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Low birth weight and lead exposure: An etiological approach

Ozgur Oztan[1], Mehmet Erdem Alaguney[2], Vugar Ali Turksoy[3], Lutfiye Tutkun[1], Serdar Deniz[4], Turkan Ornek[5], Coskun Simsir[5]

[1]HLC Medical Center,Department of Medical Management, Ankara, Turkey
[2]Health Sciences University, Konya Sehir Hospital, Konya, Turkey
[3] Yozgat Bozok University, Department of Public Health,Yozgat, Turkey
[4]Provincial Health Directorate, Malatya, Turkey
[5]Yüksek İhtisas University, Faculty of Medicine, Department of Obstetrics and Gynecologia

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Abstract

Low birth weight (LBW) is a worldwide public health problem as it is the most important cause of infant deaths and contributes significantly to the burden of childhood problems. There are many studies that have investigated the relationship between LBW and lead exposure, but the mechanism underlying lead exposure and increased risk of LBW are still unknown. In our study, we aimed to determine the effect of lead on endothelial dysfunction by investigating the relationship between the severity of exposure, birth weight and methylated arginines in pregnant women. The study was carried with 165 pregnant women. Placental methylated arginines (ADMA, SDMA, L-NMMA), arginine, citrulline, homoarginine cadmium and lead levels were analyzed. Pb level was significantly higher in the 25% and below percentile group compared with other groups. There was a negative correlation between birth weight and Pb levels. A statistically significant correlation was found between Pb and birth length, Cd, ADMA and SDMA. It is possible to say that the underlying mechanism in fetal growth retardation due to lead exposure can be linked to placental endothelial dysfunction.

Keywords: Lead exposure, Low Birth Weight, fetal toxicology, ADMA, SDMA, endothelial dysfunction

Introduction

Low birth weight (LBW) is a conventional term to define the infants whose birth weights are less than 2,500 grams. It is also a worldwide public health problem as it is the most important cause of infant deaths and contributes significantly to the burden of childhood problems [1]. It also has a high economic cost due to both delivery and long-term intensive health care need [2]. LBW also poses on indirect costs as it causes post-traumatic acute stress disorders in mothers requiring treatment [3].

It has been demonstrated in scientific studies that infants born with LBW experience significant health problems, both in acute period and during childhood and even adulthood. Serious health problems such as respiratory distress syndrome (RDS), intraventricular hemorrhage, nosocomial infections, necrotizing enterocolitis, premature retinopathy, bronchopulmonary dysplasia [4-7]. There is also an increased risk for mental health problems, beginning in childhood and extending at later ages [8]. Many adult health problems have been linked to LBW, including obesity and metabolic syndrome, respiratory diseases [9].

The maternal age is a well-known risk factor for LBW. There are also constitutional risk factors including heredity and environmental factors: maternal chronic hypertension, renal diseases, glucose metabolism disorders, and gestational diabetes mellitus, maternal nutrition and chronic respiratory diseases and other disorders that involve hypoxemia [10, 11].

There are many studies that has investigated the relationship between LBW and lead exposure, but the mechanism underlying lead exposure and increased risk of LBW is still unknown [12].

Lead is used in various industries and also is a concern of residential exposure. In 1999, Fletcher et al. found in their study that almost half of the lead exposed women at child-bearing age had occupational lead exposure and 24% were exposed during home renovation, however the cause of the remaining could not be identified [13]. In some cases, pica behavior was a cause of lead

*Corresponding Author: Vugar Ali Turksoy, Department of Public Health, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey
E-mail: v.aliturksoy@bozok.edu.tr; dr.turksoy@gmail.com

exposure in pregnant women [14].

However, take-home exposures may also be a source of lead exposure in pregnant women. Take-home exposure is defined as transferring of lead dust via worker's skin, clothes, etc. to their homes. In the US, NIOSH found out that take-home exposures are a serious health problem [15].

Nitric oxide (NO) is an important mediator of vasodilatation and is generated by enzymatic activities of NO synthases (NOSs). Endothelial NOS (eNOS) is one of the three major isoforms of NOSs. Methylated arginines (N-monomethyl-arginine, L-NMMA; asymmetric dimethylarginine, ADMA; symmetric dimethylarginine-SDMA) are endogenous inhibitors of eNOS catalytic activity and they compete with L-arginine for binding to the catalytic side of NOS [16]. Lead is known to alter NO concentrations and eNOS generation [17,18].

In our study, we aimed to determine the effect of lead on endothelial dysfunction by investigating the relationship between the severity of exposure, birth weight and methylated arginines in pregnant women.

Materials and Methods

Study Population

The study was carried out prospectively between January, 2019-August, 2019 at the Department of Obstetrics and Gynecology, Liv Hospital, Ankara, Turkey. The protocol was approved by the Ethics Committee for Clinical Research of Liv Hospital and an informed consent was taken from all participants and strictly adhered to the Criteria of the Helsinki Declaration.

165 pregnant women were enrolled in this study. The patients who had hypertension, preeclampsia, diabetes, hyper/hypothyroidism, and smokers and food supplement users were excluded from the study. Pregnancies resulting from in vitro fertilization and pregnant women who had intrauterine fetal death and family history of preeclampsia were not included to the study. Birth weights, placental weights, birth heights and head circumference of all newborns were measured. Routine hemoglobin and hematocrit measurements were made before delivery.

Placental samples were taken from each case for placental measurements after delivery. All samples were collected in sterile polypropylene containers and stored at -80oC until analyses.

ADMA, SDMA, L-NMMA, arginine, citrulline and homoarginine analyses

Placental methylated arginines (ADMA, SDMA, L-NMMA), arginine, citrulline and homoarginine were analyzed with LC-MS/MS. Applied Biosystems MDS SCIEX (USA) API 3200 mass spectrometry with positive mode electrospray ionization and Shimadzu LC-20AD system (Japan) with Phenomenex Luna C18 column utilized for optimization and validation analyses [19]. The d7-ADMA used for the internal standard. Each placenta samples entreated with methanol and centrifuged at 13.000 rpm for 10 minutes in the extraction procedure. The supernatant collected and nitrogen gas was used for drying each solution. Extracts entreated with 200 µL of a freshly prepared butanol solution containing 5% (v/v) acetyl chloride and kept at 60°C for 20 minutes. Then this samples dissolved in 100 µL of 90 water- 10 methanol (v/v) containing 0.1% formic acid. The 40 µL injection volumes were used for each samples and standards measurement. 2.7%, 3.9%, 4.2%, 2.1%, 4.0% and 4.1% coefficient of variations (CV) obtained for ADMA, SDMA, L-NMMA, arginine, citrulline and homoarginine methods, respectively.

Cadmium and lead measurements

0.2 gr of each dried placenta samples used for the analyses of the cadmium and lead levels. Each dried samples of the placenta were put into Teflon tubes and digested with Microwave Digestion System (Milestone, USA). Then 5 ml ultrapure water and 5 mL nitric acid (HNO3 65% Suprapure) were added to these tubes. Digested samples transferred to the 50 ml polypropylene tubes and each sample was completed to the 20 mL with ultrapure water [20]. The samples were stored at + 4°C until the analysis with inductively coupled plasma mass spectrometry (ICP-MS, Thermo Scientific ICAP Qc, USA). The operating parameters were set as follows: RF power 1,550 W, nebulizer gas 0.90 L/min, plasma gas 0.80 L/min, nebulizer pressure 3.0 bar, dwell time 0.01, spray chamber temperature 3.2°C. 2% HNO3 used for blank solution. The r2 values of the 11 points calibration curves of cadmium and lead measurements were calculated as 0.9998 and 0.9999, respectively [21]. The Whole Blood Levels-2 (CRM-SeronormTM, Billingstad, Norway) was used for validation of the cadmium and lead methods.

Statistical Analysis

Statistical analyses were performed by using the SPSS version 25.0 statistical software package. The descriptive statistics of continuous variables were expressed as mean ± standard deviation. Kolmogorov Smirnov test was used to determine whether or not they are normally distributed. The values of the variables were found not to distribute normally. For this reason, Kruskal Wallis test was used to compare more than two groups and Spearman Correlation analysis was applied to determine the relationship between parameters.

Results

The study group was divided into 3 groups in terms of birth weights (first group (n=41): 25% and below percentile; second group (n=81): 25-75% percentile; third group (n=43): 75% and over percentile). The study aimed to determine the effect of lead on endothelial dysfunction. At the same time, the study investigated the relationship between the severity of exposure, birth weight and methylated arginines in pregnant women. The percentile values of birth weight are presented in Table 1.

Table 1. Birth weight percentile values

Groups no	Percentiles (%)	Birth weight (gr)
1	25% and below (≤ 25) percentile	2525
2	25-75 percentile	3190
3	75% and over (≥ 75) percentile	3600

Placental weight, birth size, head circumference, hemoglobin values were found to be significantly lower in the 25% and below percentile group compared with those in the other groups ($p < 0.05$). However, Pb level was significantly higher in the 25% and below percentile group compared with other groups ($p < 0.05$). Maternal age, hematocrit, Cd, ADMA, SDMA, arginine, citrulline, homoarginine, L-NMMA, arginine/ADMA, SDMA/ADMA and total methylarginine values were found to be similar in all groups ($p > 0.05$). Averages of variables according to percentiles obtained from birth weight are presented in Table 2.

Table 2. Averages of variables according to percentiles obtained from birth weight

n =165	Birth Weight Percentile Categories *	Mean	S.E.	Median	S.D.	Minimum	Maximum	p
Placental Weight (PW) (gr)	1	503.78	9.24	525	59.18	400	610	<0.001**
	2	571.17	9.02	575	81.16	400	795	
	3	632.56	8.19	630	53.73	535	750	
Birth Length (cm)	1	46.63	0.61	49	3.9	40	50	<0.001**
	2	49	0.45	50	4.04	40	56	
	3	51.3	0.27	51	1.78	48	55	
Head Circumference (cm)	1	33.32	0.15	34	0.96	31	34	<0.001**
	2	33.77	0.12	34	1.11	30	36	
	3	34.56	0.21	34	1.35	33	37	
Hemoglobin (g/dL)	1	11.45	0.33	10.8	2.13	8.2	15	0.019**
	2	12.35	0.14	12.1	1.28	9.9	15.4	
	3	12.28	0.21	12	1.36	9.3	14.7	
Cd (µg/g)	1	0.15	0.07	0.03	0.46	0	2.98	0.468
	2	0.16	0.04	0.06	0.34	0	2.73	
	3	0.15	0.04	0.06	0.27	0	1.09	
Pb (µg/g)	1	0.75	0.09	0.49	0.6	0.01	2	0.037**
	2	0.68	0.09	0.36	0.85	0.01	3.3	
	3	0.66	0.14	0.13	0.92	0.01	3.59	
ADMA (umol/L)	1	0.82	0.05	0.79	0.29	0.06	1.95	0.567
	2	0.85	0.03	0.82	0.27	0.03	1.94	
	3	0.89	0.05	0.79	0.34	0.37	1.93	
SDMA (umol/L)	1	0.99	0.05	1.05	0.31	0.02	1.46	0.717
	2	1.04	0.03	1.05	0.29	0.52	2.41	
	3	1.01	0.03	0.99	0.23	0.61	1.69	
Arginine (umol/L)	1	710.51	42.99	638	275.29	324	1370	0.128
	2	799.65	40.92	694	368.31	327	2620	
	3	699.23	47.22	633	309.66	317	1750	
	2	2	0.04	1.96	0.39	1.04	3.28	
		1.9	0.06	1.92	0.39	1.05	2.69	

*1:≤ 25 percentile; 2:25-75 percentile; 3:≥ 75 percentile; **p<0.05 and p<0.01; S.E. (Standard Error); S.D. (Standard Deviation)

Significant positive correlations were found between birth weight of participants and placental weight, birth length and head circumference levels (r=0.554, p<0.508 and r=0.378; p<0.01, respectively). There was a negative correlation between birth weight and Pb levels (r=-0.212, p<0.01). A statistically significant correlations were found between Pb and birth length (r=-0.276, p<0.01), Cd (r=0.562, p<0.01), ADMA (r=0.235, p<0.01) and SDMA (positive and weak) (r=0.235, p<0.01) (Table 3). Graphs of significant relationships between main parameters are showed in Figure 1 and Figure 2.

Table 3. The correlation relationships of all parameters

n =165	Placental Weight (PW) (gr)	Birth Weight (BW) (gr)	Birth Lenght (cm)	Head Circumference (cm)	Hemoglobin	Hematocrit (%)	Cd (µg/g)	Pb (µg/g)	ADMA (umol/L)	SDMA (umol/L)	Arginine (umol/L)	Citrulline (umol/L)	Homoarginine (umol/L)	L-NMMA (umol/L)	Arginine / ADMA ratio	SDMA / ADMA Ratio	Total methylarginines (umol/L)
Age (years)	-0.047	-0.081	-0.029	-0.052	-0.028	-0.073	0.096	-0.077	0.028	0.132	-0.01	-0.027	0.001	-0.043	0.007	0.1	0.091
Placental Weight (PW) (gr)	1	.554**	.394**	.283**	0.077	0.1	-0.025	-0.126	0.02	0.001	0.046	0.043	-0.003	-0.134	0.026	0.021	0.009
Birth Weight (BW) (gr)		1	.508**	.378**	0.125	0.066	0.051	-.212**	0.024	-0.038	-0.064	0.023	-0.007	-0.126	-0.066	-0.009	-0.051
Birth Lenght (cm)			1	.412**	0.114	0.079	-0.102	-.276**	0.08	-0.09	0.071	0.028	0.073	-0.07	0.057	-0.127	-0.01
Head Circumference (cm)				1	.171*	0.134	0.108	-0.133	0.02	-0.044	-0.075	0.096	0.116	-0.119	-0.078	-0.078	-0.077
Hemoglobin (g/dL)					1	.906**	0.027	-0.11	-0.043	-0.061	0.046	0.043	-0.028	-0.051	0.039	0.005	-0.059
Hematocrit (%)						1	0.021	-0.078	-0.063	-0.061	0.04	0.045	0.001	0.003	0.056	0.026	-0.056
Cd (µg/g)							1	.562**	.280**	.193*	-0.052	0.113	.168*	-0.135	-.211**	-0.089	0.122
Pb (µg/g)								1	.235**	.237**	0.019	0.092	0.111	-0.052	-0.103	-0.026	0.15
ADMA (umol/L)									1	.544**	.306**	.297**	.256**	-0.072	-.323**	-.466**	.689**
SDMA (umol/L)										1	.274**	.185*	.261**	-0.045	-0.043	.392**	.867**
Arginine (umol/L)											1	.432**	.338**	-.278**	.731**	-0.047	.389**
Citrulline (umol/L)												1	.171*	-.205**	.191*	-0.11	.222**
Homoarginine (umol/L)													1	-.256**	.157*	-0.044	.272**
L-NMMA (umol/L)														1	-.221**	0.012	0.065
Arginine / ADMA ratio															1	.313**	-0.065
SDMA / ADMA ratio																1	0.129

Significances: *p<0.05; **p<0.01

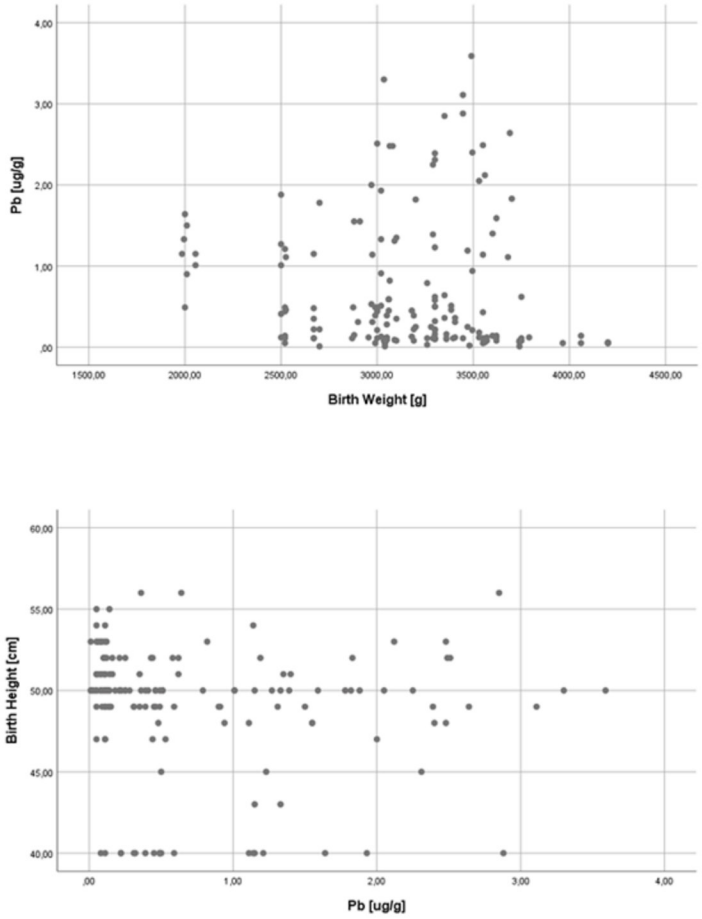

Figure 1. Significant relationships between birth height and weight and Pb levels

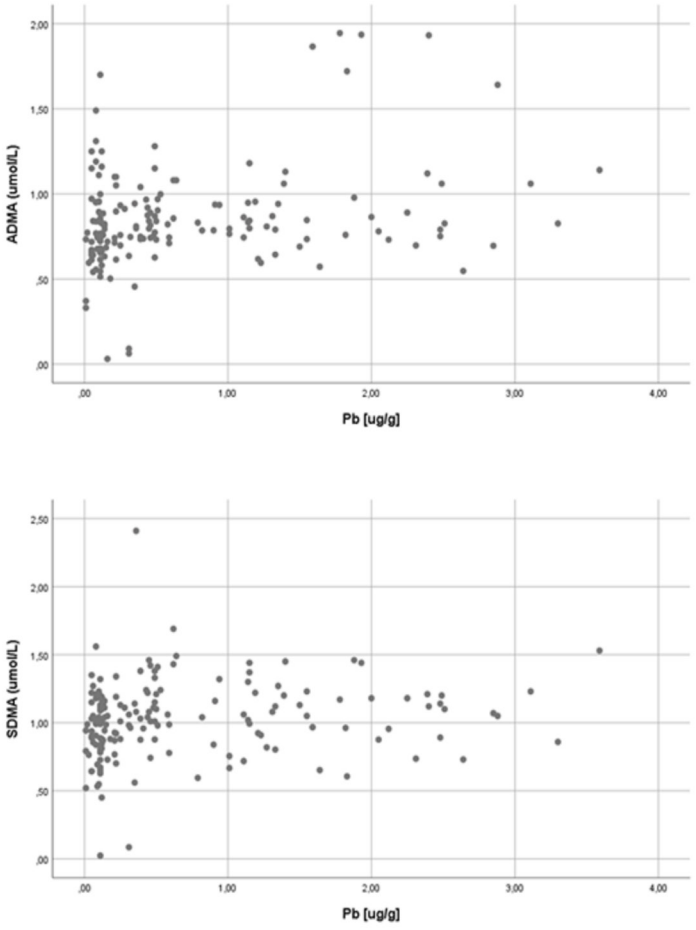

Figure 2. Significant relationships between Pb levels and ADMA and SDMA levels

Discussion

Although the mechanisms of the adverse effects of lead on the cardiovascular system have not been fully understood, there are many scientific studies that support the negative effects of lead on the NO pathway [22]. One of the most important factors for the proper development of the fetus in the intrauterine period is the adequate blood supply of the placenta and its ability to supply the blood necessary for the development of the fetus [23]. Especially in the later stages of pregnancy, this effect increases due to the increasing requirement of the fetus. Placental function has an important effect on the regulation of fetal growth as it provides critical respiratory, hepatic, and renal function of the fetus [24-26]. Abnormal placentation leading to decreased placental perfusion is the pathology most associated with fetal growth retardation [27]. Some placental disorders (detachment, infarction, circumvallate placenta, hemangioma and chorioangioma) and umbilical cord abnormalities (velamentous or marginal cord insertion) have also been associated with fetal growth restriction [28]. However, almost all of these results in a pronounced congenital anomaly or disease. Although they do not cause a significant anomaly, there are also environmental factors known to affect the intrauterine development of the fetus negatively [29].

Since lead is widely used, it is an important risk factor not only for occupational health but also for public health. Many diseases have been found to be related with lead exposure. Although its relations with certain diseases have been partially elucidated, the mechanism of many diseases associated with lead exposure has not been understood, yet. Relationship between prenatal lead exposure and fetal growth is known and has been studied several times. In one study, linear and quantile regression showed a negative association between lead exposure and birthweight, but quantile regression revealed that smaller infants present a more susceptible subpopulation [30]. The effects of lead on bone development have also been known for a long time. In a rat study, although it was found that calcium and phosphorus, which play a role in the development of plaque in intrauterine osteogenesis, were affected by lead exposure, a clear relationship could not be revealed [31]. Although cadmium was found to cause intrauterine growth retardation in some studies, the lack of difference in cadmium levels between the groups in our study ruled out the effect of cadmium, but lead exposure was found to be related to birth weight as expected ($p<0.05$) and this finding is consistent with other studies [32].

ADMA, an endogenous and competitive inhibitor of nitric oxide synthase, is closely associated with impaired endothelium-dependent vasodilatation, impaired blood flow and interfere with angiogenesis and is accepted as a prospective marker of cardiovascular disease and mortality [33-35]. In our previous study 21, we reported the effects of chronic cadmium exposure on methylated arginines, L-arginine homoarginine, and citrulline levels. No relationship was found between Cd and methylated

arginines in this study. However, in our study, a positive and weak relationship was found between ADMA and SDMA levels and lead. Changes in L-arginine, citrulline, homoarginine levels and Arginine/ADMA and SDMA/ADMA ratios were not statistically meaningful. Bassareo et al.found that advanced intrauterine growth restriction is associated with low levels of ADMA in blood levels of pregnant woman [36]. In another study conducted by Laskowska et al., preeclamptic hypertensive and normotensive patients were compared and it was determined that high ADMA blood levels and intrauterine growth retardation were associated in both groups [37]. In all these studies, ADMA, SDMA and arginine levels were measured in the blood of pregnant women. The number of studies investigating the levels of methylated arginine directly from the placenta is very limited, and it is the first study we present in which all parameters are examined in the placenta as far as can be investigated. The only study we have encountered in the literature belongs to Zheng et al., and as a result, ADMA was found to be elevated in placenta tissue in preeclampsia [38].

Conclusion

The clear conclusion from previous studies is that ADMA and SDMA impair effective blood supply by causing endothelial dysfunction. In addition, it is now scientifically proven that lead negatively affects the growth of the fetus during pregnancy. When this information is evaluated together with the data we obtained in our study, it is possible to say that the underlying mechanism in fetal growth retardation due to lead exposure can be linked to placental endothelial dysfunction. The main weakness in our study is the necessity of studying with higher number of severe LBW infants.

It is obvious that the development of our findings in this study with more comprehensive studies will make significant contributions in the follow-up of the intrauterine negative effects of lead exposure.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The protocol of the study was approved by the Ethics Committee for Clinical Research of Liv Hospital (Decision No:12.2020/007).

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