Biol Trace Elem Res (2013) 155:169–175
DOI 10.1007/s12011-013-9775-8

Tobacco Smoke Exposure During Pregnancy Increases Maternal Blood Lead Levels Affecting Neonate Birth Weight

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Received: 2 June 2013 / Accepted: 26 July 2013 / Published online: 10 August 2013

Abstract To assess the effect of lead exposure from cigarette smoke on fetal growth, blood lead concentrations were measured using inductively coupled plasma mass spectrometry in 150 healthy pregnant women. Mean lead concentrations in plasma and whole blood were significantly higher in the smoking group compared with the nonsmoking group in each trimester of pregnancy ($p<0.001$). Logistic regression analysis showed the highest impact of the number of cigarettes smoked per day for serum lead concentration ($\beta=0.238$; $p<0.05$), while in whole blood, it was duration of smoking before conception ($\beta=0.297$; $p<0.001$). Birth weight of the smoking mothers' infants was significantly lower (mean±SEM, 3,192±50.8 and 3,569±49.6 g, respectively; $p<0.001$) and negatively correlated with lead levels in plasma ($r=-0.38$; $p<0.001$) and in whole blood ($r=-0.27$; $p<0.001$). Therefore, it is suggested that smoking during pregnancy increases lead concentrations in maternal blood. Fetal exposure to low doses of lead in utero may be a serious risk factor causing lower birth weight.

Keywords Blood lead · Pregnant women · Tobacco smoking · Birth weight

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Introduction

Cigarette smoking may be one of the most common sources of lead (Pb) exposure affecting the general population. Tobacco contains lead, which enters mainstream smoke and is inhaled by smokers [1]. It has been estimated that between 1 and 5 μg of lead could be inhaled from smoking 20 cigarettes per day [2]. According to the World Health Organization (WHO), tobacco smoke from burning one cigarette could contain from 17 to 980 ng Pb [3]. Despite the fact that in the last years a decrease in the number of active smokers has been observed, cigarette smoking still plays a significant role among hazardous health-related behaviors. This is particularly disturbing for pregnant women. Epidemiology studies conducted at the Institute of Mother and Child indicated that in Poland between 25 and 30 % of pregnant women were active smokers and close to 60 % were passive smokers (home and/or occupational exposure) [4].

At present, acute lead poisoning has become rare but chronic low-level exposure to lead remains a public health issue. Chronic low-level exposure may result in lead accumulation in renal tubule, lung, hepatocyte, and calcified tissues. It is well-known that lead accumulates mostly in the bones of the body [5–8]. The body burden of lead stored in maternal bone can be released during pregnancy and contribute to fetal lead exposure since there is no protective barrier to the transplacental transport of lead [9–11]. Because the body burden of lead in smoking mothers is higher than in nonsmoking ones, lead in maternal bones may therefore be mobilized during pregnancy even if the mother has stopped cigarette consumption [5, 11–13]. Elevated blood lead levels of pregnant women can be a risk factor for gestational hypertension/preeclampsia, spontaneous abortion, preterm labor, and premature rupture of the fetal membrane (PROM) [14–17]. In addition, low-dose lead exposure in utero may have an adverse effect on birth weight and developmental delays in children [18, 19]. A variety of studies have shown that chronic low-dose lead can

be associated with higher concentrations of this heavy metal in the blood of mothers and infants, but information on the effect of smoking on lead storage through pregnancy is limited [20–23].

Therefore, the main objective of this study was to evaluate the effect of cigarette smoking on plasma and whole blood lead levels in pregnant women. The correlations between concentrations of lead and markers of estimated intensity of cigarette smoking (serum cotinine level, number of cigarettes/day, duration of smoking before conception) were studied. The relationship between maternal lead status and birth weight was also determined.

Materials and Methods

Patients

This was a case–control association study, which examined the lead status of tobacco smoking pregnant women engaged in regular clinic visits in the Department of Obstetrics and Gynecology Institute of Mother and Child and the Warsaw Medical University, Warsaw, Poland. All pregnant volunteers were made aware of the objectives of the study and signed a written informed consent form. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of the Institute of Mother and Child.

One hundred and fifty healthy pregnant women were recruited for the study. Inclusion criteria were uncomplicated singleton pregnancies and the first trimester of pregnancy. Gestational age was estimated by the last menstrual period and confirmed by ultrasonographic measurements of the crown-rump length. Exclusion criteria were preeclampsia, hypertension, diabetes mellitus, active hepatitis, renal and cardiovascular diseases, and inflammatory conditions. The socioeconomic status of all subjects was similar. All of them were living in an urban area; none of the mothers drank alcohol; none of the fetuses showed abnormalities.

At the first control visit, a history of smoking was obtained by direct questioning of the pregnant women. Smokers were defined as those women who reported their smoking habit as maintained at a rate of minimum five cigarettes per day and minimum 2 years before conception and continued smoking during pregnancy. Nonsmokers were defined as those women who had never smoked and were not exposed to environmental tobacco smoke during their pregnancy (smoking spouse or co-workers). The classification was confirmed by measurement of serum cotinine concentration in pregnant women—the major metabolite of nicotine. The concentration of serum cotinine at a level of 15 μg/L was accepted as the limit value between the nonsmoking and smoking group.

Collection and Analysis of Blood Samples

Fasting blood was obtained from women by venipuncture in the first, second, and third trimester of pregnancy. Blood was collected in the usual manner, but the full blood count sample was collected into verified trace metal free EDTA tubes (BD, UK). In order to obtain plasma, the blood was centrifuge at 2,500×*g*, at 4 °C for 10 min. Whole blood samples as well as plasma and serum were frozen until measurements of lead and cotinine concentrations were performed (−20 °C, max. 2 months).

An Inductively Coupled Plasma Mass Spectrometer (Elan 6100, Perkin Elmer, Canada) equipped with a Mainhard spray chamber, quartz Scott's chamber, and platinum cones was used. The experimental conditions were optimized according to standard procedure by setting the flow of nebulizer gas (argon), position of the nebulizer, positions of the cones, and focusing lenses. Under optimized conditions, it was possible to obtain adequate sensitivity and to reduce interference from doubly charged ions and oxides. Three isotopes of lead (206Pb, 207Pb, 208Pb) were monitored during the measurements. The instrumental parameters were as follows: nebulizer gas flow, 0.81 L/min; auxiliary gas flow, 1.20 L/min; plasma gas flow, 14.50 L/min; lens voltage, 7.8 V; and ICP RF Power, 1,100 W.

Blood samples were diluted 10×, and plasma samples were diluted 5× with Mili-Q (Milipore, USA) high purity water before measurements. In order to prevent clogging of the nebulizer tubes, all aliquots were filtered using syringe polyamide-nylon filters with a pore size of 0.45 μm. Pb concentration was determined using an external calibration curve. The calibration standards were prepared by appropriate dilution of the multi-elemental ICP-MS stock standard solution (Merck, Germany). Accuracy of the determinations was verified by analyzing the reference material (Seronorm blood serum) with certified lead content. The obtained results were in accordance with the certificate.

Cotinine levels in serum were determined by immunoenzymatic method using a commercially available kit (Cotinine one-step ELISA, Calbiotech Inc., USA).

Statistical Analysis

Statistical analysis was done using STATISTICA 8.0 (StatSoft, Poland) software. The results are presented as means±standard error of the mean (SEM) for normally distributed data or medians and interquartile range (25th–75th percentiles) for non-normally distributed variables. Shapiro–Wilk's test was used for evaluation normality of data distribution prior to statistical analysis. Student's *t* test was used for comparison of normally distributed data and nonparametric Wilcoxon's test for non-normally distributed variables. Pearson and Spearman correlation coefficients were calculated for

the determination of the association between the studied markers. Univariate and multivariate linear regression models with natural logarithm-transformed concentration of lead as a dependent variable were estimated to examine the potential impact of number of the cigarettes/day, duration of smoking before conception, and cotinine level. In the univariate model, we analyzed each factor separately whereas in the multivariate one, they were all analyzed simultaneously. Results were expressed as the value of β standardized regression coefficient and its significance. The differences were regarded as statistically significant at $p<0.05$.

Results

The clinical characteristics of the pregnant women are shown in Table 1. A total of 150 patients were included in the study, 70 smoking and 80 nonsmoking women in similar weeks of gestation. Maternal characteristics were comparable in the studied groups except for cigarette smoking habits. The mean number of cigarettes per day for smokers was 8.8, and the mean duration of smoking before conception was 8.4 years. In the group of smoking mothers, serum cotinine concentration amounted 76.1 μg/L and correlated positively with the daily number of cigarettes consumed ($r=0.70$; $p=0.009$). In the tobacco abstinent group, serum cotinine was present only in two women in trace amounts (1.2 and 5.9 μg/L). Newborn gestational age was similar in the two studied groups, and there were no negative pregnancy outcomes or complications during delivery in the nonsmoking as well as smoking women. The birth weight of the smoking mothers' infants was significantly lower ($p<0.001$), but length, head circumference, and Apgar score was similar in the two groups.

There was a negative correlation between birth weight and lead level in maternal plasma ($r=-0.38$; $p<0.001$) as well as in whole blood ($r=-0.27$; $p<0.001$) in the group of smoking women. Additionally, lead concentrations in the mothers' plasma correlated negatively with birth length ($r=-0.28$; $p<0.001$) and head circumference ($r=-0.27$; $p=0.006$). Both plasma and whole blood median concentrations of lead were significantly higher in the smoking group compared with the nonsmoking one (Tables 2 and 3). Similar results were observed in the case of the mean values (plasma: I trimester, 0.28 vs 0.09 μg/dL; II trimester, 0.24 vs 0.07 μg/dL; III trimester, 0.39 vs 0.06 μg/dL; whole blood: I trimester, 2.2 vs 1.5 μg/dL; II trimester, 2.2 vs 1.3 μg/dL; III trimester, 2.6 vs 1.6 μg/dL; $p<0.001$). In the group of smokers, plasma Pb concentration correlated positively with whole blood levels of this element ($r=0.34$, $p<0.001$).

In Table 4, we presented the results of univariate and multivariate model of linear regression. In the univariate model, all three factors were significant predictors of the level of lead both in the serum and in whole blood. The highest impact of the number of cigarettes smoked per day was indicated for the serum lead concentration while in whole blood, it was duration of smoking before conception. In multivariate

Table 1 Characteristics of the study population

Characteristics	Smoking ($n=70$)	Nonsmoking ($n=80$)
Age (year)	29.5 (26.9–32.2)[b]	30.1 (28.4–33.8)[b]
Gestational age (week)		
I Trimester	12 (12–13)[b]	12 (12–13)[b]
II Trimester	21 (20–24)[b]	20.5 (20–22)[b]
III Trimester	31 (30–33)[b]	31 (30–32,5)[b]
Gestational age of birth (week)	38 (39–40)[b]	38.5 (39–40)[b]
Number of cigarettes/day	8.8±0.47[a]	0
Duration of smoking before conception (year)	8.4±0.50[a]	0
Serum cotinine (μg/L)	76.1±4.22[a]	0
Birth weight (g)		
Whole group	3,192±50.8[a, *]	3,569±49.6[a]
Girls	3,239±50.3[a, *]	3,509±49.4[a]
Boys	3,147±49.5[a, *]	3,603±49.9[a]
Birth body length (cm)		
Whole group	54.6±0.25[a]	55.6±0.21[a]
Girls	54.3±0.25[a]	55.1±0.22[a]
Boys	54.8±0.26[a]	55.9±0.21[a]
Head circumference (cm)		
Whole group	34.7±0.24[a]	35.0±0.12[a]
Girls	33.8±0.22[a]	34.6±0.10[a]
Boys	35.6±0.23[a]	35.4±0.12[a]
Apgar score (5th min)		
Whole group (100 %)	10 (10–10)[b]	10 (10–10)[b]
Girls (40 %)	10 (10–10)[b]	10 (10–10)[b]
Boys (60 %)	10 (10–10)[b]	10 (10–10)[b]

*$p<0.001$

[a] Values are means±standard error of the mean (SEM);

[b] Values are median and interquartile range (25th –75th percentiles)

Table 2 Lead concentration in plasma in smoking and nonsmoking women in the course of pregnancy

Lead concentration (μg/dL)					
Gestational age	Smoking ($n=70$)		Nonsmoking ($n=80$)		p value
	Median	First and third quartiles	Median	First and third quartiles	
I Trimester	0.22	0.14–0.40	0.05	0.02–0.11	<0.001
II Trimester	0.21	0.14–0.30	0.04	0.02–0.08	<0.001
III Trimester	0.25	0.17–0.34	0.06	0.02–0.10	<0.001
Entire pregnancy	0.23	0.15–0.35	0.05	0.02–0.10	<0.001

Table 3 Lead concentration in whole blood in smoking and nonsmoking women in the course of pregnancy

Lead concentration (μg/dL)					
Gestational age	Smoking (n=70)		Nonsmoking (n=80)		p value
	Median	First and third quartiles	Median	First and third quartiles	
I Trimester	1.99	1.23–3.22	1.33	0.84–1.85	<0.001
II Trimester	2.01	1.25–2.46	1.30	0.81–1.69	<0.001
III Trimester	2.01	1.56–3.45	1.35	0.93–2.25	<0.001
Entire pregnancy	2.00	1.36–2.99	1.33	0.85–1.90	<0.001

analysis, cotinine concentration did not qualify for final models probably because it has a strong correlation with other factors (for the number of cigarettes/day, r=0.723). The multivariate analysis model estimated for serum lead levels showed only a significant association with the number of cigarettes/day (p=0.014). However, when cotinine level was excluded, the remaining two factors appeared to be significant, with p<0.001 and p=0.001, for the number of cigarettes/day and duration of smoking before conception, respectively (data not shown).

A similar multivariate model estimated for lead in whole blood showed only a significant impact of duration of smoking before conception (p<0.001). The result obtained for the number of cigarettes/day was close to significance level (p=0.054). In the model without cotinine, the number of cigarettes/day and duration of smoking before conception were significant at a level of p=0.001 and p<0.001, respectively (data not shown).

Discussion

Chronic exposure to low doses of lead is increasingly examined in the context of reproductive health. In order to assess personal exposure of pregnant women and their children to lead, the Center for Disease Control (CDC) in Atlanta, USA, developed criteria for interpreting test results, which are now widely used in Poland. Blood lead levels of 10 μg/dL are considered borderline and safe for pregnant women and their children [20, 24]. However, a lead concentration below 5 μg/dL is now regarded to be safe for pregnant women as a result of numerous observations of the negative effects of low doses of lead levels [14, 15, 25]. According to the World Health Organization, blood lead levels of 10–15 μg/dL can cause adverse reproductive outcomes [3].

Research on lead concentration in the blood of pregnant women has been conducted for many years, but the results have been inconclusive. The average concentrations of lead in blood of pregnant women reported by other authors have been presented in Table 5. Our results obtained in the full group of pregnant women without taking into account the duration of addiction to smoking and gestational age were similar to those observed in the population of the US, Brazil, and Sweden and belong to the lowest among the cited research. An important contributory factor to the differences in concentrations of lead among these studies is the differential bioavailability of trace elements due to nutrient–nutrient interaction [18]. Recent research documented that metal bioavailability (particularly in edible plant products) was affected by the metal species, gastrointestinal acidity, and the composition in the stomach and intestine, including inorganic and organic components and digestive enzymes [35, 36]. The relatively low level of lead in the studied group may be due to the fact that all of our patients confirmed consumption of multivitamins containing calcium and iron, and in the course of prevention of neural tube defects were supplemented with folic acid, which can reduce the absorption of lead in the intestinal tract [37]. Similarly to others authors, we observed a decline in blood lead levels between 12 and 20 weeks of gestation, which can be explained by severe fetal organogenesis and decreased concentrations of red blood cells due to the increase in plasma volume during pregnancy. After 20 weeks, blood lead levels rose, peaking in the third trimester [32, 38–40].

Cigarette smoking has been identified as a significant predictor of increased blood lead levels in the general adult population [37, 41–44]. There are several published studies that analyze the association between maternal smoking and its

Table 4 Linear regression analysis examining the relation of log blood lead levels and covariates both in univariate and multivariate models

Independent variable	Plasma lead concentration				Whole blood concentration			
	Univariate model		Multivariate model		Univariate model		Multivariate model	
	β	p value	β	p value	β	p value	β	p value
Number of cigarettes/day	0.337	<0.001	0.238	0.014	0.359	<0.001	0.177	0.054
Duration of smoking before conception (year)	0.269	<0.001	0.142	0.061	0.409	<0.001	0.297	<0.001
Cotinine level	0.291	<0.001	0.051	0.600	0.344	<0.001	0.075	0.424

Table 5 Reported value for concentration of lead (μg/dL) in whole blood of pregnant women

Country	*N*	Lead (μg/dL)	References
Mexico	272	8.90±4.10[a]	Gonzales-Cossio et al. (1997)[26]
Sweden	88	1.14 (0.21–4.76)[b]	Osman et al. (2000)[27]
Canada	160	2.10±1.70[a]	Smargiassi et al. (2002)[28]
USA	140	1.96±0.84[a]	Harville et al. (2005)[12]
Turkey	143	2.80±1.50[a]	Kirel et al. (2005)[29]
Russia	48	5.00±3.00[a]	Eik Anda et al. (2007)[30]
Portugal	182	7.10±2.80[a]	Reis et al. (2007)[31]
France	865	1.90±1.20[a]	Yazbeck et al. (2009)[17]
Nigeria (Lagos)	214	59.50±2.10[a]	Adekunle et al. (2009)[32]
Brazil	120	1.74±0.09[a]	Amaral et al. (2010)[33]
Iran	296	3.69±1.85[a]	Vigeh M et al. (2010)[14]
China	128	5.95±2.27[a]	Jiang et al. (2011)[34]
Saudi Arabia	1,577	2.89±1.85[a]	Al.-Saleh et al. (2011)[11]
Nigeria (Abakaliki)	349	36.37±18.45[a]	Ugwuja et al. (2011)[18]
Poland	150	1.89±1.10[a]	Present study (2013)

N number of studied participants

[a] Mean ± standard deviation (SD)

[b] Median and range

effect on blood lead levels during pregnancy Moreover, the results of these studies were controversial since significant differences were found in some of them [17], while no differences were observed in others [34, 45]. In the presented study, similarly to our previous results, concentrations of blood lead among smokers were significantly higher compared with tobacco abstainers in each trimester of pregnancy [46]. In agreement with Miranda et al. [23], the frequency of lead levels above 2 μg/dL (amounts considered to require observation) was 15–20 % higher in the studied smoking group compared with the nonsmokers. Rhainds and Levallois [2] found a correlation between the daily number of cigarettes smoked by the mother and the concentration of lead in cord blood. The results of the presented study, both in univariate and multivariate analysis, demonstrated a positive relationship of these indicators both in whole blood and in plasma, which confirms the negative impact of smoking on the blood levels of this element. Another important issue is that mothers who stopped smoking during pregnancy had higher concentrations than nonsmoking mothers, which may be a reflection of the release of lead from bones [5, 12, 13]. We have demonstrated the relationship between blood lead concentration and duration of cigarette smoking before conception, which seems to confirm these observations.

Lead concentration both in whole blood and plasma has been used for a more complete characterization of assessment of lead status in pregnant women. Whole blood level has been a generally acceptable biomarker to diagnose lead exposure, but this measurement reflects recent exposure, while the plasma Pb level is probably more relevant to assess health risk [5, 47–49]. Recent studies pointed to the toxic effects of lead, mainly associated with the most rapidly exchangeable fraction (the plasma fraction) which is associated with the harmful effects of Pb [50, 51]. Although 99 % of lead in whole blood is bound to red blood cells, only lead that is available to cross the placenta is derived from lead that is in the free-state in plasma [5, 26, 51]. Chuang et al. [5] showed that exposure to lead in the air, including cigarette smoke, significantly affects its level in the plasma, without affecting its concentration in whole blood. In addition, the authors presented a model which demonstrated a significant contribution of lead from the skeletal system to plasma during pregnancy, a contribution that is independent of the influence of maternal RBC lead [5]. In our study, tobacco smoking influenced lead status both in plasma and in whole blood. However, we found that in plasma at the end of pregnancy when the processes of mobilization of calcium from the bones along with the release of lead was most expressed, the concentration was at the highest value while in whole blood, it did not differ significantly between trimesters. Moreover, we observed the strongest negative correlation between the level of these elements in plasma and parameters of fetal growth. In agreement with Chuang et al. [5], we suggested that plasma lead can be an important biomarker for endogenous and exogenous lead exposure in pregnant women and their fetus.

Maternal smoking during pregnancy and prenatal exposure to chronic low doses were shown to be potentially associated with reduced weight at birth, length, and head circumference [20, 36, 52, 53]. To our knowledge, the present study is the first to assess the association between concentrations of lead in blood of mothers who smoke tobacco during each trimester of pregnancy and birth anthropometric parameters. We found that children of smoking mothers were about 300–400 g smaller than newborns of the tobacco abstinent group. Among all the participants, 5.4 % of newborns had a birth weight below 2,500 g, which was accompanied by the mother's whole blood lead level in excess >4 μg/dL. In our study, comparable to the findings of The Port Pirie cohort study, prenatal lead exposure and birth weight were in an inverse relationship with maternal blood lead values [54]. Negative correlations between plasma maternal lead concentration and newborn length and head circumference seem to confirm the negative effect of this element on fetal growth. An association with occupational lead exposure and birth weight of under 2,500 g was found, but the authors did not directly measure lead levels or control smoking status, which is a common confounding variable [21]. Some clinical data demonstrated that prenatal lead exposure may not affect growth as an isolated factor; the cumulative effects of prenatal and postnatal lead exposure may

affect extrauterine growth [51, 55]. Several investigators observed the influence of blood lead levels on reduced weight at birth in newborns of mothers who drank and smoked during pregnancy. In this case, the effect of both alcohol and tobacco smoking on size at birth could be related to lead toxicity [2, 54]. In our research, all the studied women declared abstinence from alcohol during pregnancy and they were not exposed to an additional source of lead at work.

There is an increasing number of evidence that prenatal exposure to low doses of lead can be a risk factor for many health complications for both mother and child [13–16, 20, 22, 56]. Information on the risk of intrauterine exposure to low doses of lead resulting from smoking during pregnancy may be useful in the practice of gynecology and obstetrics. Our data confirm that lead concentration below 5 μg/dL may be a risk factor affecting lower birth weight, the latter being one of the strongest predictors of neonatal survival, mental impairment, and future health status. It is therefore extremely important to provide educational activities and interventions designed to reduce smoking in the population of pregnant women.

In conclusion, we found that blood lead levels in all three trimesters in the tobacco smoking pregnant women were higher than in the nonsmoking group. The significant relationship between the elevated concentration of this element in the blood and the intensity of cigarette smoking seems to confirm that the increase is a direct result of the inhalation of lead from the smoke. The results of our study also suggest that in smokers, fetal exposure to low doses of lead in utero may be a serious risk factor affecting lower birth weight compared with the tobacco abstinent group.

Acknowledgments This work was supported by a grant from the Ministry of Science and Higher Education—NN 404131536—Warsaw, Poland.

Conflict of interest The authors declare that they have no conflict of interest.

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