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Maternal and Fetal Hemodynamics of Chronic Pregnant Smokers: A Doppler Study

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Abstract

Objectives: To evaluate the influence of chronic smoking on maternal-fetal hemodynamics through Doppler study of maternal uterine (UtA), fetal umbilical (UmA) and fetal middle cerebral (MCA) arteries compared to pregnant non-smokers. The effect of the degree of nicotine addiction on this hemodynamics was also analyzed.

Methods: Observational cross-sectional study conducted in 98 chronic pregnant smokers and 102 pregnant non-smokers. Doppler study was performed for measuring Pulsatility Index (PI) and Resistance Index (RI) of UtA, UmA and MCA. Fargeström and exhaled Carbon Monoxide (COex) tests were analysed.

A multivariate general linear model with re sampling was applied. The significance level of 95% and 95% confidence intervals were adopted.

Results: Comparison of Doppler indexes between the two groups showed that only UtA RI and UmA PI had significant effect ($p<0.001$ and $p=0.032$, respectively), with higher values in pregnant smokers than non-smokers, indicating vasoconstriction and increase impedance in the studied vessels. Smoking had a positive effect for PI ($p=0.045$) and RI ($p=0.007$) of MCA, with significantly decreased indexes in smokers with high and very high dependence compared to low and moderate dependence. COex analysis showed elevated Um PI in moderate *vs* light smokers ($p=0.035$) whereas MCA RI was higher in light *vs* heavy smokers ($p=0.024$).

Conclusions: Chronic smoking interfered negatively on maternal-fetal vascular hemodynamics, as demonstrated by increased impedance in the maternal uterine and fetal umbilical arteries. Moreover, the greatest exposure to tobacco caused vasodilation effect in the fetal MCA, demonstrating that higher nicotine dependence, the greater the maternal-fetal hemodynamic changes.

Keywords: Doppler; Pregnancy; Smoking; Ultrasonography

Introduction

Smoking remains a public health problem worldwide [1,2]. The cigarette has 4,000 active substances, including nicotine, tar, nitrosamines, polyaromatic hydrocarbons, formaldehyde hydrogen, cyanide and carbon monoxide [3]. Recent data indicate that one-third of US pregnant women and a quarter of Brazilian pregnant women are smokers [4]. Besides causing perinatal risks, maternal smoking can also affect the postnatal mental, intellectual and behavioral development of children exposed to smoking in fetal life [5].

In pregnancy, smoking is responsible for 20% of fetuses with low birth weight, 8% of premature births and 5% of all perinatal deaths [3]. Mothers who smoked during pregnancy had higher (66%) perinatal complications compared to non-smokers [6]. Although the greatest benefits for the fetal development occur if smoking cessation is still done in early pregnancy [5], stopping at any point in pregnancy, or even in the postnatal, has a significant impact on family health.

The effects of maternal smoking on the placental blood flow and vascular resistance are still controversial [7,8] but it is believed that their consequences on the fetal growth are probably mediated, at least in part, by a decrease of blood flow in the vascular beds of the placenta [9]. The mechanisms of action and damage caused by the cigarette consumption during pregnancy are complex, since it is the result of inhalation of a number of vasoactive substances, which have a range of effects that can be complementary or antagonistic at various levels within the vascular tree [10].

Several studies in the literature have used the Doppler method for analyzing the flow patterns in the maternal and fetal arteries of pregnant smokers with some divergent results [7,8,10-13]. The present study becomes relevant by analyzing the pulsatility and resistance indexes of the uterine, fetal umbilical and fetal middle cerebral arteries in chronic pregnant smokers who had the degree of nicotine dependence evaluated by specific tests.

The objective of this study was to evaluate the influence of chronic smoking on maternal and fetal hemodynamics by using Doppler study of the uterine, fetal umbilical and fetal middle cerebral arteries compared to a group of pregnant non-smokers. Furthermore, it was examined whether the degree of nicotine dependence causes effect in this hemodynamic profile. Our hypothesis is that there is a main effect of smoking on maternal and fetal hemodynamics. Moreover, when only pregnant mothers are considered, we hypothesized that

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there will be main effects of the Fagerström and Coex tests, but no interaction effect of these measures in the evaluation of the maternal and fetal hemodynamics.

Methods

Study design

This is an observational and analytical cross-sectional study conducted at the Clinic Hospital, Federal University of Uberlândia (UFU), Uberlândia, MG, Brazil. A total of 200 pregnant women, 98 smokers and 102 non-smokers, were subjected to analysis of six Doppler parameters between October 2011 and October 2013. This study was approved by the Research Ethics Committee of the Institution (number 420/10) and all patients who agreed to participate of the study signed an informed consent.

Patients were consecutively included in the study among those sent from the low risk prenatal in the Prenatal Clinic of UFU and municipal health units to perform obstetric ultrasonography. The inclusion criteria of study group were pregnant women with tobacco use for more than two years, with no known disease and using no medicines. The following criteria were met for inclusion in the study: single pregnancy, Gestational Age (GA) of 20 to 40 weeks, as defined by the embryonic and fetal cephalocaudal length in the 1st trimester of pregnancy, normal fetal anatomy during obstetric ultrasound examinations performed up to inclusion in the study; absence of placental abnormalities, such as placenta previa, circumvallate placenta with suspected acretism or any type of tumor; absence of changes in the umbilical cord, such as changed number of vessels, nodes, tumors or velamentous insertion into the placenta; absence of maternal diseases or conditions associated with changes in the fetal development, such as preeclampsia, diabetes or use of illegal drugs. The exclusion criteria was pregnant women who delivery in another Hospital or that stopped the prenatal at the Institution cited above. Five patients were excluded from the study.

To compare the variables between the groups, exposed and not exposed to tobacco, patients were divided into 5 subgroups according to the GA: 20 to 23 weeks + 6 days; 24 to 27 weeks + 6 days; 28 to 31 weeks + 6 days; 32 to 35 weeks + 6 days and>36 weeks.

Doppler ultrasound

All ultrasound examinations were performed by two experienced operators who used the Sonace 8000 equipment with convex transducer 2-6 MHz (Medison, South Korea). The fetal anatomy, the amount of amniotic fluid, and the characteristics and position of the placenta were evaluated in ultrasonography. In addition, the basic fetal biometry (biparietal diameter, head circumference, abdominal circumference and femur length) and the Doppler Velocimetry of the Uterine (UtA), Umbilical (UmA) and fetal Middle Cerebral (MCA) Arteries.

The evaluation was carried out with electronic convex Doppler transducer (3-5 MHz), 2-Hz PRF, 100-Hz filter and sample volume of 1.5 to 3 mm, depending on the analyzed vessel, with an angle less than 20 degrees. At least five waves of uniform flow velocities were obtained for the calculation of Resistance Index (RI) and Pulsatility Index (PI), which were made automatically by the instrument. The patients remained in semi-Fowler position during the examination.

Evaluations of the UmA and MCA were performed during fetal complete rest (including absence of breathing movements). The Doppler velocimetryof the UmA was made in manually. In the evaluation of the MCA, the sample volume was positioned in the proximal third of the vessel. For Doppler velocimetry of the UmA, the Doppler window was positioned up to two cm above the crossing of this vase with internal iliac arteries. The average of the RI and PI values obtained in both umbilical arteries were used for analysis [14].

Maternal and perinatal variables evaluated in this study were the maternal age at study entry and parity. The two groups were matched for gestational age. The birth weight of 75 newborns of smoking mothers was analyzed as well as the median gestational age at which the birth occurred.

Evaluation of the degree of nicotine dependence

Each patient programmed for ultrasound examination was submitted to the Fagerströmtest for Nicotine Dependence (FTND), which can be accepted as a useful measure of chronic ingestion of nicotine [15]. The FTND was presented by Fagerström, Heatherton and Kozlowski [16] and shows credibility in reports as a low-cost approach to obtain accurate information about the smoking behavior between men and women [17]. This instrument consists of a questionnaire with six questions with scores 0-2 and 0-3, and the degree of nicotine dependence evaluated on an increasing scale with the following values: 0-2, too low; 3-4, low; 5, moderate; 6-7, high; and 8-10, very high dependence. The FTND was translated and validated for the use in Brazil [18]. For teaching purposes, the patients were divided into two major subgroups: one with women with very low, low and moderate degree of dependence, and another with women presenting high and very high degree of dependence.

At this point, one sample of exhaled Carbon Monoxide (COex) was also collected using a portable breath carbon monoxide monitor (piCO+Smokerlyzer®, Bedfont Scientific Ltd, England).The exhaled CO is the most widely used biomarker for the diagnosis of smoking due to its reliability, simplicity and low cost [19]. The patients were instructed to take a deep breath, hold your breath for 20 sec and then exhale slowly through a nozzle. The estimated values of COex are as follows: up to 10 ppm, light smoker; 11-15 ppm, moderate smoker; over 16 ppm, heavy smoker.

Statistical analysis

The minimum sample size was calculated using the G* Power software [20,21], including the following parameters: effect size, f = 0.20; significance level, $\alpha = 0.05$; test power, $\beta = 0.95$; six dependent variables; 10 subgroups. The 10 subgroups were composed of two categorical variables, that is, a combination of experimental conditions (control and experimental groups) and gestational ages, as described above. The calculation showed that the minimum sample size for this study would be 100 participants, which were divided by the 10 subgroups to identify the minimum sample size of each gestational age in each experimental condition. This procedure was adopted to prevent a confounding variable for gestational age.

A multivariate General Linear Model (GLM) with re sampling was applied to generate two different models. The first model was constructed to assess the main effect of experimental conditions. The second model, considering only the experimental group (smokers),

Table 1: Distribution of pregnant women for gestational age ranges in each experimental group.

Group	Nº and % of patients	Gestational age range (weeks + days)					Total
		20-23 + 6	24-27 + 6	28-31+ 6	32-35 + 6	36-41	
Smokers	n	25	16	21	16	20	98
	%	25.5	16.3	21.4	16.3	20.4	
Non-smokers	n	24	13	23	22	20	102
	%	23.5	12.7	22.5	21.6	19.6	

Table 2: Test of the main effect between variables of the maternal-fetal Hemodysnamic profile of pregnant smokers and non-smokers.

Variables	Smokers		Non-smokers		p value
	Mean	95% CI	Mean	95% CI	
UtA PI	0.9	0.06	0.84	0.06	0.215
UtA RI	0.58	0.02	0.53	0.02	0.000*
UmA PI	1.16	0.06	1.06	0.06	0.032*
UmARI	0.68	0.02	0.66	0.02	0.121
MCA PI	1.95	0.08	1.85	0.08	0.083
MCA RI	0.85	0.02	0.83	0.02	0.275

UtA: uterine artery; UmA: umbilical artery; MCA: middle cerebral artery; PI: Pulsatility index; RI: Resistance index; 95% CI: 95% confidence intervals.*statistically significant ($p < 0.05$).

tested the main effect of the categories of the Fagerström and Coex tests, in addition to the effect of interaction between these measures. In both models, the dependent variables were PI and RI of the UtA, UmA and MCA. For all analyzes, the significance level of 5%, bootstrap re sampling of 1000 samples and 95% confidence intervals were adopted.

Results

Among the 98 pregnant smokers the birth weight of newborns could be assessed in 75 cases, with an average birth weight of 2931 ± 546 g and median birth age of 39 weeks, ranging between 32 and 41 weeks, with most births in fetuses to term. Table 1 shows the pairing of the number of pregnant women, study and control groups in different intervals of gestational age.

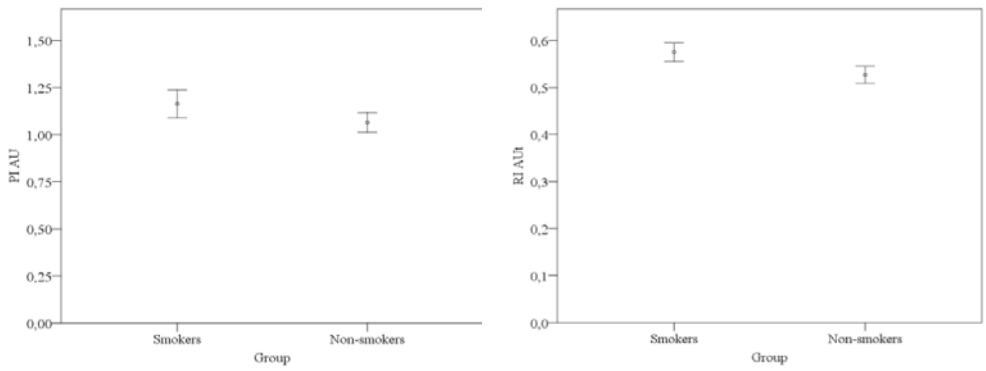
When the mean Doppler indices were compared between the two groups through the univariate test, the uterine artery RI and the umbilical artery PI showed significant effects ($p < 0.001$ and $p = 0.032$, respectively), with both parameters more elevated in the group of smokers (Table 2). These results demonstrated vasoconstriction signals with increased impedance in the uterine artery of study group. Analysis between other Doppler variables demonstrated no significant difference ($p < 0.083$) (Figure 1).

Regarding the degree of nicotine dependence, the mean COex level was 13 ppm (SD = 8.12), and 72.5% of patients were classified as light smokers whereas 27.5% of patients were included in the group of frequent, addicted and heavily addicted smokers (> 15 ppm).

The FTDN identified that 57.5% of patients had low or very low to medium degree of dependence (score < 5) and 42.5% of patients were considered as high and very high nicotine dependence (score > 5).There was a difference between the percentages of patients in nicotine dependence groups when comparing the Fagerström and Coex tests in the group of pregnant smokers. The mean and standard deviation of the number of cigarettes smoked per day was 14.5 ± 8 units. Table 3 shows the effect of the Fagerström and COex tests in the group of pregnant smokers who had a significant difference for each factor when analyzed separately, and that these effects showed no interaction between them.

When the nicotine dependence was analysed by the Fagerström test within the subgroups, low to moderate dependence and high to very high dependence, smoking showed positive effect in PI and RI of the MCA, with significant reduction of these indexes in the group of pregnant smokers, revealing vasodilation signals in the MCA (Table 4) (Figure 2).

When the group of light smokers was compared with the moderate smokers group, the Coex factor showed significant difference for



(A) (B)

Figure 1: Pulsatility index (PI) of the umbilical artery (A) and Resistance index (RI) of the uterine artery (B) in pregnant smokers and non-smokers. Data are expressed in mean and 95% confidence intervals.

Table 3: Statistical test for the multivariate general linear model presenting the main effect and interaction of the independent variables.

Variables	Multivariatemodel		
	F	df	p value
Fargerström	2.34	6.87	0.038*
COex	2.17	12.176	0.015*
Interaction	1.51	12.176	0.124

*Statistically significant ($p < 0.05$).

Table 4: Test of the main effect of Fagerström between variables of the maternal and fetal hemodynamics of pregnant smokers.

Variables	Verylowtomoderate		High tovery high		p value
	Mean	95% CI	Mean	95% CI	
UtA PI	0.94	0.09	0.86	0.09	0.241
UtA RI	0.59	0.03	0.57	0.03	0.209
UmA PI	1.26	0.11	1.14	0.11	0.143
UmA RI	0.69	0.03	0.69	0.03	0.773
MCA PI	2.04	0.14	1.84	0.14	0.045*
MCA RI	0.87	0.02	0.83	0.02	0.007*

UtA: uterine artery; UmA: umbilical artery; MCA: middle cerebral artery; PI: Pulsatility index; RI: Resistance index; 95% CI: 95% confidence intervals. *Statistically significant ($p < 0.05$).

the UtAPI, showing vasoconstriction in this artery (Table 5). When comparing light smokers with heavy smokers, there was a significant increase in the MCARI, showing vasoconstriction in the cerebral area, differing from the previous result (Figure 3).

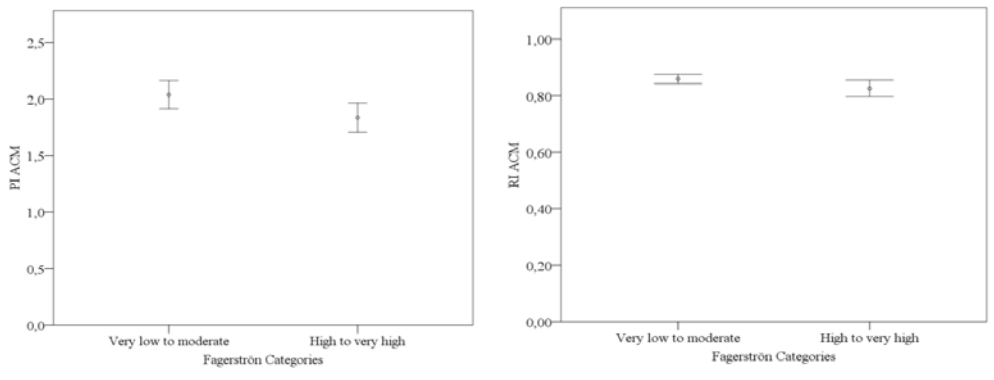
Discussion

Several studies have described changes in maternal and fetal circulation associated with chronic tobacco consumption [8,11,22-29] but most of these studies do not standardized the amount of cigarettes used by pregnant women, the degree of nicotine dependence, and the relationship of this dependence by gestational age with pulsatility and resistance indexes of the uterine, umbilical and middle cerebral arteries. The most commonly used indexes in Doppler studies are RI, PI and A/Bratio, which have been widely accepted as relevant parameters in the analysis of blood flow in obstetrics [27]. In the present study, the two Doppler indexes (PI and RI) were used to analyze the maternal and fetal hemodynamics, thus becoming more reliable the interpretation of vascular impedance in the evaluated vessels. The positive point of this study was the pairing of patients for gestational age, based on the fact that artery Doppler indexes havemodulation and modification during pregnancy. There authors did not find in the literature studies analyzing the both indexes, pulsatility and resistance, of three arterial vessels (UtA, UmA and MCA) as described in our study, which brings more information on the behavior of maternal-placental-fetal bed arteries caused by cigarette smoking.

The main findings of this study were signs of increased impedance in placental and maternal vessels; the PI and RI values reflect resistance to the distal flow of the artery under investigation, and an increase in these values corresponds to increased impedance distal to blood flow, indicating vasoconstriction and hypoperfusion [30]. Increased impedance of placental and uterine vessels may reflect an abnormal trophoblast and vascular remodeling, along with poor placental adaptation and imbalance between vascular pro-angiogenic and anti-angiogenic factors, with a predominance of the latter, similar to those observed in preeclampsia [31]. The exposure to cigarette appears to induce changes in the vascular flow of pregnant smokers, leading to an abnormal arterial blood reactivity that can oppose to the vasodilation events typically observed in preeclampsia [32]. Despite this event, placental changes caused by smoking are very similar to those seen in placental abnormalities in preeclampsia [10], such as thickening of trophoblastic basement membrane, swelling and irregularity of endothelial cells, with hypovascularization and swelling of fetal villi and arterioles [33,34].

Uterine artery Doppler

An increase of the uterine artery RI was observed in pregnant smokers between 20 and 40 weeks of pregnancy. This finding was similar to those reported by Machado etal. [12] And Pinto and Botelho [22] in 2nd trimester pregnant women, whereas Kho et al. [23] found increased uterine artery RI in pregnant women with 20 weeks of pregnancy. However, Albuquerque et al. [8] and Yildiz et al. [11] observed no change in uterine artery RI in 3rd trimester pregnant smokers. On the other hand, Castro et al. [24] observed a decrease in the uterine artery RI in pregnant smokers. It is noteworthy that in this latter study, the Doppler exam was performed during acute



(A) (B)

Figure 2: Pulsatility index (PI) (A) and Resistance index (RI) (B) of the middle cerebral artery for Fagerström categories. Data are expressed in mean and 95% confidence intervals.

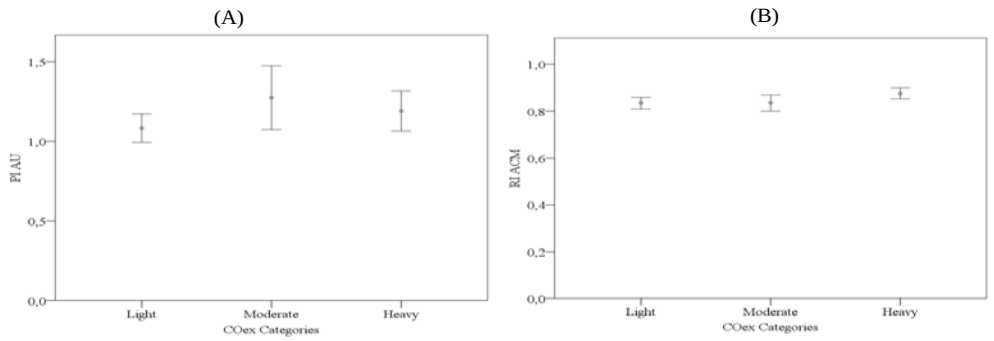


Figure 3: Pulsatility index (PI) of the umbilical artery (A) and Resistance index (RI) of the middle cerebral artery (B) for COex categories. Data are expressed in mean and 95% confidence intervals.

Table 5: Test of the main effect of COex between variables of the maternal-fetal hemodynamics of pregnant smokers.

Variables	Light		Moderate		Heavy		p value		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Light *vs* Moderate	Light *vs* Heavy	Moderate *vs* Heavy
UtA PI	0.88	0.1	0.83	0.12	1	0.11	0.999	0.347	0.137
UtA RI	0.56	0.03	0.57	0.04	0.61	0.04	0.999	0.113	0.458
UmA PI	1.08	0.12	1.33	0.15	1.19	0.14	0.035*	0.744	0.504
UmA RI	0.66	0.04	0.7	0.04	0.71	0.04	0.577	0.199	0.999
MCA PI	1.89	0.15	1.85	0.18	2.06	0.17	0.999	0.406	0.291
MCA RI	0.82	0.03	0.85	0.03	0.88	0.03	0.761	0.024*	0.504

UtA: uterine artery; UmA: umbilical artery; MCA: middle cerebral artery; PI: Pulsatility index; RI: Resistance index; 95% CI: 95% confidence intervals. *Statistically significant ($p < 0.05$).

exposure to tobacco. This finding of reduced uterine artery RI reflects a temporary vasodilation in the studied site and was also described by Castro et al. [24], Tulzer et al. [35], and Paes et al. [36] that analyzed the reactivity of other arteries facing to cigarette consumption.

Our results were similar to those in the literature with regards to the increase of uterine artery RI in pregnant smokers without stratification by gestational age groups [12,22,23]. Machado et al. [12] found data similar to ours with increased uterine artery RI in 30 pregnant smokers in the 3rd trimester of pregnancy; Kho et al. [23] examined 248 pregnant smokers and observed increased uterine artery RI from 20 weeks onwards, whereas Pinto and Botelho [22] found the same effect from 36 weeks onwards. On the other hand, Saraivaet al. [26] examined 34 pregnant smokers who showed no change in uterine artery RI. Also, Albuquerque et al. [8] and Yildiz et al. [11] studied 3rd trimester pregnant women and observed no changes of uterine artery RI. In contrast, Castro et al. [24] observed decrease in uterine artery RI in a study conducted with acute smoking (smoking patient to perform ultrasonography/USG exam), which would lead to a temporary vasodilation of vessels, as already described by other authors [36]. It is noteworthy that this is the only study that evaluated the maternal and fetal arteries in acute cigarette consumption stage [36].

Umbilical artery Doppler

The umbilical artery PI had a significant increase in pregnant smokers in relation to control group, findings that were consistent with those of Geelhoed et al. [25] and Pinto and Botelho [22], who were the only authors to measure the umbilical artery PI.

The umbilical artery RI had no change in pregnant smokers during the study period. An increase of the umbilical artery RI has been described by Kho et al. [23], Machado et al. [12] and Saraiva et al. [26] in different gestational ages. Regarding the umbilical artery RI in pregnant smokers, the literature is controversial. Some authors have identified increased umbilical artery RI [12,23,26]. However, when the analysis is done by gestational age, Saraiva et al. [26] detected increased umbilical artery RI only in pregnant women with 32 weeks. Kho et al. [23] also observed increased umbilical artery RIat 20-week pregnancy, which disagrees with the findings of Machado et al. [12] who demonstrated increased umbilical artery RI in 3rd trimester pregnant women. Therefore, it is evident that there is no full agreement between data reported in the literature, demonstrating the need for further studies on the subject.

Middle cerebral artery Doppler

Analysis of middle cerebral artery Doppler showed a decrease in the PI and RI indexes related to the degree of nicotine dependence; pregnant smokers with high and very high dependence had significant differences for the PI and RI values, demonstrating that the amount of used cigarettes and dependence degree was associated with Doppler changes, resulting in fetal cerebral vasodilation. Kho et al. [23] and Machado et al. [12] showed a reduced middle cerebral artery RI, agreeing with the data found in our study. In addition, Machado et al. [12] related the worsening of Doppler indexes with increased urine cotinine marker, that is, higher tobacco dependence; the greater the middle cerebral artery RI changes [5].

Analysis of middle cerebral artery PI was only performed by Geelhoed et al. [25] who demonstrated an increased PI, contrasting to the results obtained from our study and showing that there is

controversy, with decreased or increased vascular resistance.

When the results of exhaled carbon monoxide were analyzed, there was a significant effect only in the comparison between light and moderate subgroups, which showed an increase in the umbilical artery PI. Also, when the light and heavy subgroups were compared, an increase in the middle cerebral artery RI was found, indicating vasoconstriction in fetal vascular site, but not dependent on the amount of exhaled carbon monoxide. These findings were not coinciding with previous data and may have happened type 2 error due to the differences in sample group or changes linked to cigarette use time. COex measures are linked to cigarette use time, a factor that can change the Coex results, since the acute cigarette use causes an acute vasodilation, as demonstrated in the study of Castro et al. [24] and Paes et al. [36].

The vasoconstriction in the cerebral vascular bed, detected only in Coex subgroups, can also be justified by the acute cigarette use, since it is considered a marker of acute tobacco use. Another likely explanation is the loss of modulation of the fetal adrenal medulla due to neurotoxicity of nicotine that interacts with cholinergic and nicotinic receptors in early and inadequate phase during pregnancy [37]. We hypothesize that the fetus may exhibit an adaptation to the increased impedance of the maternal-placental system that causes a reduction in the blood flow velocity sent to the unborn child.

Smoking is responsible for changes in fetal growth rate, causing higher incidence of Intrauterine Growth Retardation (IUGR). These changes are due to modifications in placental mass and its vascular network. Furthermore, there are metabolic changes that may interfere with fetal development. The Doppler analysis of maternal and fetal arteries can quantify the pattern of perfusion in the assessed area. One of the limitations of Doppler ultrasound is the unfeasibility of performing a direct assessment of endothelial injury or vascular resistance that could lead to clinical events caused by smoking. However, as the Doppler mode can be used to measure quantitatively blood flow velocity, one can assume that the increases of the impedance indexes represent functional changes in vascular perfusion and vasospasm.

Histomorphologic and histomorphometric studies of placentas from smoking mothers have shown minor parenchymal tissue mainly by reducing the intervillous space and peripheral villi, with decreased volume and area of capillary exchange [27]. These changes in placental anatomy were considered responsible for the reduced fetal growth in pregnancy of smoking mothers [27,33]. Rizzo et al. [28] evaluated 80 pregnant smokers by means of the placental Doppler study and found reduced placental flow index and vascularization rate, but no significant difference in volume, between smokers and non-smokers. These two data show that there is a disparity between the two tests performed and that there is no agreement between the COex and Fageström tests probably because the COex is dependent on the time that the patient has smoked prior to testing. However, these results agree with the literature that shows correlation between these two methods ranging from weak to moderate [38].

The limitation of this study is that Doppler ultrasound is a method that estimates the flow velocity in the assessed vessel and does not allow the direct assessment of endothelial injury or blood flow that could lead to clinical events caused by smoking. The present study extends the data on the arterial hemodynamic knowledge in the group of chronic pregnant smokers. Since there is no consensus in the literature on vascular modulation caused by numerous chemical components of cigarette, new studies should be focused to the best knowledge of the vascular changes facing to the tobacco. Control of tobacco consumption and education of pregnant women about the importance of not consuming cigarettes during pregnancy should be emphasized.

Conclusion

Chronic smoking interfered negatively on maternal and fetal vascular hemodynamics, as demonstrated by increased impedance in the maternal uterine and fetal umbilical arteries. Moreover, the greatest exposure to tobacco caused vasodilation effect in the fetal middle cerebral artery, demonstrating that higher tobacco dependence, the greater the maternal and fetal hemodynamic changes.

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