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

Magdalena Chelchowska · Jadwiga Ambroszkiewicz · Katarzyna Jablonka-Salach · Joanna Gajewska · Tomasz M. Maciejewski · Ewa Bulska · Teresa Laskowska-Klita · Jerzy Leibschang

Received: 2 June 2013 / Accepted: 26 July 2013 / Published online: 10 August 2013 © The Author(s) 2013. This article is published with open access at Springerlink.com

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 (β=0.238; p<0.05), while in whole blood, it was duration of smoking before conception (β=0.297; 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

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 preecampsia, 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 centrifuged 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 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)\(^a\) | 30.1 (28.4–33.8)\(^a\) |
| 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) | | |
| Number of cigarettes/day | | |
| 8.8±0.47\(^b\) | 8.4±0.50\(^a\) |
| Duration of smoking before conception (year) | | |
| 0 | 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)\(^b\) |

\(^a\)\(p<0.001\)

\(^a\) Values are means±standard error of the mean (SEM);

\(^b\) Values are median and interquartile range (25th–75th percentiles)

The lead concentration in plasma in smoking and nonsmoking women in the course of pregnancy is presented in Table 2.

| Table 2 Lead concentration in plasma in smoking and nonsmoking women in the course of pregnancy |
|-----------------------------------------------|
| Gestational age | Smoking \((n=70)\) | Nonsmoking \((n=80)\) |
|-----------------|----------------|----------------|
| 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

| Gestational age | Smoking (n=70) | Nonsmoking (n=80) | p value |
|-----------------|---------------|------------------|---------|
|                 | Median & 1st | Median & 1st     |         |
|                 | third quartile | third quartile    |         |
| 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 |

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).

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

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.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Bernhard D, Rossmann A, Wick G (2005) Metals in cigarette smoke. IUBMB Life 57:805–809
2. Rhainds M, Levallois P (1997) Effects of maternal cigarette smoking and alcohol consumption on blood lead levels of newborns. Am J Epidemiol 145:250–257
3. World Health Organization (WHO) (1986) Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach. Environ Health Crit, 59, Geneva: WHO
4. Laskowska-Klit A, Chelchowska M, Oltarzewski M, Gajewska J, Ambroszkiewicz J (2010) The effect of tobacco smoking during pregnancy on birth mass on the basis of population study—preliminary results. Przegl Lek 67:830–834
5. Chuang HY, Schwartz J, Gonzales-Cossio T, Cortez Lugo M, Palazuelos A, Hu H, Hernandez-Avila M (2001) Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environ Health Perspect 109:27–32
6. Ernhart CB (1992) A critical review of low-level prenatal lead exposure in the human: effects on the fetus and newborn. Reprod Toxicol 6:9–16
7. Gomaa A, Hu H, Bellinger D, Schwartz J, Tsaih SW, Gonzales-Cossio T, Schnaas L, Peterson K, Arz A, Hernandez-Avila M (2002) Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study. Pediatrics 110:110–118
8. Gulson BL, Mizon KJ, Palmer JM, Korsch MJ, Taylor AJ, Mahaffey KR (2004) Blood lead changes during pregnancy and postpartum with calcium supplementation. Environ Health Perspect 112:1499–1507
9. Kutlu T, Karagozler AA, Gozukara E (2006) Relationship among placental cadmium, lead, zinc, and copper levels in smoking pregnant women. Biol Trace Elem Res 114:7–17
10. Amaya E, Gil F, Freire C, Olmedo P, Fernandez-Rodriguez M, Fernandez MF, Olea N (2013) Placental concentrations of heavy metals in mother–child cohort. Environ Res 120:63–70
11. Al-Saleh I, Shinhari N, Mashhour A, El Din Mohamed G, Rabab A (2011) Heavy metals (lead, cadmium and mercury) in maternal, cord blood and placenta of healthy women. Int J Hyg Environ Heal 214:79–101
12. Harville EW, Hertz-Picciotto I, Schramm M, Watt-Morse M, Chantala K, Osterloh J, Parsons PJ, Rogan W (2005) Factors influencing the difference between maternal and cord blood lead. Occup Environ Med 62:263–269
13. Needleman H (2009) Low level lead exposure: history and discovery. Ann Epidemiol 19:235–238
14. Vige M, Yokoyama K, Shinozaka A, Afshinrokh M, Yunesian M (2010) Early pregnancy blood lead levels and the risk of premature rupture of membranes. Reprod Toxicol 30(3):477–480
15. Vige M, Yokoyama K, Seyedaghdamiri Z, Shinozaka A, Matsukawa T, Chiba M, Yunesian M (2011) Blood lead at currently acceptable levels may cause preterm labour. Occup Environ Med 68(3):231–234
16. Chen XK, Yang Q, Smith G, Krewski D, Walker M, Wen SW (2006) Environmental lead level and pregnancy-induced hypertension. Environ Res 100:424–430
17. Yazbeck C, Thiebaugeorges O, Moreau T, Goua V, Debotte G, Sahaquillo J, Forhan A, Foliguet B, Magnin G, Slama R, Charles M, Huel G (2009) Maternal blood lead levels and pregnancy-induced hypertension: The EDEN cohort study. Environ Health Perspect 117:1526–1530
18. El U, Ejikembe B, Obuna JA (2011) Impact of elevated prenatal blood lead on trace element status and pregnancy outcomes in occupationally non-exposed woman. Int J Occup Environ Med 2(3):143–156
19. Jelliffe-Pawlosski LL, Miles SQ, Courtney JG, Materna B, Charlton F (2006) Effect of magnitude and timing of maternal pregnancy blood lead (Pb) levels on birth outcomes. J Perinatol 26:154–162
20. Bellinger DC (2005) Teratogen update: lead and pregnancy. Birth Defects Res A Clin Mol Teratol 73:409–420
21. Gardella C (2001) Lead exposure in pregnancy: a review of literature and argument for routine prenatal screening. Obstet Gynecol Surv 56:231–238
22. Vige M, Saito H, Savada S (2011) Lead exposure in female workers who are pregnant or childbearing age. Ind Heal 49:255–261
23. Miranda M, Edwards S, Swamy G, Paul C, Neelon B (2010) Blood lead levels among pregnant women: historical versus contemporaneous exposures. Int J Res Public Health 7:1508–1519

24. Centers of Disease Control and Prevention (2010) Preventing lead poisoning in young children. Atlanta. http://www.cdc.gov/exposurereport/

(Accessed August 2010)

25. Nedelman HL, Landrigan PJ (2004) What level of lead in blood is toxic for a child. Am J Public Health 94:8

26. Gonzales-Cosio T, Peterson KE, Sanin LH, Fishbein E, Palazuelos E, Aro A, Hernandez-Avila M, Hu H (1997) Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics 100:856–862

27. Osman K, Akesson A, Berglund M, Bremme K, Schutz A, Ask K, Valter M (2000) Toxic and essential elements in placental from Swedish women. Clin Biochem 33:131–138

28. Smargiassi A, Taekser L, Masse A, Sergerie M, Merger D, St-Amour C, Blot P, Hellier G, Huel G (2002) A comparative study of manganese and lead levels in human umbilical cords and maternal blood from two urban centers exposed to different gasoline additives. Sci Total Environ 290:154–157

29. Kirel B, Aksett MA, Bulut H (2005) Blood lead levels of maternal–cord pairs, children and adults who live in a central urban area in Turkey. Turk J Pediatr 47:125–131

30. Eik Anda E, Nieboer E, Dudarev AA, Sandanger TM, Odland JO Kirel B, Aksit MA, Bulut H (2005) Blood lead levels of maternal–cord pairs, children and adults who live in a central urban area in Turkey. Turk J Pediatr 47:125–131

31. Reis MF, Sampaio C, Brantes A, Aniceto P, Melim M, Cardoso M, Gabriel C, Simão F, Segurodo S, Miguel JP (2007) Human exposure to heavy metals in the vicinity of Portuguese solid waste incinerators—Part 2: biomonitoring of lead in maternal and umbilical cord blood. J Hgy Environ Heal 210:447–454

32. Audekunle IM, Ogundele A, Oguntoke O, Akinloye OA (2010) Assessment of blood and urine lead levels of some pregnant women residing in Lagos, Nigeria. Environ Monit Assess 170:467–474

33. Amaral JH, Rezende VB, Quintana SM, Gerlach RF, Barbosa F Jr, Tanus-Santos JE (2010) The relationship between blood and serum lead levels in peripartum women and their respective umbilical cords. Basic Clin Pharmacol Toxicol 107:971–975

34. Jiang Y, Wang H, Chen J, Zhang G, Chen L, Dai W, Zhou W, Yang H, Shi H (2011) Blood lead levels during different trimesters of pregnancy and the possible influencing factors in Chengdu, China. Bio Trace Elem Res 144:27–35

35. Li SX, Lin LX, Zheng FY, Wang QX (2011) Metal bioavailability and risk assessment from edible brown alga Laminaria japonica, using biomimetic digestion and absorption system and determination by ICP-MS. J Agric Food Chem 59:822–828

36. Zheng FY, Chen LH, Li SX, Qiu YQ (2013) Effect of edible plants combination on mineral bioaccessibility and bioavailability, using in vitro digestion and liposome-affinity extraction. Food Res Int 53:174–179

37. Lee MG, Chun OK, Song WO (2005) Determinants of the blood lead level of US women of reproductive age. J Am Coll Nutr 24:1–9

38. Rothenberg SJ, Karchmer S, Schnaas L, Perroni E, Zea F, Fernandez AJ (1994) Changes in serial blood lead levels during pregnancy. Environ Health Perspect 102:876–880

39. Hertz-Picciotto I, Schramm M, Watt-Morse M, Chantala K, Anderson J, Osterloh J (2000) Patterns and determinants of blood lead during pregnancy. Am J Epidemiol 152:829–837

40. Ademuyiwa O, Arowolo T, Ojo DA, Odukoya O, Yusuf AA, Akinhamini TF (2002) Lead levels in blood and urine of some residents of Abeokuta, Nigeria. Trace Elem Electron 19:63–69

41. Gonzales-Estecha M, Trasobares E, Fuentes M, Martinez MJ, Cano S, Vergara N, Gaspar MJ, Gonzalez-Revalderie J et al (2011) Blood lead and cadmium levels in a six hospital employee population. PESA study 2009. J Trace Elem Med Biol 25S:S22–S29

42. Jangid AP, John PJ, Yadav D, Mishra S, Sharma P (2012) Impact of chronic lead exposure on selected biological markers. Ind J Clin Biochem 27(1):83–89

43. Massadeh A, Gharibeh A, Omari K, Al-Momani I, Alomari A, Tumah H, Hayajneh W (2010) Simultaneous determination of Cd, Pb, Cu, Zn, and Se in human blood of Jordanian smokers by ICP-OES. Biol Trace Elem Res 133:1–11

44. Mannino DM, Homa DM, Matte T, Hernandez-Avila M (2005) Active and passive smoking and blood lead levels in U.S. adults: data from Third National Health and Nutrition Examination Survey. Nicotine Tob Res 4:557–564

45. Llop S, Aguinagalde X, Vioque J, Ibarués J, Guexens M, Casas M, Murcia M, Ruiz M, Amurrio A, Rebagliato M, Marina LS, Fernandez-Somoano A, Tardon A, Ballester F (2011) Prenatal exposure to lead in cord: blood lead levels and associated factors. Sci Total Environ 409:2298–2305

46. Chelchowska M, Gajewska J, Ambroszkiewicz J, Laskowska-Klima T, Bulska E, Leibschang J, Szymbanski M, Barciszewski J (2010) The influence of lead on concentration of the pregnancy-associated plasma protein A (PAPP-A) in pregnant women smoking tobacco—preliminary study. Przegl Lek 65:470–473

47. Barbosa F Jr, Tanus-Santos JE, Gerlach RF, Parsons PJ (2005) A critical review of biomarkers used for monitoring human exposure to lead: advantages, limitations, and future needs. Environ Health Perspect 113:1669–1674

48. Smith D, Hernandez-Avila M, Tellez-Rojo MM, Mercado A, Hu H (2002) The relationship between lead in plasma and whole blood in women. Environ Health Perspect 110:263–268

49. Montenegro MF, Barbosa F Jr, Tanus-Santos JE (2008) Assessment of how pregnancy modifies plasma/whole blood lead ratio in ALAD 1–1 genotype women. Basic Clin Pharmacol Toxicol 102:347–351

50. Hu H, Rothenberg S, Schwartz BS (2007) The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ Health Perspect 115:455–462

51. Hu H, Tellez-Rojo MM, Belfinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, Schwartz J, Schnaas I, Mercado-Garcia A, Hernandez-Avila M (2006) Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect 114:1730–1735

52. Król M, Florek E, Piekoszewski W, Bokiniec R, Kornacka MK (2012) The impact of intrauterine tobacco exposure on cerebral mass of the neonate based on the measurement of head circumference. Brain Behav 2(3):243–248

53. Zhu M, Fitzgerald EF, Gelberg KH, Lin S, Durschel C (2010) Maternal low-level lead exposure and fetal growth. Environ Health Perspect 118:1471–1475

54. Baghurst PA, McMichael AJ, Vimpani GV, Robertson EF, Clark PD, Wigg NR (1987) Determinants of lead concentration in cord blood and umbilical cord. Environ Health Perspect 1475–1519

55. Sluka R, Bomschein RL, Dietrich KN, Buncher CR, Berger OG, Hammond PB, Sucop PA (1989) Fetal and infant lead exposure: effects on growth in stature. Pediatrics 84:604–612

56. Wells EM, Navas-Acien A, Herbstman JB, Apelberg BJ, Silbergeld EK, Caldwell KL, Jones RL, Halden RU, Witter FR, Goldman LR (2011) Low-level lead exposure and elevations in blood pressure during pregnancy. Environ Health Perspect 119:664–669