Original Article

Indian Journal of Forensic Medicine and Pathology
Volume 12 Number 3, July - September 2019
DOI: http://dx.doi.org/10.21088/ijfmp.0974.3383.12319.15

Impact of Zinc on Birth and Placental Weight in Cadmium and Lead Exposure during Pregnancy

Vugar Ali Turksoy[1], Ethem Serdar Yalvac[2], Ozlem Tanın Simsek[3], Vusale Aziz[4], Serhat Kocoglu[5], Engin Tutkun[6], Bhoopendra Singh[7]

Abstract

Background: Exposure to toxic metals in the prenatal period may have a negative impact on birth weight and placental weight (BW/PW). Low birth weight is an important etiological factor for chronic diseases in advanced ages. The levels of essential elements are also important for healthy progress of pregnancy, but abnormal levels may be harmful, such as excessive zinc (Zn) in the body increases BW/PW. Placental tissue directly provides information to clinician about maternal and foetal exposure. *Aims:* To investigate the impact of cadmium (Cd), lead (Pb) and zinc (Zn) levels on birth weight. *Methods:* This study involved the measurement of metal levels in 150 participants by inductively coupled plasma mass spectrometry (ICP-MS). *Results:* There were positive significant correlations with BW/PW ratio and gestational age (r=0.205, p = 0.012), number of births (r=0.182, p = 0.025), birth weight (r=0.505, p<0.001), and birth size (r=0.296, p < 0.001). Maternal blood Cd levels positively correlated with placental weight (r=0.256, p=0.002) and negatively correlated with BW/PW ratio (r=-0.188 p = 0.021). Foetal placenta Pb levels were positively correlated with BW/PW ratio (r=0.198, p=0.015). Differences between maternal and foetal placenta Zn levels were found to be statistically significant (23.90 ± 3.26 and 25.50 ± 4.69, respectively, p < 0.001). Furthermore, Zn maternal levels of healthy births were found to be statistically different (p = 0.014) when compared with pregnancies with curettages and stillbirths. *Conclusion:* The findings are consistent with the hypothesis that increased Pb and Cd levels in pregnancy results in a low birth weight and these effects cannot be reversed by Zn, the levels of which are positive related with healthy births. Environmental heavy metal exposure in pregnancy should be routinely examined for baby health.

Keywords: Prenatal Care; Stillbirth; Heavy Metals; Zinc supplementation; Birth Weight.

How to cite this article:

Vugar Ali Turksoy, Ethem Serdar Yalvac, Ozlem Tanın Simsek *et al.* Impact of Zinc on Birth and Placental Weight in Cadmium and Lead Exposure during Pregnancy. Indian J Forensic Med Pathol. 2019;12(3):246-254.

Introduction

Exposure to toxic metals such as cadmium (Cd) and lead (Pb) in the prenatal period may cause several adverse birth outcomes. Low birth weight has become one of the major risk factors for global disease burden and is known to be associated with coronary heart disease, stroke, hypertension, and non-insulin dependent diabetes mellitus in adulthood.[1,2]

The main routes of human exposure to metals are the ingestion and inhalation of contaminated dust and food, as these toxic metals easily contaminate the food chain, accumulating in different target organs, including the placenta and can cause many deleterious effects on foetus development.[3,4,5] Lead exposure primarily affects the central nervous system development, causing irreversible damage[3] and Cd has developmental toxic effects in the prenatal period.[6,7] Although the placenta acts as a protective and preventive barrier for toxic materials, it is well known that most heavy metals, including Cd and Pb, readily cross it, especially in severe exposure.[8] The adverse effects of these metals

Authors Affiliation: [1]Assistant Professor [6]Associate Professor, Department of Public Health, [2]Professor [3]Consultant, Department of Obstetrics and Gynecology, Faculty of Medicine, Bozok University, Yozgat, Turkey. [4]Consultant, Department of Obstetrics and Gynecology, Karabuk Education and Research Hospital, Karabuk Turkey. [5]Lecturer, Food Processing Department, Kahramankazan Vocational School, Başkent University, 06980 Ankara, Turkey. [7]Professor cum Toxicologist, Department of Forensic Medicine & Toxicology, Rajendra Institute Medical Sciences, Ranchi, Jharkhand 834009, India.

Corresponding Author: Bhoopendra Singh, Professor cum Toxicologist, Department of Forensic Medicine & Toxicology, Rajendra Institute Medical Sciences, Ranchi, Jharkhand 834009, India.

E-mail: drsinghb@gmail.com

Received on 09.07.2019, **Accepted on** 16.09.2019

can be acute, sub-acute or chronic. Furthermore, intrauterine toxic metal exposure can cause low birth weight of the foetus.[9,10] In contrast, zinc (Zn) is an essential metal for the development of foetal endocrine system as well as foetal growth and is known to have a supportive effect on BW/PW.[11,12] Studies in rats, mice, pigs and sheep indicate that severe Zn deficiency increases foetal death due to abortions or anomalies.[13,14]

Disproportionate BW/PW ratio has been linked to many conditions, including increased risk for cerebral palsy, preeclampsia, low birth weight, preterm or post-term labour and low Apgar scores.[15,16] The placenta has been used as a "non-invasive" tool for the prediction of intrauterine toxicity, so the routine use of placenta was proposed for the monitoring of toxic exposure during gestation.[17] The association between placental histopathologic lesions and adverse birth outcomes are controversial, but in notable studies, placental and maternal stromal vascular lesions and villitis of unknown aetiology (VUE) have been found to be more common.[18,19,20] Toxic metals such as Cd and Pb are ubiquitous and environmentally persistent toxic metals that have been implicated in neurotoxicity, carcinogenesis and obesity, whereas essential metals including Zn may alter these outcomes.[21] This study aimed to investigate the positive effect of Zn on BW/PW ratios of Cd and Pb exposed placentas in the prenatal period and was conducted on birth deliveries in Yozgat Bozok University Hospital in 2017.

Materials and Methods

Study area and design

The present study was conducted at the Department of Obstetrics and Gynaecology, Medical Faculty Yozgat Bozok University, in collaboration with the Science and Technology Application and Research Center (Occupational and Environmental Toxicology Laboratory), Yozgat Bozok University, Bozok. The present study included the women who were identified as pregnant during one calendar year, from July 2017 to December 2017, who were enrolled in the Department of Obstetrics and Gynaecology, Medical Faculty Yozgat Bozok University. In the case of a positive pregnancy test, the women were asked to donate cord blood and placenta tissue sample for future analysis and thereafter were invited to the hospital for further examination.

The study has been approved by the research and ethical review committee at the Yozgat Bozok University, Bozok. Oral and written consents were obtained from the all the women those participated to study.

Exposure assessment

Of the 162 women, 150 were donated samples of cord blood and placenta tissue at the delivery. 45 cord blood samples were excluded from analysis due to coagulation. These cord blood and placenta tissues were used for assessment of Cd, Pb and Zn exposure. Information related to age, body mass index (BMI), socioeconomic status (SES), parity, gestational days, characteristics of their new-borns (birth weight, length, head and chest circumference).

Total 150 biological specimens of placenta and cord blood were collected and precautions were taken to prevent contamination between samples. Cord blood samples were stored at 4°C, and the maternal and foetal parts of the placental tissues were separately labelled and stored at -20°C until further analysis.

Outcomes and covariates

Birth weight and placental weight were measured with electronic or beam scales (brand name – BEURER BY 80, Germany), length with a locally produced wooden length board (accurate to 1 mm), and head and chest circumference with a flexible non stretchable measuring tape (accurate to 1 mm). Gestational age was calculated by subtracting the date for the last menstrual period from the date of birth. The date of last menstrual period was obtained by interviewing the women immediately after identification of pregnancy. For women who had forgotten this date, we used the last menstrual period estimated by ultrasound measurements.

Detailed information about various socio-demographic status, maternal tobacco smoking and betel/tobacco chewing during pregnancy, occupation, habitat etc were collected from patients and their relatives. Gender and other informations are processed in voluntary consent form.

Metal Analyses

Standards and Reagents

Nitric acid (Suprapur®, 65%, Merck) and hydrogen peroxide (Emprove®, 30%, Merck) were used for sample and standard reference material digestion. Ultrapure water (Direct-Q®, Millipore) was used for dilution standard (6020 Cal - Inorganic

Ventures; Denge 24 - Inorganic Ventures; 19E Multi Element Standard - Chem-Lab) and sample preparation.

Materials and Methods

Collected samples were sent to Science and Technology Application and Research Center (Occupational and Environmental Toxicology Laboratory), Yozgat Bozok University, for the measurement of heavy metal and trace element levels using a cold chain procedure. Placenta tissues were stored frozen, after thawing at room temperature, the wet tissues were weighed on a precision scale, then transferred onto a glass table. The surfaces of the glass tray and table were pre-dried at 75°C for 24h in an incubator. Tissue samples collected from the incubator were weighed to determine dry matter using a precision scale and transferred to high temperature resistant microwave Teflon tubes. Dry tissue weights were used in all calculations related to placenta.

All blood and tissue samples were digested by Milestone - Start D - Microwave Digestion System. Briefly, 10 ml of 65% HNO_3 was added to the tissues, acid etching was performed in the microwave and the tissue specimens were transferred to 15 ml polypropylene tubes with a rotary cap. The total volume was adjusted to 10 ml with deionised water.[22] One ml of serum and blood samples was placed in high temperature resistant microwave quartz tubes, before the addition of 2.5 ml HNO_3 (65%) and 0.5 m H_2O_2 (30%). The total volume was adjusted to 10 ml with deionised water in 15 ml polypropylene tube. Samples were stored at 4°C in covered polypropylene prior to analysis.

The metal levels of the samples were determined by inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Scientific brand, Icap Qc model). The operating parameters were set as follows: RF power 1550W, nebuliser gas 0.90L min-1, plasma gas 0.80L min-1, nebuliser pressure 3.03 bar, dwell time 0.01, spray chamber temperature 2.9°C. The sampler probe was washed between injections by rinsing with ultrapure water for 30s, followed by washing with 2% HNO_3 for 45s, then rinsing with ultrapure water for 45s. After the wash steps, the instrument automatically ran the next sample. The instrument was operated in the quantitative mode (linear calibration; R^2>0.99) and the interval of calibration was set at 0.5–1000 µg/l for all elements (^{111}Cd, ^{208}Pb and ^{66}Zn). The limit of detection (LOD) of Pb, Cd and Zn were determined based on the standard deviation of the response and the slope of the calibration curves. The LOD values were calculated for Pb, Cd and Zn and found to be 0.007 µg/l, 0.026 µg/l and 0.321 µg/l, respectively. Sample and standard of measurements were performed in triplicate. The methods were validated with Certified Reference Materials (CRM-Seronorm™ Trace Elements Whole Blood L-2), with CRM measured five times on the same day and on different days, moreover the average of the repeated measurements was used for the validation of the methods, whereby the relative standard deviation (RSD) values did not exceed 5%.

Statistical analysis

The relationship between individual information and outcomes was assessed using the SPSS 20.0 statistical programme. The Pearson test was used to evaluate the correlations among variables. Differences in education levels were analysed by post-hoc (Tukey) test and differences originating in groups by post-hoc (Dunnett) test. Regression analysis was used to understand how BW/PW ratios were related to the blood and tissue metal levels. All tests were considered significant at p<0.05 and p<0.01.

Results

Total 162 women were interviewed for participation in the study but 150 were given consent to include in this study. The main parameters including toxicological and demographic are presented in Table 1. Age of participants, gestational days and number of births were found as 27.89 ± 5.44 year, 269.87 ± 10.31 day and 2.20 ± 0.99 respectively (Table 1). The average birth weight, Neonatal length at birth, Head circumference, Placental weight, and Birth and Placental weight ratio were 3.2 ± 0.44 kg, 49.89 ± 2.22 cm, 34.39 ± 2.0 cm, 0.58 ± 0.07 and 5.59 ± 0.75 respectively. In this study, valuable data related to the permeability of Cd, Pb and Zn through the placenta was also obtained. Differences between maternal and foetal placenta in terms of Zn levels were found to be statistically significant (23.90 ± 3.26 µg/l and 25.50 ± 4.69 µg/l, respectively, p<0.001).

Descriptive statistics of the various socio-

demographic data of this study are shown in Table 2. No birth anomalies were detected and about 96% (n=144) of the total births were over 2.5 kg birth weight. Only 10% of the age groups were classified in the risky group (>35 years) and 82% of the pregnant women lived in urban areas. As shown in SI Table 2, only 6.7% of the pregnant women smoked. In addition, the total number of passive smokers were 31 (20.7%) (Table 2).

Table 1: The descriptive statistics of the study variables

N= 150		Mean	SD	Minimum	Maximum
Age (year)		27.89	5.44	18	45
Gestational age (day)		269.87	10.3	210	294
Number of birth		2.2	0.99	1	5
Placental weight (kg)		0.58	0.070	0.40	0.78
Birth weight (kg)		3.21	0.44	1.8	4.2
Birth weight / Placental weight (BW/PW)		5.59	0.75	3.13	9.83
Neonatal Length at Birth (cm)		49.89	2.22	42	56
Head circumference (cm)		34.39	2	30	53
Zn	Maternal blood (mg/L)	0.83	0.08	0.641	1.13
	Maternal placenta (mg/kg)	23.9	3.26	19.17	38.99
	Fetal placenta (mg/kg)	25.5	4.69	18.51	48.07
	Cord blood (mg/L) (n=105)	0.59	0.17	0.24	1.14
Cd	Maternal blood (ug/L)	0.16	0.53	0	5.86
	Maternal placenta (mg/kg)	0.07	0.1	0	1.01
	Fetal placenta (mg/kg)	0.08	0.1	0	0.55
	Cord blood (ug/L) (n=105)	0.46	0.08	0.11	0.66
Pb	Maternal blood (ug/L)	6.8	10	0	97.4
	Maternal placenta (mg/kg)	0.43	0.85	0	8.49
	Fetal placenta (mg/kg)	0.49	0.91	0.02	7.1
	Cord blood (ug/L) (n=105)	11.7	13.3	3.9	84.8

Table 2: Number and percentage of socio-demographic categorical variables related to pregnancy

n=150		n	%*
Gender (n=153)	Girl	72	47
	Boy	75	49
	Twin (boy)	6	4
Birth weight (kg)	<2.5	6	4
	2.5-4.2	144	96
Presence of anomaly	No	150	100
BW/PW percentile groups	<%10	9	6
	%10-90	82	54.7
	>%90	59	39.3
Gestational age (day)	<259	12	8
	259-294	138	92
Delivery method	Normal	53	35.3
	Cesarean	97	64.7
Zn supplematation	No	32	21.3
	Yes	118	78.7
History of stillbirth, curettage or miscarriage	No	106	70.7
	Yes	44	29.3
Number of birth	1	42	28
	2	54	36
	3	37	24.7
	4 and upper	17	11.3
Age groups	≤35	135	90
	>35	15	10
Mother education status	Secondary School and under	77	51.3
	High School	43	28.7
	University	30	20
Mother's occupation	Riskless occupation (housewife and so on)	128	85.3
	Risky occupation (industry and so on)	22	14.7

Place of residence	Village	27	18
	City	123	82
Vegetable consumption	Rarely	106	70.7
	Everyday	44	29.3
Smoking (mother)	Disuse	140	93.3
	Use	10	6.7
Passive smoking (father)	Disuse	77	51.3
	Use	73	48.7
Passive smoking (mother)	No	119	79.3
	Yes	31	20.7

*Row percentages used

Table 3. Pearson correlations of all continuous variables with BW/PW

n=150	BW/PW	Maternal Blood			Maternal Placenta			Fetal Placenta			Cord Blood***		
		Cd	Pb	Zn	Cd	Pb	Zn	Cd	Pb	Zn	Cd	Pb	Zn
Age (year)	0.028	0.007	0.020	0.008	0.014	-0.034	0.077	0.103	-0.067	-0.072	0.112	0.008	-0.053
Gestational age (day)	0.205 *	0.037	0.009	0.023	-0.048	-0.004	-0.108	0.089	0.034	-0.033	-0.168	0.172	0.175
Number of birth	0.182*	0.006	-0.009	-0.056	-0.073	-0.028	-0.124	0.095	0.019	-0.030	0.065	-0.017	0.081
Placental weight (kg)	-0.392**	0.256**	0.144	-0.113	0.024	-0.007	0.013	-0.017	-0.119	0.030	-0.015	0.016	-0.039
Birth weight (kg)	0.505**	0.001	-0.040	-0.041	-0.033	0.034	-0.104	0.035	0.045	0.028	-0.160	0.157	0.062
Birth size (length) (cm)	0.296**	0.061	0.039	0.083	-0.104	-0.096	-0.033	0.035	-0.004	-0.086	-0.248*	0.265**	0.126
Head circumference (cm)	0.053	-0.019	-0.064	-0.077	-0.100	-0.077	-0.042	-0.033	-0.032	-0.085	-0.437**	0.486**	0.100
BW/PW	1.000	-0.188*	-0.136	0.076	-0.065	0.033	-0.134	0.058	0.198*	-0.003	-0.159	0.175	0.146

*p<0.05, **p<0.01, *Cord Blood (n=105)

Table 4. Impact estimates of BW / PW ratio determinants (multiple regression analysis)

Model (n=150)	Point estimate	95,0% Confidence Interval		Adjusted R-squared*
		Lower Bound	Upper Bound	
Zn MB	0	-0.003	0.003	0,967
Cd MB	0.187	0.058	0.316	
Pb MB	-0.043	-0.117	0.03	
Zn MP	-0.001	-0.009	0.007	
Cd MP	0.04	-0.264	0.343	
Pb MP	-0.002	-0.038	0.035	
Zn FP	-0.001	-0.006	0.004	
Cd FP	-0.14	-0.417	0.137	
Pb FP	0.03	-0.004	0.063	
Gestational age	0.001	-0.001	0.004	
Birth weight	0.002	0.002	0.002	
Birth length	0.016	0.003	0.029	
Head circumference	-0.011	-0.023	0.002	
Placenta weight	-0.011	-0.012	-0.011	

Dependent Variable: BW/PW rate; MP: Maternal Placenta, MB: Maternal Blood, FP: Fetal Placenta; *p<0.001

Significant positive correlations were found between BW/PW ratio of participants and gestational age, number of births, birth length and birth weight levels (r=0.205, p<0.05; r=0.182, p<0.05; r=0.296, p<0.001 and r=0.505, p<0.001, respectively). There was a negative correlation between BW/PW ratio and placental weight levels (r=-0.392, p<0.001) (Table 3). The correlation coefficients BW/PW ratio with Cd, Pb and Zn (maternal blood, maternal placenta and foetal placenta) values are shown in Table 3.

In the present study, Zn maternal levels of healthy births were found to be statistically significant (p=0.014) when compared with pregnancies with curettages and stillbirths. The groups from which the differences originated were determined by the post-hoc (Dunnett) test. The mean foetal placental Zn in the age group 35 years and under was higher than the mean age group of 35 years (p<0.05).

The Impact of estimates of BW / PW ratio determinants (multiple regression analysis) are dipicted in Table 4. The Regression analysis was

performed to explain the relationship between BW/PW ratio and all parameters. BW/PW ratios were divided into three categories as low, normal and high, with values below the 10th percentile categorised as "low", while 10–90 and higher than the 90th percentile were categorised as "normal" and "high", respectively. The total parameters included in the model can explain 96.7% of the BW/PW ratios (p<0.001) (Table 4).

Discussion

Environmental and occupational exposure to heavy metals, such as Pb and Cd are major health problems for human health.[1,23,24,25,26,27,28] Many investigations concluded that toxic metals have negative effects on neonate head circumference, birth weight, and height.[29,30] Pb and Cd are toxic substances of interest in pregnancy due to their teratogenicity[31,32], the toxic metal poisoning of the mother indirectly causes diseases, such as chronic kidney disease, hypertension and neurological complications, in the foetus.[33,34] This is the first study to provide possible effects of Pb, Cd and Zn on the BW/PW in Turkish women who experienced environmental toxic metal exposure.

Zn deficiency has been shown to limit growth in young children and deteriorates foetal growth in animal models.[35,36,37,38] Cd and Pb are common environmental pollutants associated with low birth weight. Some important metals can alleviate exposure, but the data are inconsistent.[39] Zn deficiency is common in the developing world, being prevalent in pregnant women and young children.[40] This is supportive for Zn supplementation during pregnancy and the dose regimen should be revised. Pb and Cd are known to interact with essential metals supplied by foods. Pb replaces Zn on heme enzymes and Cd replaces Zn on proteins synthesis, such as metallothionein. In addition, Pb competitively interferes with divalent cations including Zn[41,43,44,45,46] and low zinc levels have been reported to be consistent with heavy metal levels.[9,41,42] However, no inverse correlation was found in the present study. Low birth weight is considered an important public health problem with a high risk of neonatal mortality and increased chronic diseases in adulthood[47], which supports the need to monitor Pb and Cd levels, and recommend Zn supplementation.

Several studies have discussed the effects of heavy metal exposure during pregnancy on birth weight.[48,49,50,51] In our study, maternal blood Cd levels were positively correlated with placental weight (r=0.256, p=0.002) and negatively correlated with BW/PW ratio (r=-0.188, p=0.021). Foetal placenta Pb levels were positively correlated with BW/PW ratio (r=0.198, p=0.015). As these findings are consistent with gestational diabetes, the etiological role of Cd and Pb exposure and pregnancy should be investigated more extensively for gestational diabetes.[52] Conversely, Dwivedi et al.[10] did not detect a correlation of Pb and Cd levels in maternal venous blood with birth weight. Zhu et al.[49] found that maternal low toxic metal levels, in particular Pb, correlated, but there was no association between low toxic metal levels and gestational day or/and preterm birth. In our study, there was a significant relationship between term/preterm birth and BW/PW ratios (p<0.01). These results provide information for the role of exposure of heavy metals on foetuses and possible health outcomes.

BW/PW ratios were divided into three categories as low, normal and high, with values below the 10th percentile categorised as "low", while 10–90 and higher than the 90th percentile were categorised as "normal" and "high", respectively. A low BW PW ratio is associated with an increased risk of cardiovascular diseases and diabetes in childhood. [53,54]

Maternal blood, maternal placental and foetal placental Cd, Pb and Zn levels were examined according to the categories of BW/PW ratios. Cd levels in the maternal blood among categories were different (F = 6.118, p = 0.003). According to the post-hoc test results, different Cd levels in maternal blood may be a result of a low BW/PW ratio (> 10th percentile). The increased maternal Cd level seems to cause decreased birth weight and foetal growth retardation.[12,21] Our data supports the reversal of the deleterious effects of Pb and Cd exposure, but this should be clarified by further studies of larger groups.

Conclusion

This study assessed the relationship between Pb and Cd levels in pregnant women and low birth weight, presenting data consistent with the hypothesis that increased Pb and Cd levels in pregnancy results in low birth weight and that Zn does not reverse these effects, as there was no correlation between the heavy metal levels and Zn. Pregnant women with high toxic metal levels, low gestational age and low birth weight, as well as high placenta weight had a significantly higher health risk of infants or low BW/PW ratio above the 90th percentile. Therefore, it is recommended that environmental heavy

metal exposure in pregnancy should be routinely examined to protect maternal health and foetal intrauterine healthy development.

Acknowledgements

The study was performed with financial support from the Yozgat Bozok University Project Coordination Implementation and Research Center (Project number: 6602c-TF/17- 103).

Conflict of interest: The authors declare no conflict of interest.

Source of Funding: Institution level.

References

1. Hu H. Exposure to metals. Prim Care. 2000;27: 983–96.
2. World Health Organization. World health report 2002. Reducing Risks, Promoting Healthy Life. Geneva 2002.
3. Yilmaz FM, Yilmaz, H, Tutkun E, *et al.* Serum biochemical markers of central nerve system damage in children with acute elemental mercury intoxication. Clin Toxicol (Phila.) 2014;52(1):32–8.
4. Kirat G. Pb – Zn - Cd accumulator plants grown around the görgü Pb – Zn mine, Yeşilyurt-Malatya, Turkey. Bull Min Res Exp. 2017;155:161–73.
5. Tutkun L, Iritas SB¸ Deniz S, *et al.* TNF-a and IL-6 as biomarkers of impaired lung functions in dimethylacetamide exposure. J Med Biochem 2019;38:1–8.
6. Lin CM, Doyle P, Wang D, *et al.* Does prenatal exposure affect fetal and child growth? Occup Environ Med. 2011;68:641–6.
7. Lin CC, Chen YC, Su FC, *et al.* In utero exposure to environmental lead and manganese and neurodevelopment at 2 years of age. Environ Res. 2013;123:52–7.
8. Caserta D, Graziano A, Lo Monte G, *et al.* Heavy metals and placental fetal-maternal barrier: a mini-review on the major concerns. Eur Rev Med Pharmacol Sci. 2013;17:2198–206.
9. Osman K, Akesson A, Berglund M, *et al.* Toxic and essential elements in placentas of Swedish women. Clin Biochem. 2000;33:131–8.
10. Dwivedi D, Jain M, Jain S. An association between maternal lead and cadmium levels and birth weight of the babies in North Indian population. J Obstet Gynecol. 2013;3:331–6.
11. Jyotsna S, Amit A, Kumar A. Study of serum zinc in low birth weight neonates and its relation with maternal zinc. J Clin Diagn Res. 2015;9:01–03.
12. Sabra S, Malmqvist E, Saborit A, *et al.* Heavy metals exposure levels and their correlation with different clinical forms of fetal growth restriction PLoS One 2017;12:0185645.
13. King JC. Determinants of maternal zinc status during pregnancy. Am J Clin Nutr. 2000;71:1334–43.
14. Aydemir F, Cavdar AO, Soylemez F, *et al.* Plasma zinc levels during pregnancy and its relationship to maternal and neonatal characteristics: a longitudinal study. Biol Trace Elem Res. 2003;91:193–202.
15. Jarvis S, Glinianaia SV, Torrioli MG, *et al.* Cerebral palsy and intrauterine growth in single births: European colaborative study. Lancet. 2003; 362:1106–11.
16. Parker SE, Werler MM. Epidemiology of ischemic placental disease: a focus on preterm gestations. Semin Perinatol. 2014;38:133–8.
17. Iyengar GV, Rapp A. Human placenta as a "dual" biomarker for monitoring fetal and maternal growth with special reference to potentially toxic elements. Part 3: toxic trace elements in placenta and placenta as a biomarker for these elements. Sci Total Environ. 2001;280:221–38.
18. Parra-Saavedra MM, Crovetto F, Triunfo S, *et al.* Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. Placenta. 2013;34:1136–41.
19. Sengupta P, Banerjee R, Nath S, *et al.* Metals and female reproductive toxicity. Human & Experimental Toxicology. 2015;34(7):679–97.
20. Herman HG, Miremberg H, Schreiber L, *et al.* The association between disproportionate birth weight to placental weight ratio, clinical outcome and placental histopathologic lesions. Fetal Diagn Ther. 2016;41:300–306.
21. Vidal AC, Semenova V, Darrah T, *et al.* Maternal cadmium, iron and zinc levels, DNA methylation and birth weight BMC Pharmacol Toxicol. 2015;16:20.
22. Aliyev V, Kayaalti Z, Kaplan B, *et al.* Effect of GST Polymorphisms on As Levels of Placental and Maternal Biological Samples. Paper presented at the 48th Congress of the European Societies of Toxicology, P09-09, Stockholm, Sweden. Toxicol Let. 2012;211–216.
23. Kalcher K, Kern W, Pietsch R. Cadmium and lead in the smoke of a filter cigarette. Sci Total Environ. 1993;128(1):21–35.
24. Mortada WI, Sobh MA, El-Defrawy MM. The exposure to cadmium, lead and mercury from smoking and its impact on renal integrity. Med Sci Monit. 2004;10(3):112–6.
25. Kutlu T, Karagozler AA, Gozukara EM. Relationship among placental cadmium, lead, zinc, and copper levels in smoking pregnant women. Biological Trace Element Research. 2006; 114;(1-3):7–17.

26. Aliyev V, Yalcin S, Kayaalti Z, *et al.* Influence of Smoking on Oxidative Stress, Protein Carbonyl Levels and Biochemical Parameters), Mersin Üniversitesi Sağlık Bilimleri Dergisi. 2009;2(3): 15–20.
27. Buyuksekerci M, Bal C, Alaguney ME, *et al.* Evaluation of folate and vitamin B12 levels in lead exposed workers. Dicle Medical Journal. 2015;42 (3):294–8.
28. Cetintepe SP, Iritas SB, Gunduzoz M, *et al.* Relation Between Lung Dysfunction and Blood Cadmium and Lead Levels Among Welders. Exposure and Health. 2017;1–7.
29. Chedrese PJ, Piasek M, Henson MC. Cadmium as an endocrine disruptor in the reproductive system. Immunol Endocr Metab Agents Med Chem. 2006;6:27–35.
30. Davey JC, Nomikos, AP, Wungjıranirun M, *et al.* Arsenic as an endocrine disruptor: arsenic disrupts retinoic acid receptor- and thyroid hormone receptor-mediated gene regulation and thyroid hormone-mediated amphibian tail metamorphosis. Environ Health Perspect. 2008; 116:165–172.
31. Nashashibi N, Cardamakis E, Bolbos G, *et al.* Investigation of kinetic of lead during pregnancy and lactation. Gynecol Obstet Invest. 1999;48(3):158–62.
32. Esteban-Vasallo MD, Aragones N, Pollan M, *et al.* Mercury, cadmium, and lead levels in human placenta: a systematic review. Environ Health Perspect. 2012;120:1369–77.
33. Rothenberg SJ, Kondrashov V, Manalo M, *et al.* Increases in hypertension and blood pressure during pregnancy with increased bone lead levels. Am J Epidemiol. 2002;156:1079–87.
34. Riess ML, Halm JK. Lead poisoning in an adult: lead mobilization by pregnancy? J Gen Intern Med. 2007;22;1212–15.
35. Caulfield LE, Zavaleta N, Figueroa A, *et al.* Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. J Nutr. 1999;129:1563–8.
36. Osendarp SJ, Van Raaij JM, Arifeen SE, *et al.* A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. Am J Clin Nutr. 2000;71:114–9.
37. Castillo-Dura´ n C, Marı´n VB, Alca´ zar LS, *et al.* Controlled trial of zinc supplementation in Chilean pregnant adolescents. Nutr Res. 2001;21:715–24.
38. Castillo-Duran C, Weisstaub G. Zinc supplementation and growth of the fetus and low birth weight infant, J Nutr. 2003;133:1494–7.
39. Tsikhutsu I. The prevalence of zinc deficiency in low birth weight infants at Kenyatta National Hospital. Theses and Dissertations-College of Health Sciences (CHS). 2004;1.
40. Vahter M. Effects of arsenic on maternal and fetal health. Annu Rev Nutr. 2009;29:381–99.
41. Goyer RA. Toxic and essential metal interactions. Annu Rev Nutr. 1997;17:37–50.
42. Wigle DT, Arbuckle TE, Turner MC, *et al.* Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J Toxicol Environ Health B Crit Rev. 2008;11:373–517.
43. Peixoto NC, Roza T, Flores EM, *et al.* Effects of zinc and cadmium on HgCl2-delta-ALA-D inhibition and Hg levels in tissues of suckling rats. Toxicol Lett. 2003;146:17–25.
44. Peixoto NC, Serafim MA, Flores EM, *et al.* Metallothionein, zinc, and mercury levels in tissues of young rats exposed to zinc and subsequently to mercury. Life Sci. 2007;81:1264–71.
45. Kawano Y, Furukawa Y, Kawano Y, *et al.* Cadmium Chloride Induces the Expression of Metallothionein mRNA by Endometrial Stromal Cells and Amnion-Derived (WISH) Cells. Gynecologic and Obstetric Investigation 2011;71(4):240–244.
46. Mesquita M, Pedroso TF, Oliveira CS, *et al.* Effects of zinc against mercury toxicity in female rats 12 and 48 hours after HgCl2 exposure. EXCLI J. 2016; 15:256–67.
47. Moon CS, Paik JM, Choi CS, *et al.* Lead and cadmium levels in daily foods, blood and urine in children and their mothers in Korea. Int Arch Occup Environ Health. 2003;76:282–88.
48. Rahman A, Vahter M, Smith AH, *et al.* Arsenic exposure during pregnancy and size at birth: a prospective cohort study in Bangladesh. Am J Epidemiol. 2009;169:304–12.
49. Zhu M, Fitzgerald EF, Gelberg KH, *et al.* Maternal low-level lead exposure and fetal growth. Environ Health Perspect. 2010;118:1471–75.
50. Al-Saleh I, Shinwari N, Mashhour A, *et al.* Birth outcome measures and maternal exposure to heavy metals (lead, cadmium and mercury) in Saudi Arabian population. Int J Hyg Environ Health. 2014;217:205–218.
51. Kippler MTF, Gardner R, Rahman A, *et al.* Maternal cadmium exposure during pregnancy and size at birth: A prospective cohort study. Environ Health Perspect. 2012;120:284–9.
52. Ronco AM, Urrutia M, Montenegro M, *et al.* Cadmium exposure during pregnancy reduces birth weight and increases maternal and foetal glucocorticoids. Toxicol Lett. 2009;188(3):186–91.
53. Vandraas KF, Vikanes AV, Støer NC, *et al.* Is hyperemesis gravidarum associated with placental weight and the placental weight-to-birth weight ratio? A population-based Norwegian cohort study. Placenta. 2013;34(11):990–4.