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Effect of cigarette smoking on vascular flows in pregnancies complicated by intrauterine growth restriction

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ABSTRACT

Exposure to tobacco smoke during pregnancy may result in intrauterine growth restriction (IUGR). In the study, the effect of tobacco smoke on vascular flows in the middle cerebral artery, umbilical artery, ductus venosus in fetuses and uterine artery in pregnancies complicated by IUGR was investigated.

The study subjects were divided into three groups: smoking women with IUGR ($n = 31$), women with idiopathic IUGR ($n = 28$) and healthy controls ($n = 50$). Fetal biometry and flow parameters were measured. Concentration of heavy metals and antioxidants was tested in maternal blood and fetal umbilical cord blood. The Student t test and multiple regression analysis were used.

Cotinine and cadmium concentrations were significantly higher in smokers (55.23 ± 54.23, 1.52 ± 0.9), while metallothionein was significantly higher (22.94 ± 8.64) in the idiopathic IUGR group. Strong correlations between cotinine and cadmium concentrations and cerebral–umbilical index were found.

Long-term exposure to tobacco smoke deteriorates flows in vital fetal vessels.

1. Introduction

Cigarette smoking is one of the most prevalent social habits. About 25% of Polish women smoke, and half of them continue to smoke during pregnancy [1]. From 25 to 50% of pregnant women are exposed to secondhand smoke [2]. In the USA, the percentage of female smokers reaches 20%, and 14% of pregnant women are active smokers [3]. It is estimated that the percentage of female smokers does not exceed 30% in any European country [1]. Smoking is a toxic factor in pregnancy and it causes numerous obstetric pathologies, including premature birth, premature fetal membrane rupture, oligohydramnion, premature placenta abruption, abnormal localization of the placenta and many more [4,5]. Among the best-known consequences of fetal exposure to tobacco smoke are low birthweight and intrauterine growth restriction (IUGR) [4,6–8]. IUGR is one of the most significant causes of intrauterine death and higher incidence of perinatal mortality [4,9–11].

The mechanism by which IUGR occurs more frequently in female smokers is not clearly explained. Among the components of tobacco smoke, the most harmful for the fetus are nitric oxide and carbon monoxide. The first one is considered directly vasoconstrictive and the latter one impairs the transportation of oxygen and nutrients to the placenta. In addition to the above-mentioned toxic substances, tobacco smoke contains many other compounds that affect the structure and function of the placenta i.e. nicotine and heavy metals [2]. The altered structure of the umbilical cord can also play an important role in the altered transportation of nutrients. Previous studies conducted by authors showed hyper-coiled umbilical cord, higher proportion of Wharton's jelly and smaller diameter of umbilical cord vessels in pregnancies complicated by IUGR [12,13].

The precise mechanism of IUGR development is not fully understood thus many questions arise. It is not clear how altered umbilical cord structure and impaired function of placental vessels influence vascular flows in the fetus. The key vessels for fetal–maternal circulation are umbilical artery (UA), middle cerebral artery (MCA), ductus venosus (DV). They are good predictors of neonatal outcome in IUGR as well [9,14–16]. The maternal vessel for which measured flows are recognized as markers of IUGR risk,

Abbreviations: AC, abdominal circumference; AFI, amniotic fluid index; BPD, biparietal diameter; Cd, cadmium; DV, ductus venosus; FL, femur length; GSH, glutathione; HC, head circumference; IUGR, intrauterine growth restriction; MCA, middle cerebral artery; MT, metallothionein; PI, pulsatility index; RI, resistance index; S/D, systolic/diastolic ratio; SGA, small for gestational age; UA, umbilical artery; Δ, delta; MCA/UA PI, cerebral–umbilical index for pulsatility index of both arteries; MCA/UA S/D, cerebral–umbilical index for systolic–diastolic ratio of both arteries; ΔS/D UA, delta S/D in the umbilical artery; ΔPI UA, delta PI in the umbilical artery; ΔRI UA, delta RI in the umbilical artery.

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particularly in cases of pregnancy-induced hypertension (PIH), is the uterine artery.

Determining the cause of IUGR would assist in early diagnosis and its evaluation. In addition, pregnancies complicated by IUGR are highly heterogenic and the progress of the disease may have different outcomes [17]. Among the known causes of IUGR, smoking is one of the most significant and one of the most common.

The best marker of current exposure to tobacco smoke is cotinine, one of the nicotine metabolites [18,19], while cadmium (Cd) is a marker of both long-term and recent exposure, as the element accumulates in the bodies of both mother and fetus. Metallothionein (MT) and glutathione (GSH) are antioxidants known to participate in mechanisms responsible for detoxification of tobacco smoke components [2,19,20].

Searching for possible mechanisms of IUGR development in pregnant smokers, the question arises about the relation between the concentration of toxic substances such as nicotine or heavy metals and the prevalence of pathologies in fetuses such as low body mass, low growth rate, and impaired blood vessel function. How effective are cellular detoxification mechanisms at eliminating the toxic substances in healthy organisms and fetuses of pregnant women exposed to long-term tobacco smoke?

The aim of the study was to evaluate the effect of tobacco smoke measured by concentrations of cotinine and Cd in maternal and fetal blood on values of fetal vascular flows in the MCA, UA, DV, and in the uterine artery of the mother. Another objective was to evaluate the correlation between flow factors in those vessels and the antioxidative factors of MT and GSH in maternal and fetal blood.

2. Materials and methods

109 women whose pregnancies ranged from 23 to 40 weeks gestational age were included in a prospective study. All the patients were hospitalized in Wroclaw Medical University, Department of Obstetrics and Gynecology. All women gave written, informed consent for participation in the study. The study protocol was approved by the Commission of Bioethics at Wroclaw Medical University (KB No: 573/2005). The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki.

The research group consisted of 31 female tobacco smokers displaying IUGR symptoms with no other pathology than tobacco smoking during pregnancy (group 1), 28 pregnant women suffering from idiopathic IUGR with no known cause of this pathology (group 2), and a control group of 50 healthy non-smoking pregnant women without complications occurring during pregnancy (group 3). The examinations did not reveal any abnormalities in the body of the fetuses included in the study that might have suggested the presence of congenital malformations or genetic disorders. Small for gestational age (SGA) fetuses were not included in the study. SGA was defined as an estimated fetal weight below the 10th percentile without typical features of growth retardation, with constant though slower growth, and without impairment in vascular flows typical for IUGR.

The data concerning cigarette smoking, which had been obtained from a direct personal interview with each patient, were verified by determination of serum cotinine, a metabolite of nicotine, concentration. Women with a serum cotinine concentration exceeding 50 ng/ml were classified as smokers. Such cotinine concentration was equivalent to 5–20 cigarettes smoked a day. Based on these criteria, women were divided into smokers or non-smokers. In the two non-smoking groups passive smoking was eliminated on the basis of cotinine concentration below 10 ng/ml.

The fetal monitoring (including non-stress test, biophysical profile with amniotic fluid volume assessment, Doppler examinations, and serial fetal biometry) was performed according to the procedures described by Lausman et al. [21] All patients were enrolled in the study at 23 gestational weeks. At the beginning they were monitored in the outpatient settings with regular control visits every two weeks. After 26 weeks of gestation the Doppler flow measurements were performed. In case of deterioration of flow parameters in the UA, reduction of amniotic fluid volume and further growth restriction of the fetus the patients underwent the Doppler flow measurements in the fetal MCA and fetal biophysical profile assessment (Manning's score) twice a week. They were next hospitalized until the delivery. During hospitalization with every woman non-stress test was performed twice daily and Doppler flow assessment in the UA and fetal venous–arterial system every one or two days. Results of ultrasounds measurements analyzed in the study were obtained from patients between 29 and 36 weeks of gestation. The number of patients in the study groups (smoking and non-smoking pregnant women with IUGR and healthy controls) was similar in every gestational week. Ultrasound measurements taken for analysis were obtained at the same day as blood sampled for biochemical examinations.

Each of the patients underwent an ultrasound examination to measure the size of the fetus. Fetal weight was estimated by ultrasound biometry assessment: biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). Based on several ultrasound examinations, we estimated the percentile and rate of growth of each fetus. Flow parameters were measured and analyzed. Amniotic fluid was measured and amniotic fluid index (AFI) was calculated. Taking into consideration these ultrasound parameters we qualified the fetuses to the IUGR group.

The fetal Doppler flow measurements were obtained in the absence of fetal breathing movements. The following fetal vessel flow parameters were measured:

(a) umbilical artery: PI (pulsatility index), RI (resistance index), S/D (systolic–diastolic ratio),
(b) middle cerebral artery: PI, RI S/D,
(c) ductus venosus: PI,
(d) MCA/UA PI (cerebral–umbilical index for pulsatility index of both arteries),
(e) MCA/UA S/D (cerebral–umbilical index for systolic–diastolic ratio of both arteries).

Flow parameters PI, RI, S/D in the umbilical artery were measured in the placental attachment and free loop of the umbilical cord.

The measured maternal vessel flow parameter was uterine artery – PI. The flows were measured in the two uterine arteries, however only the results from placental uterine artery were included in the analysis. Due to the strict study criteria, correlations presented below were observed only between placental uterine artery and other parameters (Figs. 1 and 2).

In addition to the above, the delta (Δ) parameter was introduced by the authors, in the purpose to objectivize values of flow parameters. This is a novelty in vessel flow studies. The delta makes the assessment independent of gestational age and weight percentile. It was calculated as the difference between the value obtained by measuring the flow parameter in a given vessel of a given fetus and an average value of flow in the particular vessel for a given weight percentile obtained from ultrasounds examinations and given week of pregnancy provided in the tables published in the Callen's book [22,23].

A mathematical model of delta calculation at every moment of every fetal measurement (I) can be described with the use of state vectors $[I \rightarrow x_p\ (m, t, p)]$. In this formula I denotes number of measurements, m denotes weight percentile at the moment