

# Acute Effects of Maternal Smoking on Fetal-Placental-Maternal System Hemodynamics

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**Objective** - To study acute hemodynamic alterations in the fetal-placental maternal system immediately after maternal exposure to nicotine.

**Methods** - This is a noncontrolled experimental study involving 21 pregnant smoking women, randomly selected, with uncomplicated pregnancies and without risk factors for fetal heart disease. Patients underwent ultrasound and fetal echocardiography before and after smoking a cigarette. They were asked to abstain from smoking for 12 hours before the study. The mean nicotine content of the cigarettes used in the study was 0.5mg of nicotine and 6mg of carbon monoxide.

**Results** - The average number of cigarettes smoked per a day prior to the study was 9.67. Gestational age ranged between 18 and 36 weeks. The mean maternal heart rate was elevated ( $P < 0.001$ ) as was the mean fetal heart rate ( $P = 0.044$ ). Maternal systolic blood pressure ( $P = 0.004$ ) and diastolic blood pressure ( $P = 0.033$ ) were also elevated after smoking. A decrease occurred in the systolic/diastolic ratio in the right uterine artery ( $P = 0.014$ ) and in the left uterine artery ( $P = 0.039$ ). The other hemodynamic variables remained unchanged.

**Conclusion** - Cigarette smoking can cause changes in physiologic variables of fetal-placental circulation, but it does not change fetal cardiac function, in the dose of nicotine and its components used in this study. The decrease in systolic/diastolic ratio in the uterine arteries is probably related to a dose-dependent nicotine pattern.

**Key words:** smoking, fetal echocardiography, obstetric ultrasound

Nicotine is the most common drug used during pregnancy<sup>1</sup> and is associated with harmful effects, such as prematurity<sup>2-4</sup>, low birth weight<sup>5-8</sup>, placental changes<sup>9</sup>, and changes in the respiratory system and in the neurological development of the child<sup>10,11</sup> after birth.

Tobacco smoke contains several compounds; nicotine and carbon monoxide are the most significant<sup>1</sup>.

Nicotine reaches the fetus through the placenta and is concentrated in fetal blood at levels 15% greater than those of the mother<sup>1,12</sup>. It is also transferred to the maternal milk<sup>13</sup> with a milk-serum concentration of 2.9. It acts directly in the cardiovascular system by stimulating acetylcholine receptors located in the ganglia of the autonomous nervous system, adrenal medulla, and neuromuscular junctions, releasing catecholamine and other vasoactive substances<sup>14</sup>. Its main metabolite is cotinine that has a half-life of 15 to 20 hours and is a good marker for assessing individual exposure to tobacco<sup>15-17</sup>.

Anatomopathological studies of umbilical cords and placentas of newborn infants from mothers who smoke demonstrate that tobacco increases the release of vasoactive substances (F2-isoprostanes) and decreases release of vasodilator substances (prostacyclin and nitric oxide)<sup>18</sup>.

A study of 15 healthy pregnant woman with uncomplicated pregnancies<sup>19</sup> showed an elevation in maternal heart rate and diastolic blood pressure after smoking one cigarette containing 1.6mg of nicotine. No change occurred in the mean uterine systolic/diastolic ratio. Also no elevations occurred in the fetal heart rate or in the umbilical systolic/diastolic rate, suggesting that smoking causes an increase in placental vascular resistance, which may impair oxygen exchange across the placenta and, consequently, contribute to an increase in perinatal morbidity.

A research about the effects of nicotine and carbon monoxide<sup>20</sup> showed that the pulsatility index of the umbilical artery and fetal aorta decreased in the group that smoked 2 cigarettes, when compared with the group that smoked only 1 cigarette. This group also had an increase in maternal heart rate and blood pressure (systolic and diastolic),

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in fetal heart rate, and in blood flow in fetal aorta. Therefore, we have to take into account the decrease in peripheral vascular resistance associated with the a dose-dependent action of the cigarette compounds.

In a prospective study<sup>21</sup>, which compared pregnant smokers and nonsmokers not immediately after smoking, no difference occurred in the umbilical and uterine artery systolic/diastolic ratio among the groups. The authors concluded that the effects of smoking on placental vascular resistance are periodic and not continuous.

The study of fetal middle cerebral artery resistance indices of fetuses of smoking mothers as an indirect way of evaluating fetal hypoxia did not show changes when compared with those of pregnant women using transdermal nicotine<sup>22</sup>.

Conflicting results concerning acute effects of smoking on fetal and placental blood flow in humans are observed. No studies have been conducted to evaluate the effects of maternal smoking on fetal cardiac function, pulmonary artery flow, and ductus arteriosus.

Most reports deal with the chronic effects of smoking on fetal-placental-maternal unit circulation. This study tries to identify the acute effects of smoking on fetal-placental-maternal hemodynamics that may be related to the chronic effects described above.

## Methods

This was a noncontrolled experimental study involving a sample of 21 pregnant women with uncomplicated pregnancies, who were chronic smokers and did not have risk factors for fetal heart disease. Women were randomly selected.

Patients underwent obstetric ultrasound<sup>23</sup> and fetal echocardiography<sup>24</sup>, before and after smoking 1 cigarette, containing 0.5mg of nicotine and 6mg of carbon monoxide. The following variables were evaluated: maternal and fetal heart rate, maternal blood pressure, systolic/diastolic ratio of uterine arteries, middle cerebral and umbilical arteries, systolic flow velocity in the pulmonary artery and ductus arteriosus, as well as left ventricular ejection fraction and the redundancy index of the septum primum<sup>25</sup>. The latter was obtained through a 4-chamber view of the fetal heart, measuring the maximal excursion of the foramen ovalis membrane inside the left atrium and dividing this value by the maximal diameter of this atrium during ventricular diastole.

Patients were asked to abstain from smoking cigarettes for 12 hours before the examination. Variables were evaluated before and after maternal smoking, with a maximal interval of 5 minutes to initiate the second phase of the examination, using the same equipment and the same technical staff.

Three measures were performed for all parameters, and their mean was considered the result.

Statistical analysis was conducted using the Wilcoxon test for nonparametric data. It was considered significant a p value <0,05.

## Results

Mean maternal age was 22.95 years. The subjects smoked a mean of 9.67 cigarettes a day.

Gestational age ranged between 18 and 36 (mean 29.29) weeks. An increase in maternal heart rate (P<0.001), fetal heart rate (P=0.044) (tab. I), and in maternal systolic (P=0.004) and diastolic (P=0.033) blood pressure occurred immediately after smoking (tab. II). A decrease occurred in the right uterine artery systolic/diastolic ratio (P=0.014) and in the left uterine artery systolic/diastolic ratio (P=0.039) (tab. III). The other hemodynamic variables remained unchanged.

## Discussion

An increase occurred in both maternal and fetal heart rate and in maternal blood pressure, as mentioned in the majority of studies. A decrease was also observed in the right and left uterine artery systolic/diastolic ratio immediately after smoking, which probably reflects an increase in of the flow velocity in these vessels, instead of a decrease in this velocity. It was once believed that low birth weight associated with smoking during pregnancy is due to a fetal blood hypoperfusion, which was observed in studies of intravenous nicotine effects in fetal lambs<sup>26</sup>. In this study, the authors directly evaluated uterine flow through hemodynamic intervention, and they observed that, with a 10µg/kg/min nicotine infusion, an increase occurs in uterine blood flow, whereas with greater doses, a decrease in blood flow occurs, which suggests that this effect is dose-dependent. The result obtained in the present study is probably due to the use of low-nicotine cigarette (0.5mg). In another study with a methodology very similar to ours<sup>19</sup>, but using cigarettes with a 1.6-mg nicotine content, changes in vascular resistance of the uterine arteries, evaluated by uterine systolic/diastolic ratio, were not demonstrated.

This result may be related to the findings previously mentioned in the medical literature, about the puzzling association between smoking and a reduced risk of hypertension during pregnancy<sup>27</sup>. This fact might be related to an increase in the uterine flow with vasodilatation, which was not verified by the authors. In a prospective cohort<sup>28</sup>, it was

**Table I – Maternal and fetal heart rate (bpm) before and after maternal smoking**

	N	Median	SD	Mean	P <sub>25</sub>	P <sub>75</sub>
MHR						
Before	21	81,10	11,81	80	72	90,50
After	21	91,33	15,47	92	80	100,50
FHR						
Before	21	139,48	11,04	137	132	147,75
After	21	147,05	11,40	147	139	154,75

N: sample size; SD- standard deviation; P<sub>25</sub>- percentile 25; P<sub>75</sub>- percentile 75; MHR- maternal heart rate; FHR- fetal heart rate.

	N	Median	DP	Mean	P <sub>25</sub>	P <sub>75</sub>
Systolic BP of the mother						
Before	21	117,76	14,64	120	110	128,50
After	21	124,52	11,93	120	117,50	130,00
Diastolic BP of the mother						
Before	21	66,43	6,73	65	60	70
After	21	70,24	9,01	70	65	76,25

N- sample size; SD- standard deviation; P<sub>25</sub>- percentile 25; P<sub>75</sub>- percentile 75; BP- blood pressure.

	N	Median	DP	Mean	P <sub>25</sub>	P <sub>75</sub>
R uterine artery						
Systolic/diastolic						
Before	21	2,37	0,74	2,32	2,03	2,44
After	21	2,04	0,36	1,98	1,79	2,27
L uterine artery						
Systolic/diastolic						
Before	21	2,32	0,63	2,19	1,87	2,60
After	21	2,04	0,75	1,90	1,70	2,46

N: sample size; SD- standard deviation; P<sub>25</sub>- percentile 25; P<sub>75</sub>- percentile 75; S/D- systolic/diastolic ratio; R- right; L- left.

verified that past and current smoking is associated in a dose-response pattern with a reduced risk of preeclampsia and hypertension during pregnancy. For women who smoked 10 or more cigarettes a day, the relative risk for women who never smoked were 0.6 (confidence interval 0.4-0.9) for gestational hypertension and 0.5 (confidence interval 0.4-0.7) for preeclampsia.

The umbilical artery systolic/diastolic ratio remained unchanged, in contrast with the findings of Morrow et al<sup>19</sup>, but in accordance with the study of Lindblad et al<sup>20</sup>, who did not find this effect in the group of pregnant women who smoked 1 one standard cigarette, but in those patients evaluated immediately after smoking 2 cigarettes containing 1.6mg of nicotine each. Therefore, they concluded that this effect of cigarettes due to nicotine was also related to the inhaled dose.

Increased systolic/diastolic ratio in the fetal middle cerebral artery, as for today, has been described only in animals. In a study performed in lamb fetuses, an increase was verified in vascular resistance in cerebral arteries after endovenous use of nicotine, with a consequent decrease in cerebral perfusion<sup>1</sup>. The objective of this study was to use this parameter as an indirect method of evaluating the presence of fetal hypoxia.

We did not find a difference in ejection fraction, in the redundancy index of the septum primum, or in the systolic flow of the ductus arteriosus and pulmonary artery. These

variables were studied for the first time in fetuses of smoking mothers to verify acute changes due to smoking.

Situations that affect cardiac output may alter ejection fraction<sup>29</sup>. As cigarette smoking can lead to an increase in peripheral vascular resistance, it could influence myocardial contractility, evaluated through ejection fraction, which is considered an important parameter. As the concentration of the nicotine in the cigarettes used in our study was low, it did not alter umbilical flow, and the ejection fraction remained within normal limits as was expected.

Cardiac preload evaluation, through the study of fetal venous flow, was not included in this research. Situations of hypoxia, which could be triggered by smoking during pregnancy, and an increase in blood flow in the ductus venosus may also influence fetal cardiac function<sup>30,31</sup>.

This result suggests that cigarettes in the amount and of the quality studied did not affect fetal systolic cardiac function, although they did promote a significant increase in heart rate. The study of systolic and diastolic function, inferred in this study by the redundancy index of the septum primum, related to left ventricular compliance, did not show significant modifications. We only observed a change in physiologic parameters in the fetal heart, such as heart rate, without hemodynamic changes.

We also point out here the importance of studying the blood flow in ductus arteriosus and in the pulmonary artery, taking into account the sensitivity of the ductus arteriosus to the effects of prostaglandins, whose release may be altered by cigarette smoking. Because it is the first time that flow velocity in these vessels related to maternal smoking has been evaluated, it is not possible to know whether the results were dose-dependent according to the cigarettes used in this study. It is possible that greater doses of nicotine produce different results.

This project intended to assess the repercussion of low doses of nicotine in the utero-placental and fetal hemodynamic circulation. All the studies reviewed in the medical literature that evaluated these parameters used greater doses of nicotine. A study of groups exposed to increasing doses of nicotine would elucidate the variations in findings of this study compared with data reported in the literature. The use of a lower number of parameters in studies on the effects of maternal smoking in fetal placenta circulation could lead to easier examinations and thus a larger sample size.

Further studies are necessary concerning the physiologic or pathologic changes of fetal exposure to smoking. Hemodynamic alterations that occur in fetuses of smoking mothers are still far from being completely understood, and they are obviously not limited to vasoconstriction and vasodilatation mechanisms, but rather to a complex histological and biochemical involvement that needs further elucidation.

## References

1. Lambers DS, Clark KE. The maternal and fetal physiologic effects of nicotine. *Semin Perinatol* 1996; 20: 115-26.
2. Shah NR, Bracken MB. A systematic review and metaanalysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. *Am J Obstet Gynecol* 2000; 182: 465-72.
3. Cnattingius S, Granath F, Petersson G. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. *N Engl J Med* 1999; 341: 943-8.
4. Brooke OG, Anderson HR, Bland JM, et al. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *Br Med J* 1989; 298: 795-801.
5. Windham GC, Behren JV, Waller K, et al. Exposure to environmental tobacco smoke and risk of spontaneous abortion. *Am J Epidemiol* 1999; 149: 243-7.
6. Li CQ, Windsor RA, Perkins L, et al. The impact on infant birth weight and gestational age of cotinine-validated smoking reduction during pregnancy. *JAMA* 1993; 269: 1519-24.
7. Peacock JL, Bland JM, Anderson HR, et al. Cigarette smoking and birthweight: type of cigarette smoked and a possible threshold effect. *Int J Epidemiol* 1991; 20: 405-12.
8. Sadler L, Belanger K, Saftlas A, et al. Environmental tobacco smoke exposure and small-for-gestational-age birth. *Am J Epidemiol* 1999; 150: 695-705.
9. Vorherr H. Factors influencing fetal growth. *Am J Obstet Gynecol* 1982; 142: 577-88.
10. Dwyer T, Ponsonby AL, Couper D. Tobacco smoke exposure at one month of age and subsequent risk of SIDS - A prospective study. *Am J Epidemiol* 1999; 149: 593-602.
11. Slotkin TA, Epps TA, Stenger ML, et al. Cholinergic receptors in heart and brainstem of rats exposed to nicotine during development: implications for hypoxia tolerance and perinatal mortality. *Dev Brain Res* 1999; 113: 1-12.
12. Luck W, Nau H, Hansen R, et al. Extend of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. *Dev Pharmacol Ther* 1985; 8: 384-95.
13. Luck W, Nau H. Nicotine and cotinine concentrations in the serum and milk of nursing smokers. *Br J Clin Pharmacol* 1984; 18: 9-15.
14. Giacomini CB. Cortisol e sulfato de deidroepiandrosterona no sangue de cordão umbilical de recém-nascidos normais de mães fumantes e não-fumantes. Curso de Pós-Graduação Medicina: Clínica Médica. Universidade Federal do Rio Grande do Sul. Porto Alegre, 1991.
15. Coulson CC, Thorp JM, Purrington J, et al. Effects of maternal smoking on amniotic fluid volume and fetal urine output. *Am J Perinatol* 1996; 13: 195-7.
16. Ostrea EM Jr, Knapp DK, Romero A, et al. Meconium analysis to assess fetal exposure to nicotine by active and passive maternal smoking. *J Pediatr* 1994; 124: 471-6.
17. Eliopoulos C, Klein J, Phan MK, et al. Hair concentrations of nicotine and cotinine in women and their newborn infants. *JAMA* 1994; 271: 621-3.
18. Obwegeser R, Oguogho A, Ulm M, et al. Maternal cigarette smoking increases F2-isoprostanes and reduces prostacyclin and nitric oxide in umbilical vessels. *Prostaglandins Other Lipid Mediat* 1999; 57: 269-79.
19. Morrow RJ, Ritchie JWK, Bull SB. Maternal cigarette smoking: the effects on umbilical and uterine blood flow velocity. *Am J Obstet Gynecol* 1988; 159: 1069-71.
20. Lindblad A, Marsal K, Andersson KE. Effect of nicotine on human fetal blood flow. *Obstet Gynecol* 1988; 72: 371-82.
21. Newnham JP, Patterson L, James I, et al. Effects of maternal cigarette smoking on ultrasonic measurements of fetal growth and on Doppler flow velocity waveforms. *Early Hum Devel* 1990; 24: 23-36.
22. Oncken CA, Hardardottir H, Hatsukami DK, et al. Effects of transdermal nicotine or smoking on nicotine concentrations and maternal-fetal hemodynamics. *Obstet Gynecol* 1998; 90: 569-74.
23. Zielinsky P, Hagemann LL, Zimmer LP, Ceccon G, Bonow FP, Oliveira LT. O papel da ultra-sonografia obstétrica de rotina no diagnóstico presuntivo de cardiopatias fetais. *Revista AMRIGS* 1997; 41: 181-6.
24. Zielinsky P. Abordagem diagnóstica e terapêutica pré-natal das anormalidades cardíacas fetais. *ECO Rev Bras Ecocardiogr* 1992; 17: 10-25.
25. Firpo C, Zielinsky P. Mobility of the septum primum in the developing human fetus. *Cardiol Young* 1998; 8: 67-70.
26. Clark KE, Irion GL. Fetal hemodynamic response to maternal intravenous nicotine administration. *Am J Obstet Gynecol* 1992; 167: 624-31.
27. Salafia C, Shiverick K. Cigarette smoking and pregnancy II: Vascular effects. *Placenta* 1999; 20: 273-9.
28. Zhang J, Klebanoff MA, Levine RJ, et al. The puzzling association between smoking and hypertension during pregnancy. *Am J Obstet Gynecol* 1999; 181: 1407-13.
29. Mattos SS. O Coração Fetal. Rio de Janeiro: Revinter, 1999.
30. DeVore GR. Assessment of venous flow in normal and high-risk fetuses: is the future now? *Prenat Neonat Med* 1996; 1: 329-42.
31. Hecher K, Campbell S. Characteristics of fetal venous blood flow under normal circumstances and during fetal disease. *Ultrasound Obstet Gynecol* 1996; 7: 68-83.