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Cigarette smoking during pregnancy in two regions: cross-sectional study

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ABSTRACT

Objective: Smoking in pregnancy is associated with the risk of congenital malformations and functional disorders. The aim of the study was to assess the prevalence of cigarette smoking in pregnancy, and the rate of congenital malformations in children at in utero exposure. **Methods:** The trial was designed as a cross-sectional study to measure exposure of pregnant women to adverse influence of smoking and their health status. The study consists of two arms: one was conducted at four Zagreb maternity hospitals (Croatia) and the other at the same hospitals in Novi Sad (Serbia). **Results:** Data analysis revealed the habit of cigarette smoking during pregnancy in 829 (11.9%) of 6 992 (6 099+893) women. Malformations were found in 105 (1.5%) fetuses and newborns. Major congenital malformations were present in four (0.6%), minor malformations in 73 (10.5%) and LBW in 12 (1.7%) newborns. In all these cases pregnant women smoked until becoming aware of pregnancy or during pregnancy. Tobacco smoking and congenital abnormalities that define the contingency table are not significantly related in Zagreb ($P=0.385$), as well as in Novi Sad ($P=0.345$). **Conclusions:** The rate of congenital malformations is higher in fetuses and newborns at in utero exposure to maternal cigarette smoking as well as to alcohol consumption and drug abuse than in the general population. The results of the present study did not identify the exact cause of these malformations because of fetal concurrent exposure to multiple teratogenic factors.

1. Introduction

Cigarette smoking in pregnancy is associated with the risk of congenital malformations and functional disorders or immunity suppression. Smoking in pregnancy leads to repeated spontaneous abortion, low birth weight (LBW) and perinatal mortality; congenital malformations may also occur^{1–4}.

An international epidemiological study entitled “Collaborative Study on the Use of Drugs in Pregnancy” was conducted during the 1988–1990 period, in which only Zagreb and Novi Sad took part as representatives of the region. The aim of the present study was to assess whether the habit of cigarette smoking in pregnancy has changed since then. The interest in this public health problem

pointed to the need of such studies in Croatia. The wide variety of data reported from different countries imposes the need of identifying the current situation in Croatia. It is estimated that 12% of women are smokers worldwide. According to World Health Organization data, 15% of women in industrialized countries and 8% of those from developing countries are smokers. In USA, smoking habit is recorded in 15%–30% of women, and many of them are also in pregnancy. Cigarette smoking in pregnancy poses a major public health problem, because it can cause a number of disorders in neonates.

Generally, 25%–50% (90% for deep inhalation) of nicotine is resorbed in oral cavity. Nicotine readily crosses placental barrier, yet reaching far lower concentration in fetal tissue. On cigarette smoking, about 3 800 degradation substances reach fetal circulation without filtration. Among others, mention should be made of cadmium and other heavy metals, radioactive substances and carcinogenic substances that can be demonstrated in neonatal urine⁵. Data from a number of studies conducted all over the world show that

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smoking in pregnancy is responsible for embryotoxic and fetotoxic effects, however, conclusive data on the association between smoking in pregnancy and congenital anomalies are still lacking. Smoking in pregnancy leads to repeated abortion, LBW and increased perinatal mortality. Association between smoking in pregnancy and particular malformations (cleft lip, extremity defects, urinary tract malformations and craniosynostosis) has been reported^[6–9].

The mean birth weight is about 200 g lower in neonates born by mothers who are used to smoke during pregnancy. Maternal cigarette smoking leads to delivery of LBW children. Neonates with LBW (birth weight < 2 500 g) are preterm (before 37th week of gestation) or are small for gestational age (10% smaller for gestational age). Maternal smoking is associated with a higher rate of preterm deliveries and a 2-fold risk of spontaneous abortion found in non-smoking mothers. The rate of sudden infant death syndrome is also higher in smoking mothers^[3,10].

Nicotine is believed to cause disturbances in the placental functional maturation and/or intrauterine oxygen deficiency (fetal hypoxia) due to the toxic effects of smoking. Nicotine induces vascular stenosis, reduces placental blood flow, and causes fetal blood pressure elevation. Toxic carbon monoxide produced on cigarette smoking binds to hemoglobin in red blood cells while depriving them of oxygen. In such conditions, fetus is exposed to chronic oxygen deficiency, thus fighting for air already in the intrauterine setting^[11]. Maternal smoking has possible positive effects somewhere; it is protective against preeclampsia^[12] and seems to reduce the risk of myomas^[13]. Nevertheless, some studies did not support the proposition that cigarette smoking protected women against preeclampsia^[14]. However, cigarette smoking should definitely be avoided in pregnancy.

The aim of the present study was to assess the prevalence of cigarette smoking in pregnancy and the rate of congenital malformations in children in utero exposure to nicotine. The respective results recorded in two cities from two neighboring countries were compared.

2. Materials and methods

One study arm was conducted at four Zagreb maternity hospitals: University Department of Gynecology and Obstetrics, Zagreb University Hospital Center; University Department of Gynecology and Obstetrics, Sestre milosrdnice University Hospital; University Department of Gynecology and Obstetrics, Merkur University Hospital; and University Department of Gynecology and Obstetrics, Sveti Duh General Hospital.

The other study arm was performed at the Genetic Counseling Unit, Institute for Children and Adolescents, University Department of Gynecology and Obstetrics, and Department of Pathology and Histology, Novi Sad Clinical

Center in Novi Sad, Serbia. Pregnant women presenting to the Genetic Counseling Unit for risky pregnancy and those hospitalized at University Department of Gynecology and Obstetrics for delivery or abortion were included. The trial was designed as a cross-sectional study to measure exposure of pregnant women to adverse effects of cigarette smoking and their health status and to determine the rate of malformations and pathologic conditions in children born by mothers with and without exposure to smoking.

The study included 893 pregnant women in Zagreb and 6 099 pregnant women in Novi Sad. The study was approved by independent Ethics Committee of the School of Medicine, University Novi Sad. An informed consent on study enrolment was obtained from all study subjects. Data were collected from the following sources: (1) questionnaire for pregnant women, filled in by a physician, containing two types of data: information obtained by interview and hospital records; (2) thorough physical examination of the neonate, performed by a neonatologist according to standard protocol; and (3) thorough pathologic examination of the fetus or neonate, performed by a pathologist according to standard protocols.

Pregnant women using alcohol, nicotine and opioid substances in pregnancy were included; however, only data on cigarette smoking are reported here. The analysis included 829 pregnant women (134 in Zagreb and 695 in Novi Sad). Following delivery or abortion, the newborns and fetuses were thoroughly examined or monitored for the presence of minor or major malformations. Cigarette smoking and the existence of congenital malformations in newborns and fetuses after *in vitro* exposure to nicotine effects were monitored according to gestational trimesters.

Student's *t*-test and *Chi*-square test with a significance level of $P \leq 0.05$ were used when appropriate for the evaluation of the results. All analyses were performed with SigmaStat 3.0 for Windows (SPSS Science software products, Chicago, IL, USA).

3. Results

3.1. Total rate of cigarette smoking

Although the number of pregnant women included in the Zagreb and Novi Sad study arms (893 and 6 099, respectively) greatly differed, the rate of cigarette smoking reported in pregnancy was quite comparable, 15.0% in Zagreb and 11.4% in Novi Sad. In total, cigarette smoking was reported by 829 (11.9%) study subjects, whereas congenital malformations were recorded in 5.3% (44/830) fetuses and newborns.

3.2. Zagreb arm

Cigarette smoking before pregnancy was reported by 34.0% of (304/893) study women. Fifty-six (6.3% of total samples)

women quit smoking habit for planned pregnancy and 114 (12.8%) women for having become aware of pregnancy, whereas 134 (15.0%) women reported smoking at the beginning of pregnancy (Table 1).

The largest proportion of women (8.7%) reported daily use of less than half pack, 4.9% half to one pack of cigarettes and 1.3% more than one pack (Table 2). However, this figure decreased with pregnancy progression from 134 women at the beginning of pregnancy to 123 women towards the end of the 3rd trimester, *i.e.*, immediately before delivery. Smoking habit according to trimesters is illustrated in Table 3.

Half of 26 women having delivered children with congenital malformations (50.0%) had never smoked, seven women had quit smoking when becoming aware of pregnancy, and six women continued smoking during pregnancy. Congenital malformations were recorded in children born by mothers who had smoked throughout pregnancy. The malformations included cardiovascular malformations in two children, genitourinary system and musculoskeletal system malformations in one child each, and unidentified malformations in two children. In the subgroup of women having smoked before or during pregnancy and having delivered children with congenital malformations, three (50.0%) women used less than half pack daily, two (33.3%) used half to one pack daily, and one (16.6%) woman used

more than one pack daily.

3.3. Novi Sad arm

Analysis of data collected in Novi Sad showed that 18.4% (1 123/6 099) of pregnant women had quit smoking for planned pregnancy or having become aware of pregnancy, whereas 11.4% (695/6 099) women continued smoking during pregnancy (Table 1). The number of cigarettes used daily is presented in Table 2, and smoking according to trimesters in Table 3. The majority of women quit smoking in pregnancy and only 2.5% of them continued smoking in pregnancy as compared with 13.8% recorded in the Zagreb arm.

Major congenital malformations were present in four (0.6%), minor malformations in 73 (10.5%) and LBW in 12 (1.7%) newborns, whereas sudden fetal death was recorded in one (0.1%) case, in 19th week of gestation. In all these cases, pregnant women smoked until becoming aware of pregnancy or during pregnancy. Major congenital malformations observed in the study population included Dandy–Walker malformation, anencephaly, hydrocephalus with meningocele, and occipital defect. Tobacco smoking and congenital abnormalities that define the contingency table were not significantly related in Zagreb as well as in Novi Sad (Table 4).

Table 1

Smoking during pregnancy in Zagreb and Novi Sad.

Cigarette smoking	Zagreb (n=893)		Novi Sad (n=6 099)	
	Pregnant women	Percentage (%)	Pregnant women	Percentage (%)
Never	581	65.1	4 281	70.2
Quit for planned pregnancy	56	6.3	1 123 ^a	18.4 ^a
Yes, before becoming aware of pregnancy	114	12.8		
Yes, before and during pregnancy	134	15.0	695	11.4
Unknown	8	0.9	0	0.0

^aPreganant women who had quit smoking for planned pregnancy or having become aware of pregnancy.

Table 2

Cigarette consumption in pregnant women (%).

Daily cigarette consumption	Zagreb		Novi Sad	
	Percentage in pregnant women	Incidence	Percentage in pregnant women	Incidence
<0.5 pack	58.2 (78/134)	8.7 (78/893)	22.1 (154/695)	2.5 (154/6 099)
0.5–1.0 pack	32.8 (44/134)	4.9 (44/893)	51.2 (356/695)	5.8 (356/6 099)
>1.0 pack	9.0 (12/134)	1.3 (12/893)	26.6 (185/695)	3.0 (185/6 099)

Table 3

Cigarette smoking according trimesters (%).

Study arm	Daily cigarette consumption	Trimester I		Trimester II		Trimester III	
		Percentage in pregnant women	Incidence	Percentage in pregnant women	Incidence	Percentage in pregnant women	Incidence
Zagreb	<0.5 pack	58.2 (78/134)	8.7	60.0 (75/125)	8.4	58.6 (72/123)	8.1
	0.5–1.0 pack	32.8 (44/134)	4.9	31.2 (39/125)	4.4	32.5 (40/123)	4.5
	>1.0 pack	9.0 (12/134)	1.3	8.8 (11/125)	1.2	8.9 (11/123)	1.2
	Total	100.0 (134/134)	15.0	100.0 (125/125)	14.0	100.0 (123/123)	13.8
Novi Sad	Total	100.0 (695/695)	11.4	100.0 (571/571)	9.4	100.0 (154/154)	2.5

Table 4

Tobacco smoking and congenital malformations in Zagreb and Novi Sad (pregnant women smoked during pregnancy).

Pregnant women	Zagreb		Novi Sad	
	Pregnant women	Congenital abnormalities	Pregnant women	Congenital abnormalities
Smokers	134	6	695	38
Non-smokers	751	20	5 404	350
Total	885	26	6 099	388

4. Discussion

Cigarette smoke contains substances associated with adverse effects on the fetus and on the newborn's health later in life. The children born to smoking mothers have LBW[15], while the rate of preterm deliveries is greater[16]. Smoking in pregnancy entails an almost 2-fold risk of LBW, which is associated with higher morbidity and mortality rates in perinatal period and infancy. Data from the French Epipage study show that maternal smoking is a risk factor for very preterm birth[17]. Cigarette smoking causes damage to fetal lungs at a crucial stage of development, which may lead to decreased lung capacity, higher rate of respiratory infections, asthma and emphysema later in life. Cigarette smoking entails lesions to the embryo and fetus throughout the period of perinatal development and later in infancy via breastfeeding. At the age of 16 years, these children showed lower calculating, reading and speech abilities as compared with their peers born by non-smoking mothers. Current smoking is one of the factors directly related to infertility[18]. The risk of intrapartum stillbirth associated with smoking in pregnancy is potentiated by the age of the mother[19]. Some authors talk that outcomes later in time might have a too low value to exert a positive effect on decisions to quit smoking[20]. Furthermore, some authors have detected an association between low socio-occupational status and congenital anomalies of the respiratory system, heart and circulatory system[21].

As Zagreb and Novi Sad were the only cities that took part in a previous study conducted in 1991, currently present harmful habits in pregnant women from these two cities and congenital malformations in their children that could be potentially associated with these habits were compared. The four maternity hospitals from Zagreb cover the city and county of Zagreb as a catchment area and perform some 10 500 deliveries per year, which is 2 fold that recorded in the Novi Sad hospital with the city of Novi Sad and a major part of Vojvodina as the catchment area.

Comparison of data on cigarette smoking in pregnancy showed a comparable proportion of women smoking in pregnancy in Zagreb (15.0%) and Novi Sad (11.4%). The results obtained in the present study are consistent with literature data. Nearly 2/3 of women quit smoking for planned pregnancy or when they become aware of pregnancy, whereas 1/3 continue smoking during pregnancy,

yet reducing the number of cigarettes per day. About 12% of women continue smoking in pregnancy[22–24]. In our study, the prevalence of congenital malformations recorded in fetuses and newborns in utero exposure to nicotine exceeded their prevalence in the general population. We recorded developmental retardation and sudden fetal death in one case, as in literature reports associated with cigarette smoking in pregnancy. Infants born by smoking mothers are at a 2- to 5-fold risk of sudden infant death syndrome. Maternal smoking influences later physical and intellectual development of her child. It is also a preventable prenatal risk factor associated with small decrements in offspring academic performance that continue into adolescence[25]. The risk of impairment in the child's development increases with each cigarette. These data are in line with the results obtained in our study. The risk of hyperactivity and behavioral deviation is recorded in 22% of children born by smoking mothers and only 8% of children born by non-smoking mothers. In addition, cigarette smoking in pregnancy poses a major risk factor for subsequent development of allergy, neurodermatitis and asthma as well as of aggressive and stubborn behavior in these children. Pregnant women should be repeatedly warned of the fetal risks imposed by their smoking habit, and efforts to prevent the complications described should be focused on the prevention of nicotine product use by female population of reproductive age[26]. Positive health behaviors during pregnancy (elimination of smoking and alcohol drinking) are influenced by wantedness of pregnancy as well as sociodemographic characteristics[27].

In conclusion, the proportion of pregnant women reporting cigarette smoking was quite close in Zagreb and Novi Sad (15.0% vs 11.4%). In total study population, congenital malformations were found in 5.3% (44/830 fetuses and newborns). The results obtained suggested the following conclusions: there was no statistically significant association between cigarette smoking and congenital malformations. Women frequently quit smoking for planned pregnancy or having become aware of pregnancy, whereas those who continue smoking in pregnancy reduce the number of cigarettes per day. Cases without quantitative modification in smoking habit in pregnancy were less frequently recorded.

The rate of congenital malformations is higher in fetuses and newborns in utero exposure to maternal cigarette smoking as well as to alcohol consumption and drug abuse

than in the general population. The results of the present study did not identify the exact cause of these malformations because of fetal concurrent exposure to multiple teratogenic factors.

Conflict of interest statement

The authors declare that there is no source of financial or other support or any financial or professional relationships that may pose a competing interest.

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References

- [1] Mc Donald DA, Armstrong GB, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. *Am J Public Health* 1992; **82**(1): 91–93.
- [2] Li DK, Mueller AB, Hickok ED, Daling JR, Fantel AG, Checkoway H, et al. Maternal smoking during pregnancy and the risk of congenital urinary tract anomalies. *Am J Public Health* 1996; **86**(2): 249–253.
- [3] Källén K. Multiple malformations and maternal smoking. *Paediatr Perinat Epidemiol* 2000; **14**(3): 227–233.
- [4] Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: an indication of a gene environment interaction. *Am J Epidemiol* 2000; **152**(7): 658–665.
- [5] Hull MG, North K, Taylor H, Farrow A, Ford WC. Delayed conception and active and passive smoking. *Fertil Steril* 2000; **74**(4): 725–733.
- [6] Ericson A, Källén B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. *Am J Obstet Gynecol* 1979; **135**(3): 348–351.
- [7] Khoury MJ, Weinstein A, Panny S, Holtzman NA, Lindsay PK, Farrel K, et al. Maternal cigarette smoking and oral clefts: a population-based study. *Am J Public Health* 1987; **77**(5): 623–625.
- [8] Czeizel A, Kodaj I, Lenz W. Smoking during pregnancy and congenital limb deficiency. *Br Med J* 1994; **308**(6942): 1473–1476.
- [9] Källén K. Limb reduction malformations and maternal smoking during pregnancy. *Am J Public Health* 1997; **87**(1): 29–32.
- [10] Källén K. Maternal smoking and craniosynostosis. *Teratology* 1999; **60**(3): 146–150.
- [11] Samet JM, Yoon SY. Women and the tobacco epidemic: challenges for the 21st century. Geneva: World Health Organization in collaboration with the Institute for Global Tobacco Control, Johns Hopkins School of Public Health; 2001.
- [12] Xiong X, Wang FL, Davidge ST, Demianczuk NN, Mayes DC, Olson DM, et al. Maternal smoking and preeclampsia. *J Reprod Med* 2000; **45**(9): 727–732.
- [13] Parazzini F, Negri E, La Vecchia C, Rabaiotti M, Luchini L, Villa A, et al. Uterine myomas and smoking. Results from an Italian study. *J Reprod Med* 1996; **41**(5): 316–320.
- [14] Iloka A, Tsukuma H, Nakamuro K. Lifestyles and pre-eclampsia with special attention to cigarette smoking. *J Epidemiol* 2003; **13**(2): 90–95.
- [15] Rasmussen S, Irgens LM. The effects of smoking and hypertensive disorders on fetal growth. *BMC Pregnancy Childbirth* 2006; **6**: 16.
- [16] Mohsin M, Jalaludin B. Influence of previous pregnancy outcomes and continued smoking on subsequent pregnancy outcomes: an exploratory study in Australia. *BJOG* 2008; **115**(11): 1428–1435.
- [17] Burguet A, Kaminski M, Abraham-Lerat L, Schaal JP, Cambonie G, Fresson J, et al. The complex relationship between smoking in pregnancy and very preterm delivery. Results of the Epipage study. *BJOG* 2004; **111**(3): 258–265.
- [18] Kelly-Weeder S, Cox CL. The impact of lifestyle risk factors on female infertility. *Women Health* 2006; **44**(4): 1–23.
- [19] Aliyu MH, Salihu HM, Wilson RE, Alio AP, Kirby RS. The risk of intrapartum stillbirth among smokers of advanced maternal age. *Arch Gynecol Obstet* 2008; **278**(1): 39–45.
- [20] Ortendahl M, Uttermalm A, Simonsson B, Näsman P, Wallsten T. Estimated time for occurrence of smoking-related consequences among pregnant and non-pregnant women. *Int J Environ Res Public Health*. 2009; **6**(5): 1665–1675.
- [21] Varela MM, Nohr EA, Llopis-Gonzales A, Andersen AM, Olsen J. Socio-occupational status and congenital anomalies. *Eur J Public Health* 2009; **19**(2): 161–167.
- [22] Wang X, Zuckerman B, Pearson C, Kaufman G, Chen C, Wang G, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *JAMA* 2002; **987**(2): 195–202.
- [23] Erić M. Research of teratogenic effects of medicines on embryo. Novi Sad (Serbia): University of Novi Sad; 2004.
- [24] Leppée M. Drugs in pregnancy. Zagreb (Croatia): Josip Juraj Strossmayer University Osijek; 2008.
- [25] O'Callaghan FV, Al Mamun A, O'Callaghan M, Alati R, Williams GM, Najman JM. Is smoking in pregnancy an independent predictor of academic difficulties at 14 years of age? A birth cohort study. *Early Hum Dev* 2010; **86**(2): 71–76.
- [26] Ilijčić M, Krpan M, Ivanišević M, Djelmiš J. Influence of smoking during pregnancy on early and late development of the child. *Gynaecol Perinatol* 2006; **15**(1): 30–36.
- [27] Altfeld S, Handler A, Burton D, Berman L. Wantedness of pregnancy and prenatal health behaviors. *Women Health* 1997; **26**(4): 29–43.