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Abstract

The effect of prenatal lead exposure on child development has been a topic of public health concern for decades. To estimate prenatal lead exposure effects on early childhood development, maternal blood ($n = 364$) and umbilical cord blood ($n = 224$) samples were collected during pregnancy and at delivery. Mental development was assessed using the Harold Ireton Early Child Development Inventory from 174 children. Maternal whole blood lead levels in the first trimester were significantly higher in children with developmental scores $<20\%$ than in those with normal scores (mean \pm standard deviation: 6.3 ± 1.9 vs 4.0 ± 2.4 $\mu\text{g}/\text{dL}$, respectively, $P = .01$). Maternal blood lead levels in the first trimester were also inversely associated with the development scores ($r = -0.155$, $P = .041$). Logistic regression analysis showed a significant relationship between increasing maternal blood lead levels in the first trimester with low development scores (odds ratio = 1.74, 95% confidence interval = 1.18-2.57, $P = .005$). The findings of the present study showed a relatively low level of prenatal lead exposure (mean < 6.5 $\mu\text{g}/\text{dL}$) associated with lower developmental scores in early childhood.

Keywords

lead, children, mental development, prenatal, prenatal lead exposure

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For decades, the effect of blood lead on child development has been a topic of concern, and some studies have investigated what blood lead levels should be considered as safe for young children.¹⁻⁴ The US Centers for Disease Control and Prevention have recommended that blood lead level of <5.0 $\mu\text{g}/\text{dL}$ indicates a screening action guideline in pregnant and lactating women.⁵ Many studies have shown the effects of lead exposure on human mental/behavioral development, such as deterioration in recognition, concentration, and learning, at less than the “acceptable” level of blood lead.^{6,7} Pooled analyses by Lanphear et al⁸ and Thacker⁹ identified inverse relationships between prenatal blood lead levels lower than 10.0 $\mu\text{g}/\text{dL}$ and child mental development. However, definitive conclusions regarding the effects of relatively lower levels of blood lead (≤ 5.0 $\mu\text{g}/\text{dL}$) on mental development have not been established yet.

Because the fetal brain is in a state of rapid growth, impairment of later cognitive function can be induced by relatively minor environmental exposure, such as lead and methylmercury, during prenatal life.¹⁰ The inverse association between low levels of prenatal exposure to lead, particularly during early gestation, and neurobehavioral development have been reported in several studies.^{2,11-14} During pregnancy, in addition

to ambient exposure of lead, lead stored in bone, which is released and becomes a potential endogenous source, can contribute to raised blood lead levels.^{15,16} In addition, because clearance of lead from the body is less efficient during prenatal life, this can cause a greater increase in blood lead.⁴ Such increased maternal blood lead can freely cross the placenta and accumulate in the fetus.¹⁷ As a result, because of the sensitive nature of the fetus to toxic substances, lead can induce irreversible effects on neural cells.^{18,19}

Prenatal lead exposure has been evaluated by measurement of maternal blood lead samples during different trimesters of

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pregnancy^{13,20,21} or only at the time of delivery^{22,23} and/or in umbilical cord blood.¹ Only a few studies have measured maternal blood lead periodically from early pregnancy to delivery together with lead in umbilical cord blood. However, the effects of prenatal lead exposure on neurodevelopment remain unclear in terms of consistency and the trimester of greatest vulnerability.²⁴ To address these issues, we conducted a study on the effects of low levels of prenatal lead exposure in mothers and mental development in their children up to 3 years old.

Methods

Study Participants

A longitudinal study was conducted in 3 teaching hospitals affiliated with the Tehran University of Medical Sciences, Tehran, Iran, from October 2006 to March 2011. The study originally consisted of 364 pregnant women who attended ambulatory prenatal clinics in the hospital at the first trimester of pregnancy (gestational age of 8-12 weeks). They were nonsmoking women with singleton pregnancies who were aged 16 to 35 years, and who were free from chronic conditions, such as heart disease, hypertension, diabetes, cancer or renal failure. Mothers' blood (1 sample for each pregnancy trimester, ie, 3 times) and umbilical cord blood samples were collected. Of these 364 pregnant women, 224 mothers had their deliveries at the research hospitals. We invited the mothers and their children to participate in the study when children were up to 36 months old. A full follow-up of 174 infants whose mothers had at least valid measurement of blood lead for the first trimester of pregnancy was performed. The main reason for the attrition of subjects during this period was loss to follow-up with a small percentage of missing data either on outcomes or on relevant covariates. There was not any significant difference in characteristics between loss of follow-up and available subjects except for a higher rate of passive tobacco exposure in the missed group (data not shown).

The study was conducted under the supervision of the Mother, Fetus, and Newborn Research Center, and the Institute of Environmental Research, Tehran University of Medical Sciences. The purpose and procedures of the study were fully explained to participants and the study was conducted with their informed consent. If subjects had difficulties in reading or understanding the written informed consent (ie, less educated or uneducated mothers), an oral explanation was given. Participation in the present study was strictly voluntary.

Development Inventory Content and Evaluation of Children

We assessed mental development of children using the Early Child Development Inventory by Harold Ireton.^{25,26} This is a brief screening inventory and is easy to read and understand regardless of parent/care giver educational level. The Early Child Development Inventory obtains parents' reports of their child's present functioning. They were blinded to their pregnancy blood lead levels and the umbilical cord blood lead levels at the time of survey. The inventory includes 60 short items, among the most age-discriminating items of the Minnesota Child Development Inventory. These items cover several developmental areas, including language comprehension, expressive language, gross motor, self-help, situation comprehension, and personal-social interaction. Validity and reliability of original Minnesota Child Development Inventory²⁷ and Child Development

Inventory by Ireton²⁶ have been evaluated for the preschool child. Mental development of the children, combined of the Early Child Development Inventory 60 items, was evaluated when they were aged up to 36 months by the Persian translation of the Early Child Development Inventory using a standardized protocol. Test-retest reliability over a 4-week period for each item of the Early Child Development Inventory was evaluated in the repeated measures subgroup using the intraclass correlation coefficient in the 3 research hospitals. An intraclass correlation coefficient of ≥ 0.75 for groups and ≥ 0.90 for individual patients was considered acceptable. We found good agreements with criteria at 0.84 and 0.92, respectively. The cutoff point scores for categorization as development delay was a developmental score less than 20% of that expected for children's age (ie, 18-19 mo, 20-21 mo, and so on, with a particular cutoff point score for each age group and sex).

Clinical Assessments

In addition to the Early Child Development Inventory, each mother was given an in-person interview with questions specifically developed for the current study, including inquiries on educational level (high school or above vs lower than high school), passive tobacco exposure (amount of cigarette smoke exposure at home and/or at the workplace per day), medical history (previous or current systemic diseases/any surgery), and self-estimate of annual income (excellent, good, sufficient/middle range, low, and very low). A standard balance beam scale was used and calibrated before each examination with 1-, 5-, and 10-kg weights to the nearest 0.1 kg. Body weight of children and mothers wearing only undergarments was measured. The children's height was measured to the nearest centimeter using a rigid stadiometer, which was also rigorously checked for accuracy. Total pregnancy weight gain (kg) was calculated by subtracting the expectant woman's weight just before delivery, which was obtained at the time of admission for labor, from the participants' pre-gravid weight recorded in their prenatal files up to 3 months before the current pregnancy.

Collection and Analysis of Blood Samples

Using vacuum tubes (Venoject VP-H070K, Terumo, Tokyo, Japan), trained staff collected maternal whole blood samples (1 sample during each pregnancy trimester) from the cubital vein after the completion of interviews and umbilical cord blood at the time of delivery. Blood samples were stored at -70°C and transferred to Japan for blood metal measurement. Blood samples (in 1.0-mL volumes) were weighed and put into perfluoroalkoxy Teflon bottles, and 4 mL of concentrated nitric acid (Ultrapure Grade, Tama Chemicals Co, Kawasaki, Japan) was added to ensure the quality of the samples, which were left overnight at room temperature (18°C - 28°C). The sample mixture was then digested with 0.8 mL of hydrogen peroxide and 0.8 mL of perchloric acid (Ultrapure Grade, Tama Chemicals) using a microwave oven (MLS-1200 MEGA, Milestone SRL, Bergamo, Italy). This process was performed in 5 steps using various power levels set at 250, 0, 400, 650, and 250 W for 6, 1, 6, 6, and 6 minutes, respectively. The volume of the digested sample was then adjusted to 10.0 mL using ultrapure water. After dilution with 0.5% nitric acid solution, subsequent measurements for metal concentrations were performed by inductively coupled plasma-mass spectrometry (ICP-MS, Eran6000, PerkinElmer, Waltham, MA) using a multielement standard solution XSTC-13 (SPEX CertiPrep Inc, Metuchen, NJ). Each measurement was repeated 3 times and the average of the 3 measurements was used

Table 1. Characteristics of the Study Subjects (n = 174).

	No ^a	Mean ± standard deviation	Range
Blood lead levels (µg/dL)			
First trimester	174	4.15 ± 2.43	1.6-20.5
Second trimester	148	3.44 ± 1.28	1.1-7.5
Third trimester	145	3.78 ± 1.40	1.5-8.0
Umbilical cord	150	2.86 ± 1.09	1.2-6.9
Mothers			
Age (y)	173	25.5 ± 4.3	16-35
Weight (kg)	171	63.8 ± 10.9	40-114
Body mass index	169	25.3 ± 3.9	16-34
Pregnancy weight gain (kg)	151	13.8 ± 5.7	1-32
Length of pregnancy (weeks)	149	38.8 ± 1.4	34-41
Passive tobacco exposure	24 (14)		
Education (high school or above)	46 (27)		
Children			
Developmental score	174	54.1 ± 5.4	37-60
Age (mo)	174	29.2 ± 3.7	20-36
Birth weight (g)	147	3257 ± 449	1970-4410
Male sex	82 (47)		
First born	106 (62)		

^aTotal number less than 174 indicates missed data; values within parentheses are percentages of yes answers.

for all subsequent statistical analyses. For instrument calibration throughout the measurements, at least 10% of the analyses were external standards, and 5% were blank (pure water).

Data Analysis

Pearson correlation coefficient was calculated to assess the relationship between prenatal blood lead levels and Early Child Development Inventory scores. Differences in characteristics between children with the developmental scores in the normal range and those with lower scores (less than 20% than expected for children's age and sex) were examined by the Student's *t* test for continuous variables and chi-square test for categorical variables. To examine whether levels of blood lead during pregnancy (first, second, and third trimesters, and in umbilical cord) were independently associated with the risk of lower Early Child Development Inventory scores (as dependent variables of lower [$= 1$] and normal range [$= 0$]), we used a forward stepwise logistic regression analysis. The model adjusted for covariates that might contribute to blood lead concentrations, such as hematocrit,²⁸ and child mental development, such as the maternal educational level,²⁹ body mass index,³⁰ family income level,³¹ completed gestational age,³² birth weight,³³ and first born.²⁹ The Statistical Package for Social Sciences software (SPSS Inc, Chicago, IL) was used for all statistical analyses. A *P* value less than .05 was set as the significance level.

Results

The mean blood lead levels throughout gestation and in umbilical cord were less than acceptable level (<5.0 µg/dL) for pregnant women.⁵ About 1% of blood lead measurement were higher than 10.0 µg/dL. Maternal whole blood lead levels followed a U-shaped pattern over the course of pregnancy, with the lowest levels during the second trimester (mean ± standard deviation = 3.44 ± 1.28 µg/dL) and the highest levels during

the first trimester (4.15 ± 2.43 µg/dL) of pregnancy (Table 1). The mean umbilical cord blood lead levels reached 75% of the maternal whole blood lead levels in the third trimester of gestation (2.86 ± 1.09 µg/dL and 3.78 ± 1.40 µg/dL, respectively).

Eight (5%) children were categorized as having low Early Child Development Inventory scores (less than 20% than expected for children's age and sex) and 166 were within the normal range of scores for their age and sex. Maternal whole blood lead levels in the first trimester were significantly ($P = .01$) higher in children with low development scores (6.31 ± 1.95 µg/dL) than in those with scores in the normal range (4.05 ± 2.40 µg/dL) (Table 2). Almost the same result was found when we compared prenatal blood lead levels among the development scores percentiles (<25 , $25-75$, and >75) (Figure 1). Maternal whole blood lead levels in the first trimester (original values and after withdrawal outliers) were inversely correlated with Early Child Development Inventory scores ($r = -0.150$ and -0.173 , respectively; $P < .05$) (Figure 2). Logistic regression analysis showed significant relationships between increasing maternal whole blood lead levels in the first trimester of pregnancy with a low score of Early Child Development Inventory, adjusting for multiple covariates (odds ratio = 1.74, 95% confidence interval = 1.18-2.57, $P = .005$).

Discussion

The present study showed inverse correlations between maternal whole blood lead levels in the first trimester of pregnancy and deficits in Early Child Development Inventory scores at a relatively low-level blood lead. After controlling for covariates over the follow-up, multiple regression analysis showed about 2 times increase in the risk of relatively lower Early Child Development Inventory scores for each unit elevation

Table 2. Differences in Characteristics Between Children Developmental Scores in the Normal Range and Those With Low Scores.

Continuous variables ^a	Normal range (n = 166)	Low scores (n = 8)	P
Blood lead levels ($\mu\text{g/dL}$)			
First trimester	4.05 \pm 2.40	6.31 \pm 1.95	.01
Second trimester	3.49 \pm 1.27	2.60 \pm 1.20	NS
Third trimester	3.83 \pm 1.38	2.92 \pm 1.57	NS
Umbilical cord	2.87 \pm 1.09	2.69 \pm 1.17	NS
Age (y)	25.4 \pm 4.4	25.5 \pm 1.8	NS
Weight (kg)	63.8 \pm 10.7	62.5 \pm 14.2	NS
Body mass index (kg/m^2)	25.3 \pm 3.9	24.2 \pm 4.0	NS
Pregnancy weight gain (kg)	13.6 \pm 5.4	18.9 \pm 5.1	.020
Length of pregnancy (wk)	38.8 \pm 1.4	38.5 \pm 1.6	NS
Child's birth weight (g)	3251 \pm 453	3410 \pm 337	NS
Age of child (mo)	29.1 \pm 3.7	31.2 \pm 2.4	NS
Categorical variables ^b			
First-born child	102 (61)	4 (50)	NS
Male sex	80 (50)	4 (50)	NS
Education of mother (high school or above)	44 (27)	2 (25)	NS
Passive tobacco exposure during pregnancy	24 (14)	0 (0)	NS
Family income (middle class)	107 (65)	8 (100)	NS

Abbreviation: NS, not significant.

^a Values are mean \pm standard deviation, analyzed by the Student t test.

^b Number of subjects who answered "yes." Percentages are in parentheses, analyzed by the χ^2 test.

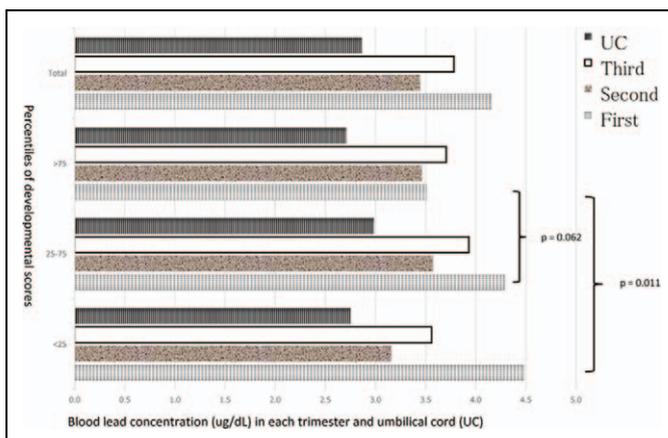


Figure 1. Comparison of prenatal blood lead levels in 3 pregnancy trimesters and umbilical cord with percentiles of development scores.

of prenatal blood lead. The findings of the present study suggest that first-trimester blood lead levels are associated with an adverse neurobehavioral development outcome in early childhood.

This prospective longitudinal study confirmed previous observational results on prenatal lead exposure and childhood neurobehavioral development. Several large studies (>400 children) showed a reduction in the full scale of Intelligence Quotient of approximately 0.5 to 3 points for doubling of blood lead at relatively low levels.³⁴ In a cohort study, Hu et al²⁴ showed an association between increased maternal whole blood lead levels (7.1 $\mu\text{g/dL}$) during the first trimester of pregnancy and a 2.4-point lower Mental Development Index score in children at 24 months of age. Similarly, associations between elevation in maternal whole blood lead

levels in other trimesters than the first trimester of pregnancy and/or umbilical cord blood with children's intellectual development, infants' memory/cognitive functioning, and the Mental Development Index at blood lead levels less than 10.0 $\mu\text{g/dL}$, have been reported.^{13,21,35} In addition, children with elevated blood lead have lower intelligence quotient scores, Stanford-Binet Intelligence Scale scores, and a higher risk for behavioral problems.^{2,36,37} Although many studies have suggested an adverse effect of low levels of prenatal blood lead on young children mental/behavioral development, some studies have failed to show a significant inverse association between prenatal^{22,38,39} and developmental deficits. Therefore, the correlations between relatively low levels of prenatal blood lead exposure and adverse mental development needs to be confirmed in future studies.

Many studies have suggested that a negative correlation between lead and mental development scores follows a dose-dependent pattern. For example, it was shown that a 1.0- $\mu\text{g/dL}$ increase in blood lead levels results in a decrease of approximately 1 point in reading scores with mean blood lead levels lower than 5.0 $\mu\text{g/dL}$.⁴⁰ In addition, a decrease of approximately 8 points in the Mental Development Index for each log unit of prenatal blood lead has been reported.⁴¹ Similarly, blood lead levels of 10 to 30 $\mu\text{g/dL}$ versus 40 to 70 $\mu\text{g/dL}$ diminish general cognitive scores by 94 versus 82, respectively, and verbal scores by 48 versus 41, respectively.⁴² This dose-dependent pattern was also found to be decreased when bone lead levels were examined; a doubling in tibial lead levels diminished full scale, performance, and verbal intelligence quotient by 5.5, 6.2, and 4.1 points, respectively.⁴³

Because most cells in the central nervous system grow and differentiate during the early stage of pregnancy, this period is a potential target for toxic substances, such as lead, and this can

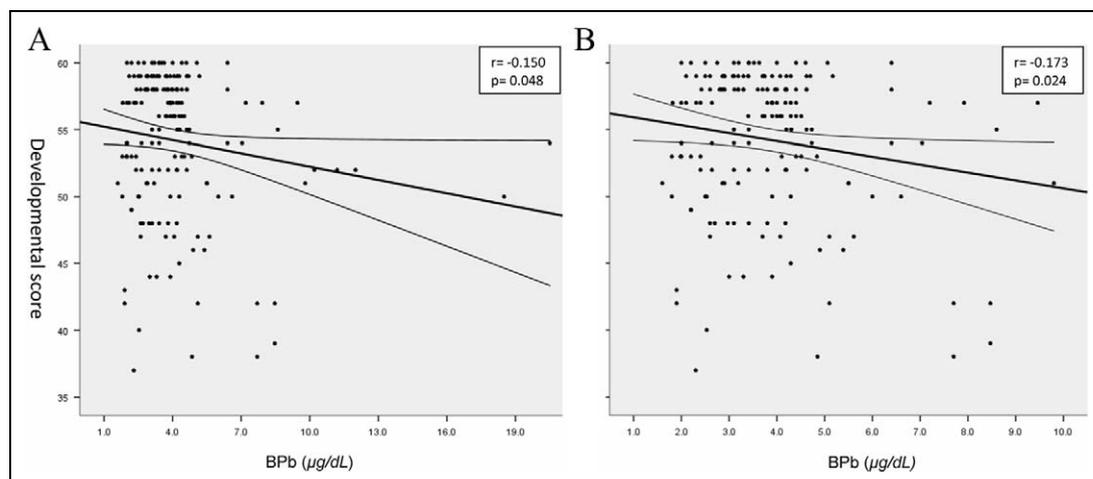


Figure 2. Scatterplot and the best-fit line with 95% confidence intervals of the child developmental score up to 36 months old and maternal whole blood lead (BPb) levels in the first trimester (A) and after withdrawal of a few outlier values (>3 standard deviation above the mean) of whole blood lead level (B); results of Pearson correlation coefficient (r).

affect mental development. Although the underlying mechanism is not clearly understood yet, there are some explanations regarding the neurotoxicity of lead. First, lead disrupts neural cell differentiation and/or neural cell myelination.^{10,44-46} Second, lead can decrease the number of synapses and changing the synaptic parameters, such as the thickness of postsynaptic density, synaptic curvature, and the width of the synaptic active zone.⁴⁷ Disruption of the “tuning” or “matching” process results in a nervous system that appears grossly normal but in which the connections are “poorly chosen.”^{46,48} Third, lead can cause a significant decline in the function of central nervous system electrophysiology¹¹ or can induce dysfunction in adenylyl cyclase activity.⁴⁹

Prenatal lead exposure has been evaluated by measurement of lead in umbilical cord blood,^{1,50} 1 or more measurements of maternal whole blood during different pregnancy stages,^{13,20,21,51-54} or only in maternal whole blood at the time of delivery.^{22,23} In contrast, we collected blood samples and measured prenatal lead levels systematically during specific pregnancy periods (between 8 and 12 and between 20 and 24 weeks of gestation, at delivery, and in umbilical cord blood). However, there are some limitations to the current study. First, a common problem in such a longitudinal study is the high rate of subject loss during follow-up. From an original sample of 364 pregnant women who were recruited in the first trimester of gestation, we assessed mental development in 174 children. Second, our results were limited by lack of information on potential confounders, such as the Home Observation for Measurement of the Environment and the parents’ intelligence score. However, the parents’ educational level was considered as surrogate for their intelligence and home environment. Third, the present study might have involved an inappropriate sampling method, because of recruitment of only women who were free from chronic conditions and non-smokers with singleton pregnancies. Therefore, our results might not be a good representation of the general population. Fourth,

although the children were at good health at the time of developmental evaluation, we did not know about mental and/or general health of missed cases. However, there was not a significant difference in blood lead levels and other major characteristics between 2 groups of children. Fifth, because more than 99% of whole blood lead is bound to red blood cells (Hu 2006) and might not freely cross the placenta to affect fetal brain, the current survey could have measured lead concentrations in the maternal plasma as well. Finally, the sample size of children with low scores in the Early Child Development Inventory was relatively small ($n = 8$), which could have limited statistical power available to detect meaningful differences, particularly in multivariable models controlling for covariates.

Previous studies and the present study results showed an inverse relationship between prenatal lead exposure and early childhood mental/behavioral development.^{24,55} Therefore, lead exposure protection or screening programs for high-risk women, such as female workers in the lead-related industries, should be considered no later than the first trimester of pregnancy to prevent fetal neurotoxic effects, because later intervention might not be sufficient to prevent neurologic damage.

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Author Contributions

MV and KY together were responsible for conception and design, statistical analysis and interpretation of data, and for drafting the article and revising it critically for important intellectual content. TM, AS, and KO were involved in data acquisition and blood sample lead measurement. All authors approved the final version for publication.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The Ethical Committees for the Vice-Chancellor of the Research Department and Institutional Review Board of Tehran University of Medical Sciences approved the study design and procedures (S89P/193).

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