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Does maternal VDR FokI single nucleotide polymorphism have an effect on lead levels of placenta, maternal and cord bloods?

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ABSTRACT

Introduction: Individual susceptibility due to genetic variations appears to be an important factor in lead toxicity. As lead, ubiquitous atmospheric pollutant, behaves very similarly to calcium, gene polymorphisms in proteins involved in calcium homeostasis can affect lead toxicokinetics. Vitamin D receptor (VDR), a DNA-binding transcription factor, activates genes that encode proteins involved in calcium metabolism. Thus, the objective of this study was to determine the effect of maternal VDR FokI polymorphism on lead levels of maternal blood, placental tissue and cord blood.
Methods: The study population comprised 116 women and their respective placenta and umbilical cord. Venous blood samples were drawn from mothers to investigate both the lead levels and VDR FokI polymorphism. Cord blood samples and placentas were collected for lead levels. VDR FokI polymorphism was detected by standard polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) method. Lead levels were analyzed by dual atomic absorption spectrometer system.
Results: Genotype frequencies of VDR FokI polymorphism were 49.2% FF, 44.8% Ff and 6.0% ff. The mean lead levels of maternal blood, placenta and cord blood were 36.76 ± 13.84 μg/L, 12.84 ± 14.47 μg/kg and 25.69 ± 11.12 μg/L, respectively. Maternal blood, placental and cord blood lead levels were found significantly to be higher in mothers with f allele for the VDR FokI polymorphism ($p < 0.05$).
Discussion: The present study indicated that this polymorphism had an effect on maternal and fetal lead levels and that mothers with F allele associated with lower lead concentration may protect their respective fetus against the toxic effects of lead exposure.

1. Introduction

Lead, the 5th most abundant metal in the earth's crust [1,2], is a naturally occurring, ubiquitous atmospheric pollutant and a food contaminant [3,4]. Lead that has been no known nutritive value has serious effects in the nervous, circulatory, skeletal, renal, hematopoietic, and endocrine systems [1]. The severity of these adverse effects depends on the dose, duration and timing of exposure as well as genetic variations influencing susceptibility of humans to lead exposure [2]. Children are more sensitive to the toxic effects of lead, a significant developmental neurotoxicant, than adults [1]. Lead exposure begins at the 21st week of pregnancy and continues throughout the life [5]. During pregnancy, maternal lead can easily across the placenta and blood–brain barrier, and can cause impaired brain function by affecting important developmental processes such as cell proliferation, differentiation, myelination and synaptogenesis by increasing spontaneous release of neurotransmitters and by disrupting the calcium metabolism [4,6]. Lower IQ, reduced frustration tolerance, attention deficit, hyperactivity and weak reaction control are possible neurodevelopmental consequences of lead exposure [7]. Studies demonstrated that intellectual development is reduced in children with history of prenatal lead exposure [8]. The development of cognitive, communication, and social functions can also be affected by pediatric lead exposure [9].

Lead entering the human body via ingestion, inhalation or dermal contact accumulates particularly in the bones since both it has a high affinity to free sulfhydryl groups within bone cells and it

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behaves very similarly to Ca^{2+} that is important for making healthy bones [1,4,10]. It has been proven that inorganic form of lead (Pb^{2+}) is able to enter into various target cells by "ionic mimicry" mechanism according to which the uptake of Pb^{2+} can be mediated by Ca^{2+} channels by mimicking and replacing Ca^{2+} at the site of voltage-insensitive Ca^{2+} channels [1,3]. Although Ca^{2+} and Pb^{2+} carry into cells through one or more same Ca^{2+} channels, there is an inverse relationship between these divalent cations. In numerous in vivo and in vitro models, it was shown that low/high dietary intake of Ca^{2+} can lead to higher/lower levels of Pb^{2+} in blood [11,12]. Thus, in addition to the dose, duration and timing of exposure, the variations in the Ca^{2+} metabolism that interacts with Pb^{2+} will in turn affect Pb^{2+} toxicokinetics [13].

The Ca^{2+} metabolism is primarily regulated by $1\alpha,25(OH)_2D_3$ (1,25D), the active metabolite of steroid hormone vitamin D, by raising the blood levels of calcium and phosphate ions via intestinal absorption and renal reabsorption and by activating bone resorption [14,15]. These biological actions of 1,25D depend on its interaction with the vitamin D receptor (VDR), a DNA-binding transcription factor. VDR is localized in cell nucleus and/or caveolae of the plasma membrane of mainly intestinal epithelial cells, kidney tubular epithelial cells and osteoblasts [14–16]. When 1,25D binds to VDR localized in cell nucleus to generate genomic responses, 1,25D-liganded VDR interacts with its heterodimeric partner retinoid X receptor (RXR) and this 1,25D-VDR-RXR complex can recognize vitamin D responsive elements (VDREs) in the promoter region of vitamin D-regulated genes [14,17]. Among 1,25D-VDR regulated genes, *TRPV6*, $CaBP_{9k}$ and *ATP2B1* encode proteins involving in intestinal Ca^{2+} absorption and transport [14,18]. Thus, genetic alterations of the VDR gene could lead to defects on calcium metabolism by affecting gene activation [19]. Furthermore, in animal studies, it was detected that intestinal Ca^{2+} absorption was impaired in VDR knock-out mice [18].

In humans, VDR protein is encoded by *VDR* gene which is localized on chromosome 12q13.1 and contains six promoter regions (1a to 1f) and eight protein coding exons (2–9) [17,20,21]. *VDR* gene, a quite large gene (>100 kb), has been reported to have 470 known single nucleotide polymorphisms [20]. In different ethnic groups, the frequency and distribution of these SNPs vary [17]. The associations between different VDR polymorphisms such as ApaI, BsmI, TaqI and FokI and some diseases as well as dietary Ca^{2+} absorption have been reported in previous studies [16,22–24]. The effects of VDR polymorphisms on Pb^{2+} levels have also been studied in lead exposed subjects, children and pregnant women by different research groups so far [6,25–28]. However, in our knowledge, there has been no study concerning the effect of maternal VDR FokI polymorphism on the Pb^{2+} levels of all maternal blood, placenta and cord blood. Therefore, the aim of the present study was to investigate VDR FokI polymorphism affecting individuals' susceptibility to lead in 116 healthy women and to compare it to the placental, maternal and cord blood lead levels.

2. Materials and methods

2.1. Study subjects

We studied 116 women coming to the Gynecology Department of Ankara University's Faculty of Medicine, from February to October in 2011. Mothers with gestational ages ≥36 weeks were screened in the hospital and asked to fill out a questionnaire, which included medical and dietary history, as well as data on occupational and potential environmental sources of metal exposure. A small questionnaire used to gather demographic information was also given to women. Only Turkish subjects were included in the study. Healthy, non-smoking, non-anemic mothers living in Ankara for more than 3 years without a history of alcohol, drug use or chronic disease were included in the study. Ineligibility criteria was a medical history of renal failure, diabetes, carcinoma, diagnosed hepatic or cardiovascular diseases that may be related to possible heavy metal accumulation from environmental or occupational exposures [29–32]. Each subject who were eligible for the study provided written informed consent and approval (approval no: 33-730 in 2011) for the use of human subjects was obtained from the institutional ethics committee. Infant characteristics such as gestational age, birth weight, birth length and head circumference were also recorded (Table 1).

2.2. Sample collection

Placenta, maternal and cord blood samples were collected at delivery by cesarean section or spontaneous labor. Sampling was performed in accordance with the principles of the Declaration of Helsinki. Two ml of venous blood sample was drawn from each woman before delivery and from the umbilical cord during delivery into tubes with EDTA and stored at 4 °C. Placentas were collected and placed in a plastic bag immediately after delivery to avoid external metal contamination. Each bag was marked with the subject's identification code and stored in a polyethylene bag at −20 °C in the Ankara University Analytical Toxicology Laboratory.

2.3. Determination of lead levels for placenta, maternal and cord blood samples

Prior to analysis, all placental samples were washed with 0.01% Triton X-100 solution and then 3 times with distilled water in order to prevent any contamination originating from maternal blood and

Table 1
Demographic characteristics of mother–infant pairs.

	Mean ± S.D.	n (%)
Mothers		
Age at birth of infant (years)	29.24 ± 4.98	
Race		
Turkish		116 (100)
Other		0 (0)
Education		
University		60 (51.7)
High school		39 (33.6)
Primary/secondary school		17 (14.7)
Occupation		
Working		72 (62.1)
Not working		44 (37.9)
Number of delivery by mothers		
1		61 (52.6)
2		39 (33.6)
3		12 (10.3)
4		4 (3.5)
Smoking habit		0 (0)
Occupational exposure to lead		0 (0)
Blood lead at delivery (μg/L)	41.33 ± 43.53	
Infants		
Gender		
Male		57 (49.1)
Female		59 (50.9)
Gestational age (weeks)	39w ± 1w0.4d	
Birth weights (kg)	3.25 ± 0.52	
Birth length (cm)	49.38 ± 2.97	
Head circumferences (cm)	35.07 ± 1.42	
Placental weights (g)	632.58 ± 158.36	
Umbilical cord blood lead (μg/L)	25.22 ± 13.22	
Placental lead (μg/kg)	12.84 ± 14.47	

*S.D.: Standard deviation.

mucus. Then, six representative samples were cut from each placenta using titanium tools, excluding the chorionic plate and decidua basalis. Two samples were taken from the center, avoiding the umbilical cord insertion, and four samples were taken from within 3 cm of the outer placental margin between the central region and the periphery. Each sample was dried for 24 h at 75 °C and weighed. Dried placenta samples and 1 ml of blood samples were dissolved in 10 ml of nitric acid in teflon microwave tubes and digested at 800 W and 220 °C for 20 min in a CEM Mars Xpress microwave oven. Afterwards, these digested solutions were diluted with 25 ml deionized water in 50-ml polypropylene tubes and Pb levels of placenta tissues, maternal and cord blood samples were quantified using Varian AA240Z Zeeman Graphite Atomic Absorption Spectrometry (GFAAS). Additionally, the AAS method was validated by evaluating certified reference materials (Seronorm™ Trace Elements Whole Blood Level-2; Ref Number: 201605) with known values. Blood lead levels were given as μg/L and placental lead levels were given as μg/kg.

2.4. Determination of the VDR FokI SNP by the polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) method

Genomic DNA was isolated from 100-μl whole blood samples using a Qiagen QIAamp DNA Mini Kit, according to the manufacturer's instructions.

The VDR FokI located in exon 2 region of the VDR gene was (SNP rs10735810; Gene access number: NM_001017536; Gene ID: 7421) genotyped using PCR RFLP method. In order to screen for the VDR gene FokI polymorphism, a 273-bp fragment was amplified by PCR with the following primers: forward: 5′-GATGCCAGCTGGCCCTGGCACTG-3′ and reverse: 5′- ATGGAAACACCTTGCTTCTTCTCCCTC-3′. Amplification was conducted on a Techne Tc 512 PCR System in a 50-μl reaction mixture containing 200 μM of dNTPs, 10 pmol each of the forward (F) and reverse (R) primers, 1 U of Hot Star Taq DNA polymerase (Qiagen), 10XPCR buffer (Qiagen) and 50 ng of genomic DNA. The PCR cycling conditions consisted of an initial denaturation step at 94 °C for 10 min; 35 cycles of 94 °C for 1 min, 60 °C for 1 min, 72 °C for 1 min; and a final extension step at 72 °C for 5 min. The PCR product (273 bp) was then digested with *FokI* (New England Biolabs, Hertfordshire, UK) and incubated at 37 °C overnight. Digestion of the PCR product by FokI yields fragments that represent the presence of the F allele (273 bp fragment) and the f allele (197 and 76 bp fragments). The undigested and digested polymerase chain reaction products were separated by gel electrophoresis on a 2.5% agarose gel, visualized by ethidium bromide staining under an ultraviolet illuminator, and then scanned and photographed using the Syngene Monitoring System. Digested and undigested PCR products separated using agarose gel electrophoresis were indicated in Fig. 1. Results of RFLP for each variant in 30 randomly selected samples were confirmed by DNA sequencing method using the Big-Dye Terminator Cycle Sequencing Ready Reaction kit on an ABI Prism 3100 Genetic Analyzer. The automated DNA sequencing was employed to confirm the authenticity of the amplified PCR products.

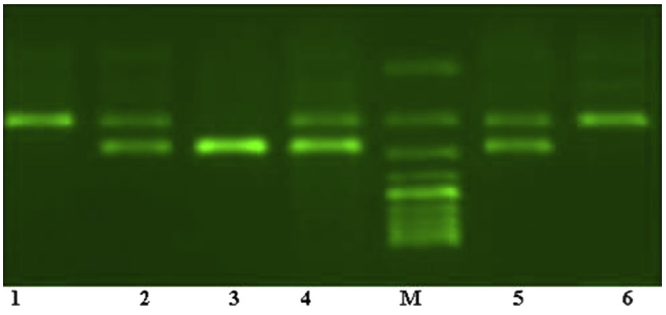

Fig. 1. A represantative agarose gel image of digested PCR products (273 bp) with FokI for VDR FokI polymorphism. M:100 bp ladder; Lanes 1 and 6: homozygote atypical (ff) (197 and 76 bp); Lanes 2, 4 and 5: heterozygote genotype (Ff) (273,197,76 bp); Lane 3: homozygote typical (FF) (273 bp).

2.5. Statistical analyses

The Statistical Package for Social Sciences (SPSS) version 16.0 software for Windows was used for the statistical analyses. The frequencies of VDR FokI alleles and genotypes were obtained by direct count, and the departure from the Hardy–Weinberg equilibrium was evaluated by the χ^2 test. In the exploratory analysis, data showed a normal distribution (by Kolmogorow–Smirnow test); therefore, parametric Student's t-test and One-way ANOVA test were used in order to compare two and more than two independent groups, respectively, in terms of metric variables. One-way ANOVA followed by Bonferroni post-hoc test was also used to locate the origin for any significant difference in placental, maternal and cord blood lead levels between genotypes. Categorical variables were compared by the χ^2 test. Linear regression analysis was used to evaluate the association between variables. Since blood and placental lead levels found to be normally distributed, they were not transformed for regression analysis. Beta coefficients and 95% confidence intervals were calculated and given. Beta coefficients from regression analysis were used to interpret a percent change in placental and umbilical cord blood lead for 1% change in maternal blood lead. Gestational ages, birth weights, birth length, head circumferences, placental weights, parity and socioeconomic status were assessed for potential confounding of the association between maternal blood lead and placental lead or umbilical cord blood lead. Pearson correlation was also used to determine whether there were a correlation between placental and blood lead levels as well as between lead levels and gestational ages, birth weights, birth length, head circumferences and placental weights. Data were shown as mean ± standard deviation (S.D.). $p < 0.05$ was considered as statistically significant.

3. Results

Descriptive characteristics for mothers and infants were given in Table 1. The mean age of 116 healthy mothers was 29.24 ± 4.98 years (ranging from 18 to 41 years). There was no history of occupational exposure to lead or smoking habit in any of the participants. Whole placentas were collected from the mothers who delivered at term neonates (mean gestational ages 39w ± 1w0.4d) with normal birth weights (mean 3.25 ± 0.52 kg), birth length (mean 49.38 ± 2.97 cm), head circumferences (mean 35.07 ± 1.42 cm) and placental weights (mean 632.58 ± 158.36 g). These descriptive characteristics for mothers and infants were compared according to VDR FokI genotypes and no significant difference was found between genotypes ($p > 0.05$).

The distribution of genotypes for the VDR FokI polymorphism showed no deviation from the Hardy–Weinberg equilibrium ($\chi^2 = 1.231$, $p = 0.36$). The VDR FokI genotype frequencies of mothers were determined as; 49.2% FF, 44.8% Ff and 6.0% ff. The allele frequencies for F and f alleles were 71.6% (n = 166) and 28.4% (n = 66), respectively.

The mean placental, maternal and cord blood lead levels were 12.84 ± 14.47 μg/kg, 41.33 ± 43.53 μg/L and 25.22 ± 13.22 μg/L, respectively. Table 2 showed the values of placenta, maternal and cord blood lead levels according to the genotypes for the VDR FokI polymorphism in women. Statistically significant association was

Table 2
Lead concentrations of maternal blood, umbilical cord blood and placenta in relation to the VDR FokI polymorphism.

Pb levels	Genotypes of VDR FokI polymorphism				Compared genotypes	Bonferroni's post hoc test ($p=$)
	FF (n = 57)	Ff (n = 52)	ff (n = 7)	Significance[a] (p =) (one-way ANOVA)		
Maternal blood Pb levels (μg/L)						
Mean ± S.D.	33.52 ± 10.51	38.53 ± 15.24	50.12 ± 18.16		FF:Ff	0.156
Minimum	14.23	15.04	77.20	**0.004**	Ff:ff	0.098
Maximum	52.49	27.11	80.19		FF:ff	0.007
Umbilical cord blood Pb levels (μg/L)						
Mean ± S.D.	22.56 ± 8.49	28.18 ± 12.15	32.64 ± 15.47		FF:Ff	0.022
Minimum	5.79	9.14	21.20	**0.006**	Ff:ff	0.913
Maximum	51.91	54.98	60.63		FF:ff	0.062
Placental tissue Pb levels (μg/kg)						
Mean ± S.D.	9.96 ± 7.00	12.34 ± 7.92	29.11 ± 21.90		FF:Ff	0.488
Minimum	3.31	4.63	8.66	**0.001**	Ff:ff	0.001
Maximum	32.68	34.12	69.15		FF:ff	0.001

[a] Significance values in the table reflect the comparison of lead levels in VDR FokI genotypes.

Table 3
Predicted influence of maternal blood lead on umbilical cord blood lead and placental lead.

VDR FokI genotypes	Maternal blood lead	β-coefficients	95% CI	p-value
FF	Umbilical cord blood lead	0.21	−0.06, 0.59	0.111
	Placental lead	0.25	0.02, 0.76	0.064
Ff + ff	Umbilical cord blood lead	0.63	0.54, 1.06	0.001
	Placental lead	0.43	0.25, 0.91	0.001
Total	Umbilical cord blood lead	0.54	0.47, 0.86	0.001
	Placental lead	0.28	0.14, 0.64	0.003

found between the maternal VDR FokI genotypes and the placental tissue, maternal and cord blood lead levels ($p < 0.05$). As it was seen in Table 2, Bonferroni's Post hoc test showed differences in lead levels of placental, maternal and cord blood comparing subjects with typical genotypes – FF:Ff, Ff:ff, and FF:ff. It was found statistically significant differences in placental lead levels (Ff:ff, $p = 0.001$; FF:ff, $p = 0.001$), in maternal lead levels (FF:ff, $p = 0.007$), and in umbilical cord blood lead levels (FF:Ff, $p = 0.022$).

There were statistically significant and positive correlations between maternal blood and placental lead levels ($r = +0.278$, $p = 0.003$); maternal and umbilical cord blood lead levels ($r = +0.535$, $p = 0.001$); placental and umbilical cord blood lead levels ($r = +0.206$, $p = 0.027$). When placental transfer of lead was investigated by linear regression analysis (Table 3), maternal blood lead was linearly associated with both placental lead ($\beta = 0.28$; CI 0.14, 0.64; $p = 0.003$) and umbilical cord blood lead ($\beta = 0.54$; CI 0.47, 0.86; $p = 0.001$) in all 116 triad of mother–placenta–fetus. When linear regression analysis were repeated according to VDR FokI genotypes, it was detected that a 1% increase in maternal blood lead is predicted to increase placental lead by 0.43% ($\beta = 0.43$; CI 0.25, 0.91; $p = 0.001$) and a 1% increase in maternal blood lead is expected to increase umbilical cord blood lead by 0.63% ($\beta = 0.63$; CI 0.54, 1.06; $p = 0.001$) in infants whose mothers with Ff + ff. However, these associations were not significant among infants born mothers with FF genotype ($p > 0.05$) (Table 3). Also, placental, maternal and cord blood lead levels were not correlated with mothers' age, parity, gestational ages, birth weights, birth length, head circumferences and placental weights ($p > 0.05$).

4. Discussion

Individual susceptibility due to genetic variations appears to be an important factor in lead toxicity in addition to dose, duration and timing of exposure [25]. The most related genes affecting lead toxicokinetics are delta-aminolevulinic acid dehydratase (ALAD) gene, Vitamin D receptor (VDR) gene and human hemochromatosis gene (HFE) [2,33,34]. The genetic polymorphisms in VDR gene are associated with lead toxicity due to the relationship between Ca^{2+} and Pb^{2+}. These metals modify each other's absorption because of having similar biochemical nature as divalent cations. Thus, gene polymorphisms in proteins involved in intestinal calcium absorption would affect Pb^{2+} absorption and toxicity. In the literature, there are a few studies concerning the association between VDR polymorphisms and lead levels in different populations [6,25–28]. Among these previous studies, Pawlas et al. (2012) studied this effect in 175 children and found that VDR FokI polymorphism did not modify the relationship between blood lead and cognitive function in children [26]. In another study, Rezende et al. (2010) examined the effect of three different VDR polymorphisms (FokI, ApaI and BsmI) in 256 healthy pregnant women and detected that these polymorphisms had no effect on blood and serum lead levels, whereas the haplotype combining the f, a, and b alleles for the FokI, ApaI and BsmI polymorphisms, respectively, was associated with lower serum lead level [6]. Haynes et al. (2003) also investigated the association between VDR FokI polymorphism and blood lead concentration in 275 children and determined that VDR FokI modifies this association [28]. On the other hand, the association between VDR FokI gene variants and lead exposure in mother–infant pairs has not been studied so far. Therefore, to the best of our knowledge, this was the first study examining the effect of maternal VDR FokI gene polymorphism on lead levels in a triad of mother–placenta–fetus in a Turkish population.

VDR, a DNA-binding transcription factor, plays a role in the regulation of various genes including *TRPV6*, *CaBP*$_{9k}$ and *ATP2B1* in calcium homeostasis [15,35]. Proteins encoded by these genes involve in the intestinal calcium absorption. Van Cromphaut et al. (2001) detected that the expression of intestinal calcium channels TRPV6 and ATP2B1 is down-regulated in VDR knock-out mice [18]. It was also observed that calcium absorption reduced by 70% due to VDR deletion in growing animals [16], suggesting that intestinal calcium absorption is dependent on VDR-targeted genes. Furthermore, observations that Pb^{2+} enters cells via voltage-insensitive

Ca^{2+} channels [3] and that calbindin D binds Pb^{2+} with high affinity [36] have suggested a relationship between VDR and Pb^{2+} toxicity. In consistent with this suggestion, in the present study, VDR FokI polymorphism was detected to be associated with lead levels in a triad of mother–placenta–fetus.

VDR gene has two potential translation initiation (ATG start codon) sites and the most upstream ATG is used when both are present [37]. VDR FokI polymorphism, also referred to as start codon polymorphism, occurs within the first ATG start codon. The T replaces C at exon 2, within the DNA binding domain, near the 5′ end of the gene, which disrupts the first initiation site and shortens VDR protein by three amino acids [17]. Therefore, f allele for the FokI gene polymorphism produces 427 amino acid hVDR protein, whereas F allele for the FokI gene polymorphism produces 424 amino acid hVDR protein [19,21,38]. Two variant forms of the VDR protein are structurally distinct [38]. Most of the experiments detected that 424 amino acid hVDR (F allele) is more transcriptionally active [16,19,21,24]. Consistently, Huang et al. (2006) compared the absorption of dietary calcium in young women in terms of VDR FokI polymorphism and observed that the Ca^{2+} absorption was higher in women with FF genotype than in women with ff and Ff genotypes [39]. In case of high intestinal Ca^{2+} absorption, Pb^{2+} absorption is expected to decrease because of the inverse relationship between these cations. In the previous studies, it was demonstrated that low dietary calcium resulted in increased lead concentrations in blood and some other tissues [12,36,40]. The reason for this association is a competition between these metals for similar binding sites and transport systems at the intestinal plasma membrane [41,42]. In parallel to these previous observations, in the present study, maternal blood lead levels were found significantly to be lower in women with F allele that is associated with increased calcium absorption. During pregnancy, for increased calcium requirements, both gut calcium absorption increases and renal calcium excretion decreases [43]. In addition to these physiological changes, genetic predisposition also affects the calcium absorption. Thus, it is plausible that intestinal Pb absorption may be lower in women with F allele in comparison to those with f allele since calcium absorption may be high due to F allele of the VDR FokI polymorphism. Beside external lead exposure during pregnancy, lead stored in the mothers' bone prior to pregnancy may also be an internal lead source. Bone turnover increases during pregnancy due to increased demands for calcium and accumulated lead can remove from bone to maternal blood stream. It is likely that less lead may accumulate in the bones of women with F allele due to low Pb absorption prior to pregnancy and, thus, less lead may remove from their bones during pregnancy. Therefore, fetuses of women with F allele may also appear to be more advantageous for exposing less lead through placenta.

Like maternal blood lead levels, both placental and cord blood lead levels was found significantly to be higher in mothers having genotypes with f allele for the VDR FokI polymorphism, indicating that this polymorphism had an effect on fetal lead levels and that mothers with FF genotype associated with lower Pb concentration protects their respective fetus against the toxic effects of lead exposure. The human placenta is the organ which is formed by both maternal and fetal tissues during pregnancy, and brings into close apposition the maternal and fetal blood circulations while separates the two blood systems. It serves as a protective barrier by extruding numerous xenobiotics found in the maternal circulation from fetal-to-maternal direction [44]. In the present study, the detection of higher levels of lead in placental tissue of mothers with ff genotype proposed that these mothers may expose their fetuses to increased lead-associated health risks. Moreover, the detection of more lead in cord blood of women with f allele suggested that more lead may reach fetal circulation by crossing the placental barrier in these mothers. In parallel with this suggestion, maternal blood lead was linearly associated with both placental lead and umbilical cord blood lead in infants whose mothers with having genotypes with f allele. On the other hand, these associations were not significant ($p > 0.05$) and the placental transfer of lead was found to be lower among infants born mothers with FF genotype (Table 3). Taken together, it may be suggested that maternal VDR FokI polymorphism seems to have an effect on transfer of lead from mother to placenta and from placenta to fetus. However, further investigations are necessary with different techniques to improve this hypothesis.

In conclusion, this study indicated that maternal VDR FokI polymorphism had a significant effect on maternal and fetal lead levels. Women with F allele of the VDR FokI polymorphism appear to protect their respective fetuses against the toxic effects of lead exposure.

Disclosure summary

The author has nothing to declare.

Conflict of interest

The author has nothing to declare.

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