



How does tobacco smoke influence the morphometry of the fetus and the umbilical cord?—Research on pregnant women with intrauterine growth restriction exposed to tobacco smoke



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ARTICLE INFO

Article history:

Received 14 January 2015

Received in revised form 5 August 2015

Accepted 21 August 2015

Available online 24 August 2015

Keywords:

Tobacco smoking

Intrauterine growth restriction

Morphometric parameters

Umbilical cord

Fetal growth

Metallothionein

Glutathione

Cotinine

ABSTRACT

Proper structure of the umbilical cord is important for the fetal development. We evaluated effects of toxic factors from tobacco smoke on fetal and umbilical cord morphometry. 109 women in weeks 29–40 of pregnancy (31 smokers with intrauterine growth restriction (IUGR); 28 non-smoking women with IUGR; 50 healthy pregnancies) were included. In smokers with IUGR, cotinine, cadmium and lead concentrations were significantly higher than in controls (mean 55.23 ng/l; 1.52 ng/ml; 14.85 ng/ml vs 1.07; 0.34; 9.42) and inverse correlation between lead concentration and uncoiled umbilical cord was significant ($r = -0.80$). In smokers with IUGR, area of Wharton's jelly was increased compared to nonsmokers and controls. Inverse correlations occurred between cotinine and cadmium concentration and fetal percentile in smokers ($r = -0.87$; $r = -0.87$) and non-smokers ($r = -0.47$; $r = -0.78$) with IUGR. Exposure to tobacco smoke measured by cotinine, cadmium and lead concentration has an impact on fetal growth and umbilical cord morphometry and correlates with intensity of IUGR.

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1. Introduction

Cigarettes are common stimulants used during pregnancy and lactation. About 8.1–30% of pregnant women smoke [1]. The most toxic substances of tobacco smoke are: nicotine, hydrogen cyanide, and tar [1,2]. Both active and passive smoking during pregnancy have various negative consequences including intrauterine growth restriction (IUGR) [1,3]. The main nicotine metabolite, cotinine, is a recognized marker of exposure to tobacco smoke [4–6]. Cadmium (Cd) is one of the two most toxic metals involved in the impairment of fetal growth and development [7,8]. The transport protein metallothionein-isoform 2 (MT), closely associated with Cd, is found in the placenta of smoking mothers [9]. This protein participates in regulation of heavy metal transport to plasma and cells. Lead (Pb) is another metal in tobacco smoke responsible for

neurotoxicity, but its elimination is more difficult and lasts longer. Alongside MT, glutathione (GSH) is another crucial antioxidant. Although both participate in cellular liquidation of the effects of smoking, they are also engaged in various other metabolic pathways [4,10].

The present study aims to evaluate the effects of tobacco smoke on fetal morphometric parameters including weight, abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC), femur length (FL) and morphometry of the umbilical cord: diameter of the umbilical cord vein and artery, Wharton's jelly and its helicity. Concentration of cotinine in the blood which reflects current tobacco exposure and the two heavy metals (Cd and Pb) which reflect current and chronic exposure to tobacco smoke were measured. The concentration of MT and GSH in maternal blood was analyzed, as well as correlations of those markers with morphometric parameters.

The manuscript is one of a series of articles which examine the influence of toxic substances from tobacco smoke on functioning of maternal-fetal compartment which is very complex problem due to a large number of factors that are being collected and analyzed. Each of the articles from this series analyses different aspect of fetal development in the environment that includes harmful substances delivered by a smoking mother. The first study focused on mor-

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; Cd, cadmium; FL, femur length; GSH, glutathione; HC, head circumference; IUGR, intrauterine growth restriction; MT, metallothionein; Pb, lead; PROM, premature rupture of membranes; SGA, small for gestational age.

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phological aspects of umbilical cords [11]. In the second study, the effect of cigarette smoking on antioxidant status was analyzed [4]. In the last one, biochemical blood findings of pregnant women and fetuses exposed to tobacco smoke were correlated with the results of Doppler flow measurements in fetal and maternal blood vessels, which allowed authors to find correlations between cigarette smoking and IUGR in the context of changes in the kinetics of fetal blood vessels [12]. The present study aims to search for possible characteristics changes in fetal morphometry and umbilical cord morphology in IUGR fetuses of smoking mothers in relation to selected toxic factors from tobacco smoke in order to assess a mechanistic basis of those deviations. The last one, on which authors are currently working, includes also smoking women without IUGR. Comparison between smokers with IUGR and smokers without IUGR gives a new insight into the problem of cigarette smoke impact on the fetus and its long-term effects. All the studies from our series build a logical presentation of changes in maternal–fetal compartment and present its impairment of functioning and structure caused by smoking from various aspects.

The topic of interest was whether fetal development deterioration in smoking mothers is evoked simultaneously by damage to placenta vascularization and the umbilical cord changes. Moreover, sonographic changes in the umbilical cord translate into extent of tobacco smoke exposure (both current and chronic), while biochemical markers tested in maternal blood reflect direct exposure of the mother and indirect of the fetus.

2. Materials and methods

This prospective study was conducted at Wrocław Medical University, Department of Obstetrics and Gynecology and was accepted by the Local Bioethics Committee of Wrocław Medical University (KBN No573). All patients gave informed consent for participation in the study. The study included 109 women in weeks 29–40 of pregnancy: 31 female tobacco smokers, displaying IUGR symptoms with no other pathology than tobacco smoking, 28 non-smoking pregnant women suffering from IUGR with unknown cause and a control group of 50 healthy pregnant women without any complications during pregnancy.

Intensity of cigarette smoking was assessed during a direct personal interview and verified by serum cotinine concentration. Women with a concentration >50 ng/ml (equivalent to 5–20 cigarettes/day) were classified as smokers. In the two non-smoking groups, passive smoking was eliminated on the basis of a cotinine concentration ≤ 10 ng/ml.

All subjects underwent several ultrasound examinations to measure fetal size (BPD, HC, AC, FL) and Doppler flow parameters in the umbilical and middle cerebral arteries. Measurements were made to estimate the mass of the fetus, characteristic percentile and for qualification to study groups. Small for gestational age (SGA) fetuses were excluded. IUGR criteria of fetuses included in our study and SGA criteria are summarized in Table 1.

For each of the measured parameters (BPD, HC, AC, FL), the difference in gestation weeks between the value appropriate for the average fetus of a given age and the value for each particular fetus was measured. Differences for each parameter were named delta HC, delta BPD, delta AC and delta FL.

Umbilical cord parameters were measured. The mean result was calculated from three measurements in various sections of the umbilical cord. The umbilical cord was measured as follows: diameter and cross-sectional area of the vessels, umbilical cord and Wharton's jelly areas were measured in cross-section, while the length of the uncoiled section was measured on the vertical cross-section of the helix as the parameter that characterizes the coiling of the umbilical cord. In all cases, the umbilical cord had three ves-

Table 1
Characteristics of IUGR and SGA fetuses in the study.

	Features of the pathology
IUGR	<ul style="list-style-type: none"> • Estimated fetal weight below the 10th percentile; • The weight deficit persisted or deepened in subsequent sonographic examinations; • Impaired BPD to AC ratio; • Pathology confirmed after delivery by neonatologist and either the birth weight or ponderal index below 10th percentile; • No abnormalities indicating congenital malformations or genetic disorders;
SGA	<ul style="list-style-type: none"> • Estimated fetal weight below the 10th percentile; • Constant though slower growth but slower than normal in in subsequent sonographic examinations; • Lack of typical for IUGR deterioration in vascular flows; • No abnormalities indicating congenital malformations or genetic disorders;

IUGR—intrauterine growth restriction; SGA—small for gestational age; BPD—biparietal diameter; AC—abdominal circumference.

sels. Ultrasound device Voluson Expert E8 (GE Medical Systems) with 3.5 MHz volumetric abdominal probe was used.

Results of ultrasound measurements were obtained from patients between 29 and 36 gestational weeks. The groups' size was similar in every gestational week. Ultrasound measurements and blood tests were performed on the same day.

Each of the biochemical parameters was tested twice—once during the pregnancy and once on the day of delivery. Heavy metal concentration was determined in whole blood using SOLAAR M6, Thermo Elemental Co. Cotinine in serum was measured using the commercial Cotinine ELISA test (ref. no: 40-101-325056, GenWay Biotech, Inc., USA). Concentration of GSH in the blood was determined using GSH-400 Assay (ref. No 21011, Oxis Research USA). Concentrations of MT was measured in the erythrocyte lysate by own method [13].

Statistical analysis was performed using the Statistica Software Package, version 10.0 (StatSoft, Kraków, Poland). Mean and standard deviation was calculated. The normality of the variables was tested by the Shapiro–Wilk test. Differences between the groups were tested using Student *t* test (Pb, GSH, MT, cotinine). In the case of a lack of normal distribution and variance uniformity, non-parametric Mann–Whitney *U* test was used (gestational age at delivery, infant birth weight, Cd). Correlation was expressed by the Spearman's product moment correlation coefficient (*r*). $P < 0.05$ was considered statistically significant.

3. Results

In the group of non-smoking and smoking pregnant women with IUGR estimated birth weight was below the 10th percentile. Gestational age of non-smokers with IUGR was significantly lower than in the controls, however, the difference between smokers with IUGR and controls was insignificant. Differences between cotinine, Cd and Pb concentrations in the blood of smokers with IUGR and the control group were statistically significant. The highest concentration of MT was found in non-smokers with IUGR. The lowest GSH concentration was detected in smokers with IUGR, about 2-fold lower than in the control group (Table 2).

The values of delta BPD, delta HC, delta AC and delta FL were increased in groups with IUGR in comparison to the controls. In all IUGR groups, lower values of umbilical cord diameter than in the control group were observed.

We did not observe statistically significant differences between IUGR groups and control group in case of umbilical artery diameter as well as area of the artery. The area of the umbilical vein of all IUGR cases was decreased in comparison to the control group. A statisti-

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