generates three-dimensional images by measuring the echo time delay and magnitude of back-scattered or back-reflected light. It functions as an optical biopsy of the retina in real time. The purpose of this study was to assess if smoking during

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doi:10.1016/j.earlhumdev.2011.01.042

pregnancy affects development of the optic nerve in the unborn offspring in a manner that could be detected later by OCT as a reduction of the RNFL thickness in children.

2. Methods

2.1. Participants

This was an observational, cross-sectional study. Seventy children were recruited from the paediatric ophthalmology unit at the Miguel Servet University Hospital (Zaragoza, Spain). All of them were assisted at the Unit for refractive or minor anterior segment problems once recovered from them. The information about the incidence of smoking during pregnancy and other medical conditions was obtained from the mothers of these children. Children who fulfilled the inclusion criteria were invited to participate in the study. The inclusion criteria were: term born infants, aged 4 to 14 years at the time of the study, no systemic disease that could affect the visual system and no ophthalmologic disease except ametropia (refractive defect). All patients with significant refractive errors (more than 5 diopters of spherical equivalent refraction or 3 diopters of astigmatism) or those exposed to other known toxics during pregnancy were excluded from the study.

2.2. Protocol

We used routinely recorded data, including demographic and clinical perinatal and childhood data. All patients underwent a complete neuroophthalmologic evaluation that included assessment of best-corrected visual acuity (using the LogMAR scale), pupillary, anterior segment and funduscopic examinations, colour vision (Ishihara pseudoisochromatic plates), binocular vision or stereoacuity (TNO test) and OCT. Examiners blinded for the perinatal data and the exposure to smoking during pregnancy made all the exams. Colour vision data were obtained from the 16 screening plates, with Transformation and Vanishing numeral designs, of the 24 plate Ishihara test.

The OCT tests were performed to measure the peripapillary RNFL by means of the Cirrus HD-OCT (Carl Zeiss Meditec Inc, Dublin, CA). The Fast RNFL thickness protocol (3.4 mm circular scans) was employed. The same experienced examiner performed all the OCT scans and no manual correction was applied to the OCT output. An internal fixation target was used since this provides the highest reproducibility [16]. The signal strength measurement of the Cirrus OCT was used to evaluate the quality of the scans. This parameter provides a scale from 1 to 10, where 1 is the poorest image quality and 10 an excellent quality image. The quality of the scans was assessed prior to the analysis and those with quality score lower than 7 were rejected and repeated. No patient was excluded because of poor quality images.

The outcome measures obtained by OCT and analyzed in the study were average, superior, temporal, inferior and nasal RNFL thickness, rim area, disc area and cup-disc ratio. The average of the measurements from both eyes was recorded for the analysis.

Smoking during pregnancy was assessed during the first visit by the mother and categorized as: i) non-smoker, ii) smoker. The amount of cigarettes smoked was also recorded. All procedures adhered to the tenets of the Declaration of Helsinki, and the local Ethics Committee for the protection of human subjects approved the protocol. The dataset used for this study was anonymized.

2.3. Statistical analysis

The population characteristics were described and compared between both study groups by a Mann-Whitney U test to detect any possible source of bias. The effect of smoking during pregnancy on the visual system of the offspring was assessed by comparing the functional and structural visual parameters by a Mann-Whitney U test between both groups. Subsequently, the association between smoking during pregnancy and RNFL thickness was assessed by means of a linear regression adjusted for possible confounding factors, such as gestational age, birth weight, gender and maternal age. The dose-effect relation was sought by linear regression. A value of $p<0.05$ was considered statistically significant.

Table 1
Characteristics of the study groups relative to exposure to cigarette smoke during pregnancy.

	NON SMOKER	SMOKER	p
N	55	15	
Birthweight (mean (SD)) (g)	3381 (395.86)	3150 (301.92)	0.074
Gestational age at delivery (mean (SD)) (week)	39.4 (1.24)	38.8 (0.87)	0.121
Maternal age (mean (SD)) (years)	32.86 (3.77)	32.94 (3.47)	0.683
Gender (males:females)	29:26	6:9	0.561
Age (mean (SD)) (years)	7.2 (2.36)	7.6 (2.47)	0.566

N: number of patients; SD: standard deviation;

3. Results

Of the 70 mothers of the children included in the study, 55 (78.6%) did not smoke during pregnancy, whereas 15 (21.4%) were smokers. The median number of cigarettes smoked per day by the smoker group was 7 (range: 2–20). Table 1 shows the demographic characteristics of the study groups. There were no differences between groups with respect to the age or gender of the patients. No case of growth restriction was included in the study since birth weights ranged from 2730 to 3900 g. None of the other potential factors influencing the development of the optic nerve was significantly different for either group. Four mothers from the non-smoker group had gestational diabetes and one from the smoker group had hypertension ($p=0.301$ and 0.176 respectively).

Although visual outcomes (visual acuity, colour vision and stereocuity) did not differ between groups, a significant decrease in the RNFL thickness was found in the group of infants exposed to cigarette smoke (Table 2). All the RNFL measurements were decreased in the group of infants from smoker mothers, though these differences were only significant for the mean RNFL thickness (95.63 vs 105.33 μm), the inferior quadrant (118.23 vs 135.44 μm) and the superior (119.5 vs 133.30 μm). These differences remained statistically significant when corrected for multiple comparisons. Using Bonferroni method a parameter needed a p value of 0.006 to be considered significant. Even when adjusted for gestational age, birth

Table 2
Functional and structural visual outcomes.

	NON SMOKER	SMOKER	p
N	55	15	
Visual acuity (mean (SD))	-0.021 (0.16)	0.019 (0.03)	0.334
Colour vision (mean (SD))	15.25 (2.63)	14.83 (3.51)	0.462
Stereocuity (mean (SD))	90.42 (94.06)	133.33 (144.03)	0.640
Optical coherence tomography			
Mean RNFL thickness (mean (SD)) (μ)	105.33 (10.59)	96.63 (8.73)	0.002
Superior RNFL thickness (mean (SD)) (μ)	133.30 (17.24)	119.5 (14.98)	0.006
Nasal RNFL thickness (mean (SD)) (μ)	80.54 (15.41)	75.6 (12.82)	0.261
Inferior RNFL thickness (mean (SD)) (μ)	135.44 (16.18)	118.23 (19.47)	0.001
Temporal RNFL thickness (mean (SD)) (μ)	71.26 (10.38)	67.63 (8.58)	0.220
Rim area (mean (SD)) (μ)	1.62 (0.34)	1.62 (0.25)	0.959
Disc area (mean (SD)) (μ)	2.16 (0.41)	2.24 (0.36)	0.641
Cup/disc ratio (mean (SD)) (μ)	0.41 (0.20)	0.49 (0.15)	0.292

N: number of patients; SD: standard deviation.

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