



Effects of tobacco smoking on the maternal foetal circulation in quantitative terms

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Abstract

Background: Maternal exposure to tobacco smoke in pregnancy is a key modifiable risk factor for baby death and disability. Smoking is linked to preterm birth (birth before 37 weeks' gestation), stillbirth, and neonatal mortality, as well as to miscarriage, fetal growth restriction, and infant morbidity.

Methodology: Using a prospective cohort design study, 30 pregnant smokers and 34 pregnant non-smokers were recruited between March 2022 and March 2023 from Institute of Dental Sciences, Bhubaneswar, SOA University.

Results: Thirty pregnant smokers and 34 pregnant non-smokers women were included in this study analysis. No significant difference was observed between the two groups in regards to age, amniotic fluid index, cultural and social status, number of prior miscarriages or placenta grade. Smokers had a greater number of pregnancies and births than non-smokers, with values of 3.0 [95%CI 3.0- 11.0] vs. 2.0 [95%CI 1.0-5.0] $p = 0,04$; 1.5 [95% CI 0.0- 7.0] vs. 1.0 [0.0 - 4.0] $p = 0,04$ respectively.

Conclusion: It was discovered that placental blood flow had a dose-dependent effect, and resistance indices rose as tobacco smoking exposure increased. In addition, we discovered that readings of COex and urine cotinine increased in correlation with a drop in foetal birth weight.

Keywords: maternal exposure, tobacco smoke, pregnancy, foetal circulation

Introduction

Maternal exposure to tobacco smoke in pregnancy is a key modifiable risk factor for baby death and disability. Smoking is linked to preterm birth (birth before 37 weeks' gestation), stillbirth, and neonatal mortality, as well as to miscarriage, fetal growth restriction, and infant morbidity^[1]. The worldwide prevalence of maternal smoking in pregnancy is 2%, with Europe having the highest prevalence at 8%^[2]. Although rates of maternal smoking in pregnancy are decreasing in many high-income countries^[2], this decline is slower among women of lower socioeconomic status, contributing to health inequalities^[3]. In certain low- and middle-income countries, maternal smoking rates are static or rising^[4, 5, 6].

Smoking during pregnancy can lead to reduce the oxygen supply to you and your developing child, increase the heart rate of your unborn child, raise the risk of stillbirth and miscarriage, the likelihood that your child will be born preterm or with low birth weight, increases the likelihood that your kid will experience breathing or lung issues, birth abnormalities, sudden infant death syndrome (SIDS), and more increase the likelihood of placental issues including placental abruption, which occurs when the placenta prematurely separates from the uterine wall, or placenta previa, which occurs when the placenta is in a position where it could burst during contractions^[5]. The more cigarettes you smoke per day, the greater your baby's chances of developing these and other health problems. There is no "safe" level of smoking while pregnant.

From 3% and 10% of patients claim they no longer smoke when they actually still do; this rate varies from patient to

patient. Objective tests are required to verify abstinence during smoking cessation therapy, and biochemical markers have been implemented in clinical practice^[7, 8]. The most often employed marker is the carbon monoxide content in exhaled air (COex)^[8]. It is reasonably priced and measured using a non-invasive method that yields fast and accurate findings^[9]. The cotinine concentrations in saliva, plasma, and urine are regarded as the gold standard for objective evidence, but measurements are difficult, expensive, and not appropriate for clinical use. Doppler velocimetry is a tool employed in obstetrics to gauge blood flow in uterine arteries and characterise the flow of blood from the mother to the foetus. The flow in the foetal brain can be seen when the blood flow in the middle cerebral artery is examined. There are databases containing values that have been established and are regarded as normal^[10]. The methodology has already been standardized and we have followed such guidelines in this study.

The present investigation looked for a correlation between smoking behaviours as determined by objective methods (cotinine content and COex) and resistance indices of the uterine, umbilical, and middle cerebral foetal arteries using Doppler velocimetric ultrasonographic evaluation. Smoking's effects on foetal development and birth weight were also investigated. Our primary objective was to assess whether there is a proportional change in vascular resistance as quantitative exposure to smoking during pregnancy increases. The hypothesis is that smoking reduces the maternal-fetal blood flow related to increased tobacco smoking and effects fetal growth.

Methodology

Using a prospective cohort design study, 30 pregnant smokers and 34 pregnant non-smokers were recruited between March 2022 and March 2023 from Institute of Dental Sciences, Bhubaneswar, SOA University. The inclusion criteria were: pregnant women between 18 and 35 years of age, in the third trimester of gestation (dated in the first trimester), regularly receiving prenatal care, had no gestational complaints and agreed to participate in the study by signing the consent form. The exclusion criteria were: ultrasonographic diagnosis of fetal malformations, clinical situations related to the pregnancy or any other disease that could interfere with fetal growth, illiteracy, psychiatric disorders, alcoholism, former smokers and the possibility to move to another city and to lose contact during the study. Patients who discontinued prenatal care and those that stopped or started smoking during their pregnancy were also excluded. No patient was excluded after inclusion in the study because no patient discontinued the follow up during the prenatal period.

Smoking was determined according to the report of using cigarettes from the periconceptional period to the day of the interview. The periconceptional period was defined as the period starting one month before the date of the last menstruation. To be considered a non-smoker, patients must have stated that they had never smoked, especially during their pregnancy, and reports were confirmed by a biochemical marker.

All patients were submitted to same tests to confirm their smoking status: concentration of carbon monoxide in the exhaled air and concentration of urinary cotinine. We found no discrepancy, that is, no patient who said was a non-smoker was detected as a smoker.

At the initial medical visit, the objectives of the study were explained and the consent form signature was obtained. Next, a standardized questionnaire was completed, pregnancy and smoking data were collected and the COex measurement was performed. A urine sample was also collected to measure cotinine levels, and an ultrasonography examination was performed. Smoking between the tests was not permitted. After the birth, patient was contacted to collect data about the newborn one month after delivery. Doppler velocimetry exam with colored mapping of the uterine arteries, umbilical arteries and fetal middle cerebral arteries was performed with an Ultrasonix machine (Sonix Model, Version 2.5, Ultrasonix Medical Corporation, Canada), and the resistance indices (RI) were recorded. We also recorded the amniotic fluid index, the placental grade, fetal biometry and the estimated fetal weight placed on a percentile curve for the gestational age to adjust for possible bias.

To decrease possible bias at ultrasonography due to a large variability of Doppler values, three measurements were taken, and the mean was recorded. COex was measured by a MicroCO Meter (MicroCO-Micro Medical Ltd., Rochester, Kent, UK) using an elec-trochemical sensor. Patients were instructed to breathe deeply, hold their breath for 20 seconds and then to exhale slowly and completely through a mouthpiece. Smokers had COex measured no more than two hours after their last smoked cigarette^[9].

For measurement of the cotinine concentration in the urine, a previously-validated high performance liquid chromatography (HPLC) method was used^[16]. Whereas the ultrasonography examinations and the exhaled CO measurements were performed by the same author (JBDM), the cotinine measurements were performed at the PUCRS Toxicology Institute by a technician blind to patient study

group. Mean \pm SD were used to describe the symmetric, continuous data and the median and range was used for asymmetric data. A percentile calculation was used for categorical data. Student's t test and ANOVA were used to compare means. Adjustments for potential confounding effects were made by covariance analysis (ANCOVA) and multiple linear regression. Possible confounding factors included in the analysis for adjustment were patient age, gestational age, degree of placenta, amniotic fluid index, number of pregnancies.

The assigned level of significance was 0.05. The data were processed by the Statistical Package for the Social Sciences (SPSS) Version 21.0. Patients were divided into four groups according to the levels of COex (Group 1: 0 ppm; Group 2: 1-4 ppm; Group 3: 5-9 ppm; Group 4: \geq 10 ppm) in order to analyze possible changes in the resistance indices. The same analyses were also performed according to the levels of urinary cotinine (Group 1: 0 ng/mL; Group 2: <50 ng/mL; Group 3: 50-500 ng/mL; Group 4 >500 ng/mL).

Results

Thirty pregnant smokers and 34 pregnant non-smokers women were included in this study analysis. No significant difference was observed between the two groups in regards to age, amniotic fluid index, cultural and social status, number of prior miscarriages or placenta grade. Smokers had a greater number of pregnancies and births than non-smokers, with values of 3.0 [95%CI 3.0- 11.0] vs. 2.0 [95%CI 1.0-5.0] $p = 0,04$; 1.5 [95% CI 0.0- 7.0] vs. 1.0 [0.0 - 4.0] $p = 0,04$ respectively (Table 1).

When the entire group of non smokers was studied, the RI in both uterine arteries (right uterine 37.3 ± 20.0 vs. 58.0 ± 23.0 $p = 0.0010$; left uterine 38.9 ± 17.6 vs. 56.1 ± 19.6 $p = 0.001$) and the umbilical artery (43.0 ± 19.0 vs. 65.0 ± 15.0 $p = 0.001$) were higher compared to smokers. The RI in the middle cerebral artery was lower (45.00 ± 15.00 vs. 36.3 ± 21.0 $p = 0.450$), but, the difference was not statistically significant (Table 2). When the participants were grouped according to COex levels (Group 1 to Group 4), progressively higher RI values were observed for the right uterine (Group 1: 36.2 ± 21.8 , Group 2: 46.9 ± 20.3 , Group 3: 44.4 ± 28.9 Group 4: 66.5 ± 17.5 , $p < 0.001$) and left uterine arteries (Group 1: 39.5 ± 18.9 , Group 2: 40.5 ± 16.8 , Group 3: 52.8 ± 19.5 , Group 4: 66.1 ± 16.7 , $p < 0.001$) and the umbilical artery (Group 1: 44.5 ± 21.3 , Group 2: 49.1 ± 17.9 , Group 3: 61.1 ± 13.1 , Group 4: 71.1 ± 16.2 , $p < 0.001$) as the mean CO-ex increased. In addition, we observed lower RI values of the middle cerebral artery (Group 1: 46.4 ± 14.3 , Group 2: 42.1 ± 17.1 , Group 3: 47.2 ± 19.5 , Group 4: 27.7 ± 22.2 , $p < 0.001$) as CO-ex increased (Table 3).

Table 1: Characteristics of the sample according to smoking habits

Characteristics	Non smokers n = 34	Smokers n = 30	P
Age	27.6 \pm 6.1	27.3 \pm 5.2	0.82
Pregnancies	2.0 [1 a 5]	3.0 [3 a 11]	0.04
Parities	1.0 [0 a 4]	[0 a 7] 0.0	0.04
Abortions	0.0 [0 a 3]	0.0 [0 a 3]	0.62
AFI	14.0 \pm 2.0	13.3 \pm 2.8	0.21
Placenta grade	1 (56%) [0 a 2]	1(70%) [0 a 3]	0.31

Data are presented as mean \pm SD or median [minimum and maximum]. AFI: amniotic fluid index. Age (years), pregnancies, abortions and parities (number), Amniotic Fluid Index(cm), Placenta grade percent type I (As classification Granumm)^[17]. P: statistical significance

Table 2: Percentile of RI among pregnant women according to smoking habits

RI Percentile	Non smokers n = 34	Smokers n = 30	P
RUA	37.3 ± 20.0	58.0 ± 23.0	0.001
UA	43.0 ± 19.0	65.0 ± 15.0	0.001
MCA	45.0 ± 15.0	36.3 ± 21.0	0.450

Data are presented as mean ± SD. P: statistical significance. RUA: right uterine artery, LUA: left uterine artery,UA:

umbilical artery, MCA: middle cerebral artery. RI: vascular resistance index.

Table 3: Percentile of RI and of birth weight between four groups according to carbon monoxide exhaled concentration

RI Percentile	COex 0 ppn = 21	COex 1 - 4 ppmm =21	COex 5 - 9 ppmm = 9	COex ≥ 10 ppmm = 13	P[1]	P[2]
RUA	36.2 ± 21.8 [10 a 90]	46.9 ± 20.3 [10 a 75]	44.4 ± 28.9 [10 a 90]	66.5 ± 17.5 [25 a 90]	0.003	<0.001
LUA	39.3 ± 18.7 [25 a 75]	40.5 ± 16.8 [25 a 75]	52.8 ± 19.5 [25 a 75]	66.1 ± 16.7 [50 a 95]	0.001	<0.001
UA	44.5 ± 21.3 [10 a 75]	49.1 ± 17.9 [5 a 75]	61.1 ± 13.1 [50 a 75]	71.1 ± 16.2 [50 a 95]	0.001	<0.001
MCA	46.4 ± 14.3 [25 a 75]	42.1 ± 17.1 [5 a 75]	47.2 ± 19.5 [25 a 75]	27.7 ± 22.2 [5 a 75]	0.022	<0.001
Percentile of birth weight	49.05 ± 22.7 [10 a 90]	49.90 ± 25.8 [3 a 90]	41.2 ± 25.3 [3 a 75]	25.1 ± 16.6 [3 a 50]	0.017	<0.001

Data are represented as mean ± SD [minimum, maximum]. COex: concentration of carbon monoxide in the exhaled air, RI: vascular resistance index, RUA: right uterine artery, LUA: left uterine artery, UA: umbilical artery, MCA: middle cerebral artery. P: statistical significance, [1]: variance analysis - ANOVA - oneway, [2]: linear tendency obtained in regression model.

The resistance indices for the left uterine artery (p = 0.037) and the umbilical artery (p 0.001) also showed a statistically significant progressive rise when the rising urinary cotinine values in the four groups of smokers were examined. The

right uterine artery showed a similar tendency, however it was not statistically significant (p = 0.267; Table 4). The RI of the middle cerebral artery did nevertheless show a declining tendency that was correlated with an elevated level of urine cotinine. This result was statistically significant in the linear regression, however the significance was lost when the potential confounding factors mentioned above were taken into account. There was a significant decrease (p < 0.001) in the percentile of the fetal birth weight in relation to increased mother’s COex as well as increased urinary cotinine values (p = 0.007).

Table 4: Percentile of RI and of birth weight between four groups according to urinary cotinine levels

	Cotinine 0 ng/mL n = 30	Cotinine < 50 ng/mL n = 10	Cotinine 50 - 500 ng/mL n = 14	Cotinine >500 ng/mL n = 10	P ^[1]	P ^[2]
RI Percentile RUA	42.8 ± 22.8 [10 a 90]	40.0 ± 25.7 [10 a 90]	55.3 ± 23.5 [10 a 90]	22.9 ± 22.9 [25 a 75]	0.201	0.267
LUA	41.1 ± 20.8 [25 a 95]	42.5 ± 20.6 [25 a 75]	58.9 ± 15.8 [25 a 75]	52.5 ± 18.4 [25 a 75]	0.033	0.037
UA	46.8 ± 20.1 [5 a 75]	46.0 ± 21.0 [10 a 75]	63.5 ± 14.6 [50 a 90]	68.5 ± 17.3 [50 a 95]	0.003	0.001
MCA	45.3 ± 15.7 [5 a 75]	42.5 ± 16.8 [25 a 75]	36.8 ± 21.8 [5 a 75]	34.5 ± 23.8 [5 a 75]	0.321	0.14
Percentile of birth weight	45.6 ± 21.5 [3 a 90]	62.4 ± 24.4 [25 a 90]	36.6 ± 24.0 [3 a 90]	27.1 ± 22.8 [3 a 75]	0.006	0.007

Data are represented as mean ± SD [minimum, maximum]. RI: vascular resistance index, RUA: right uterine artery, LUA: left uterine artery, UA: umbilical artery, MCA: middle cerebral artery. P: statistical significance, [1]: variance analysis - ANOVA - oneway, [2]: adjusted for age, number of pregnancies and AFI in ANCOVA model.

Discussion

This study showed that the resistance indices of the placental vascular bed tended to rise with a quantitative increase in tobacco smoking exposure measured by objective methods in a dose-dependent effect. As far as we know, this is the first report showing such dose-effect through objective measurements of tobacco smoking exposure.

Smoking women were divided into groups based on their COex concentrations, which were then examined for any correlations with rising resistance indices. In fact, a rise in COex levels was correlated with a rise in the RI of the uterine and umbilical arteries and a fall in the middle cerebral artery resistance. Even after correcting for potential confounding variables, all of these outcomes were statistically significant. Significant rises were also noted in the left uterine and umbilical arteries when the groups were analysed in accordance with increasing amounts of urine

cotinine, another marker of tobacco exposure investigated in this study. There was a trend favouring an elevated RI in the right uterine artery, although it was not statistically significant. Although not statistically significant, the middle cerebral artery revealed a tendency towards a decreasing resistance in relation to the rising cotinine readings.

Smoking throughout pregnancy is the main avoidable cause of restricted intrauterine growth and small size for gestational age, and it is known to affect or even decide low birth weight [11]. Our results are consistent with earlier studies, which have shown that a reduction in the volume of blood and oxygen delivered to the foetus led to smaller neonatal weights. This study contributes to those reports showing that it is probably a dose-dependent effect. We found that decreased birth weights correlated with increase in tobacco smoking exposure, confirmed by both exposure methods, urinary cotinine and COex.

Amongst the pregnant smokers, a pattern of maternal-fetal perfusion with signs of chronic hypoxia was seen. These results, which showed a rise in the umbilical artery's RI and a fall in the middle cerebral artery's RI, were comparable to the centralization phenomena. Thus, we conclude that the foetus of a smoker adjusts for the decreased placental blood flow and potential tissue hypoxia with a propensity towards

blood flow centralization^[12]. The aortic and carotid chemoreceptors are presumably triggered when the partial pressure of O₂ declines and that of CO₂ climbs above a specific threshold, despite the fact that the intricacies of these circulatory modifications and their mechanisms are not fully understood. This mechanism controls the central vasodilatory response to ensure that the foetal brain receives enough oxygen^[13].

Prior studies^[12, 14, 15] already studied the repercussions of smoking on maternal-fetal flow, but all have used patients' self-report to quantify tobacco smoking exposure. As mentioned previously, data reported by smoking patients are not always reliable, what might justify the heterogeneity of the results found in those studies^[16].

Albuquerque and colleagues^[12] compared 74 pregnant smokers with 69 controls, classifying them according to smoking status as informed by the patients. They concluded that chronic maternal smoking was associated with the increasing resistance of the uterine, umbilical and fetal middle cerebral arteries. Other studies^[13, 14] evaluated the cigarette acute effects. Kimya *et al*^[17] studied 22 pregnant smokers and 21 non-smokers by measuring Pulsatility Index, Resistance Index and Sys-tole/Diastole of the uterine and umbilical before and after smoking a cigarette default. They found no significant change in the Doppler that could be attributed to the acute effect of cigarette smoking, but all indices were significantly higher in the smoking group compared with the control group both before and after cigarette smoking. They conclude that chronic smoking caused an increase in vascular resistance of the placenta and umbilical cord.

One of the strengths of this study is that the smoking status of the patients were confirmed by biochemical quantitative measurements (concentration of exhaled CO and of cotinine in a urine sample), showing a possible dose-effect of tobacco smoking exposure on maternal-fetal blood perfusion.

Our results may be used as a tool for helping pregnant smokers to stop or at least to decrease their tobacco exposure by emphasizing that the risks to the fetus occur in a dose-dependent manner. Our objective data demonstrate that a higher smoking level results in greater hemodynamic effects on the fetus. These effects culminate in growth restriction that may have multiple effects throughout the life of children.

Conclusion

Doppler velocimetry was used in the present investigation to compare pregnant women who smoke to pregnant women who do not smoke and find differences in resistance indices. It was discovered that placental blood flow had a dose-dependent effect, and resistance indices rose as tobacco smoking exposure increased. In addition, we discovered that readings of CO_{ex} and urine cotinine increased in correlation with a drop in foetal birth weight.

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