Early pregnancy blood lead levels and the risk of premature rupture of the membranes

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Abstract

To clarify the effects of lead on fetal premature rupture of the membranes (PROM), blood lead concentrations were measured using inductively coupled plasma-mass spectrometry in 332 women, aged 16–35 years, during their early pregnancy period (8–12 weeks). Blood lead concentrations were significantly higher in the 36 PROM deliveries than in the 296 non-PROM deliveries (mean ± SD, 4.61 ± 2.37 and 3.69 ± 1.85 μg/dl, respectively; p < 0.05). The logistic regression analysis revealed that a 1-unit increase in the logarithm of the blood lead level led to a several-fold increase in the risk of PROM (unit risk = 17.98, 95% CI 1.6–198.6). Thus, it is suggested that lead can increase the risk of PROM in pregnant women with mean blood lead less than 5 μg/dl.

1. Introduction

Many studies have focused on the health effects of low blood lead levels after the exposure amount decreased sharply in the past decades [1,2]. For instance, adverse health effects and reproductive system disorders, such as pregnancy hypertension [3–5], infertility, miscarriage, spontaneous abortion, preterm delivery [6,7], premature rupture of the membranes (PROM) [8], and delay in child development [9], have been reported at ‘acceptable’ blood lead levels (≤10 μg/dl). During pregnancy, in addition to ambient exposure, lead stored in bone is a potential endogenous source that can contribute to increasing blood lead [10,11]. The mobilized lead can freely cross the placenta, affecting the fetus [12]. As a result, due to the sensitive nature of the fetus to toxic substances, elevation and accumulation of lead may induce irreversible disorders such as mental retardation and birth malformations [13,14].

Consequently with uterine contractions and cervical dilatation, rupture of the fetal membranes occurs after the onset of labor. In spite of advances in perinatal care, a high incidence of PROM remains. PROM is a major cause (up to 30%) of preterm birth and, as a result, a contributing factor to the high infant mortality rate and long-term handicap in surviving infants, which should not be minimized in any program to protect women and their children [15,16]. This pregnancy complication occurs in approximately 10% of deliveries, i.e., 120,000–250,000 deliveries in the United States annually [15–18]. An epidemiological study in Iran reported a PROM incidence of 7% for women living in Tehran during 2001 and 2002 [19].

Although the cause(s) of PROM is a subject of controversy, previous studies indicated that PROM may be related to infection, pregnancy hypertension, multiple pregnancy, intrauterine growth restriction, maternal stress, heavy physical work, and smoking [20,21]. Moreover, environmental pollutants such as lead may increase the PROM risk in exposed women [6]. Many studies have been conducted on lead exposure and reproductive disorders, but only a few focused on lead and PROM risk. The present study aimed to clarify the relationship between lead levels measured in early pregnancy and PROM risk in apparently healthy women.

2. Subjects and methods

2.1. Subjects

The study was conducted in three teaching hospitals affiliated with Tehran University of Medical Sciences, Tehran, Iran, from October 2006 to March 2008. A total of 482 pregnant women in the first trimester of pregnancy (8–12 weeks) were referred to the hospitals for continuous prenatal care up to delivery during the study recruitment period. Eighty-six of the subjects were disqualified because of
obesity (body mass index (BMI) > 30 kg/m²), cigarette smoking, multiparity (parity > 2), and/or chronic conditions such as heart disease, hypertension, diabetes, cancer, or renal failure. To ensure certainty regarding the subjects’ health status, their complete medical and prenatal records were reviewed. Thirty-two women refused to enter the study, mainly because the procedure required the taking of blood samples. Finally, 364 pregnant women were recruited into the survey, of which 16 cases delivered their babies before the 20th week of gestation (abortion). The blood lead measurements of 12 (3%) and data about PROM for 4 (1%) subjects were not available.

The Ethical Committee under the Vice-chancellor for Research, Tehran University of Medical Sciences, approved the study design and procedure. All subjects were informed verbally of the purpose and procedures of the study, and their participation was on a purely voluntary basis. This study was conducted as joint research that was financially supported by: Tehran University of Medical Sciences, Iran, for study design, data gathering, and blood sampling; a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science via Mie University, Japan, for the biochemical analysis, transportation of blood samples from Iran to Japan, and interpretation of data; and the National Institute of Occupational Safety and Health, Japan, for blood metal measurement and the paper submitting for publication.

2.2. Clinical assessment

A structural questionnaire was filled out for each subject in a face-to-face interview to determine socioeconomic background, anthropometric variables, habits, and medical/obstetric history. The subjects were followed and classified as PROM and non-PROM, which was defined as rupture of amniotic sac more than 1 h before the onset of labor. In the case of follow-up failure, the outcome was obtained by calling the mothers. The mother’s weight (kg) at the time of recruitment was measured by a standard scale, and the BMI was calculated as the weight (kg) divided by the square of the height (m²). Pregnancy weight gain just before the delivery, compared with the pre-gravid weight, was calculated.

2.3. Collection and analysis of blood samples

Blood samples were collected from the cubital vein using lead-free vacuum tubes (Venoeject VP-H070K, Terumo, Tokyo, Japan). The samples were stored at −70°C until transfer to Japan for blood lead measurement. Blood samples (in 1.0 mL volumes) were accurately weighed and put into a Perfluoroalkoxy Teflon bottle, and then 4 mL of concentrated nitric acid (Ultrapure Grade, Tama Chemicals Co., Kawasaki, Japan) was measured and left overnight. The sample mixture was digested with 0.8 mL hydrogen peroxide and 0.8 mL perchloric acid (Ultrapure Grade, Tama Chemicals Co., Kawasaki, Japan) in a microwave oven (MLS-1200 MEGA, Milestone S.R.L., Bergamo, Italy) in five steps with power set at 250, 0, 400, 650, 250 W for 6, 1, 6, 6, and 6 min, respectively; then the volume of the digested sample was adjusted to 10.0 mL with Distilled water. The measurements were repeated three times. For instrument calibration throughout the measurements, at least 10% of the analyses were external standard, and 5% were blank (pure water). The measurements were repeated three times. For instrument calibration through a standard multi-element standard XSTC-13 (SPEX CertiPrep. Inc., Metuchen, NJ, USA) at least 10% of the analyses were external standard, and 5% were blank (pure water).

2.4. Statistical analysis

Student’s t-test, Chi-square and Fisher’s exact tests were used to compare subjects’ characteristics between non-PROM and PROM cases. To reduce the influence of outliers and normalize the residual distribution, the common logarithm (log10) of the blood lead concentration was also used in the statistical analysis. A logistic regression analysis was performed stepwise method, where PROM (=1) or not (=0) was used as the dependent variable; log of blood lead concentration, age, weight, BMI, pregnancy weight gain, hematocrit, newborn sex, parity, education, passive smoking, and systolic and diastolic blood pressure were defined as independent variables. The Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) software package was used for the analysis.

3. Results

The mean ± SD blood lead concentration was 3.8 ± 2.0 μg/dl (range 1.0–20.5 μg/dl) with a geometric mean of 3.5 μg/dl in all subjects. Thirty-six (10%) subjects had PROM and 296 did not. Blood lead concentrations and other variables in the two groups of subjects are shown in Table 1. Blood lead concentration was significantly higher in the PROM deliveries than in the non-PROM deliveries (4.61 ± 2.37 μg/dl vs 3.69 ± 1.85 μg/dl, respectively).

The PROM subjects were significantly younger (1.5 years) and showed higher diastolic blood pressure (4.0 mm Hg) as compared with the non-PROM subjects. The logistic regression analysis showed that log of blood lead, age and diastolic blood pressure were significantly related to PROM (Table 2). This analysis indicated that one unit elevation in the log of blood lead concentration (μg/dl) and diastolic blood pressure (mm Hg) led to 17.98- and 1.06-fold increases in the occurrence of PROM, respectively. On the other hand, 1 year increase in age reduced the risk of PROM by 0.85-fold.

4. Discussion

In the present study, blood lead concentrations were higher in PROM deliveries than in non-PROM deliveries. Logistic regression analysis showed that elevated early gestation blood lead levels increase the risk of PROM several-fold. Thus, the result of the present study suggests that mothers’ blood lead concentrations, an average of <5 μg/dl, could be a risk factor for PROM delivery. In recent decades, several adverse pregnancy outcomes have been shown at this blood lead concentration [3,5,22]. In contrast, early fetal membrane rupture has been shown in subjects at higher blood lead concentrations (>13 μg/dl) [8]. Similarly, a modest increase in lead concentrations in umbilical cord tissues (mean 1.91 μg/g) has been reported in PROM cases [23]. In addition, a group of complicated pregnancies, including eight PROM cases, was found to have higher placental lead concentrations than a group of 53 normal deliveries (154 and 103 ng/g, respectively) [24]. However, some studies have failed to find significant relationships between increased lead concentrations and the risk of PROM delivery [25,26]. Since PROM is a multifactorial problem, individual susceptibility and/or other environmental factors could influence the results.

Table 1

<table>
<thead>
<tr>
<th>Selected explanatory variables</th>
<th>Unit risk</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logarithm of blood lead</td>
<td>1.98</td>
<td>1.53–198.58</td>
<td>0.017</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.85</td>
<td>0.76–0.96</td>
<td>0.037</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>1.06</td>
<td>1.02–1.11</td>
<td>0.007</td>
</tr>
<tr>
<td>Model p-value &lt;0.001, Cox and Snell R² 0.091</td>
<td></td>
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</tr>
</tbody>
</table>

Independent variables: log of blood lead concentrations, age, weight, BMI, pregnancy weight gain, hematocrit, newborn sex, parity, education, passive smoking, and systolic and diastolic blood pressure.

Table 2

| Logistic regression analysisa |
|-------------------------------|-----------|--------|---------|
| Unit risk                     | 1.98      | 1.53–198.58 | 0.017 |
| 95% CI                        | 0.76–0.96 | 0.037 |
| p-Value                       | 1.02–1.11 | 0.007 |
| Model p-value <0.001, Cox and Snell R² 0.091 |

a Variables were selected by forward stepwise method: PROM (=1) and non-PROM (=0) as dependent variable.
The pathophysiology and the mechanism of the lead effect on PROM are not clearly understood. The effects may be direct, when exposed lead interacts with specific reproductive target organs, or indirect, when lead disrupts reproductive hormones or other female systems. Furthermore, exposure conditions, such as timing, duration, and intensity, can be important factors for assessment of the effect of lead on PROM occurrence.

Fetal membrane rupture is not only induced by stretching at the onset of delivery, but it also needs structural weakness, such as damage in the collagen fibrils, for the rupture procedure [27,28]. For example, reduction of type III collagen causes the membranes to lose elasticity and strength, allowing PROM to occur [29]. On the other hand, fetal membrane disruption could be induced by reactive oxygen species (ROS), since collagen is a primary target for ROS [27,30]. Recent studies pointed to ROS production and/or activation as a major mediator of lead toxicity [31–33]. Thus, lead-induced ROS, or declining anti-oxidant agents, could be an important pathway for increasing PROM risk via inducing collagen damage in fetal membranes.

The main sources of lead exposure in our subjects are believed to be air pollution, drinking water, and the food chain. Contamination of agricultural water by industrial sewage and lead washed out of the air by rain, especially when the rain is acidic, results in lead entering the food chain [34]. Similarly, subjects could be exposed to lead via the city drinking water, since lead pipes and soldered joints are still used in the city water networks. As in the present survey, for better assessment of the effect of metal intoxication on pregnancy outcomes, blood samples should be taken during the first trimester of pregnancy [35]. Additionally, the measured lead could represent the pre-pregnancy levels as well, since blood lead concentrations (bone release) and pregnancy blood volume do not increase significantly before the latter half of gestation [36,37]. In light of this observation, pregnant women should be avoiding high lead exposure before pregnancy, even at blood lead levels as low as 10 μg/dl. On the other hand, lead exposure in women of reproductive age is a critical concern and the practice of decreasing the exposure level or removing women after becoming pregnant from the lead resources is of questionable value, with respect to providing sufficient protection for mothers and fetuses.

The results of the present study, both on bivariate and multivariate analyses, demonstrated a higher risk of PROM for younger mothers. Although, age and lead levels directly correlated in the US (NHANES III) [38], in this study, higher lead levels observed in younger mothers (PROM cases). Since younger age and lead levels were correlated the study cannot determine what role each variable plays in increasing PROM risk. Studies involving adolescent mothers and young pregnant women (15–25 years) have reported that they have a higher PROM risk than older mothers [39,40]. In contrast, data from German Federal States, which included 508,926 pregnancies, have clearly shown an increased PROM risk with maternal age [41]. In addition, two studies have failed to find an increased PROM rate in teenage or adolescent subjects [42,43]. Therefore, more studies are needed on the relationship between maternal age and PROM incidence.

The present study also showed higher diastolic blood pressure for PROM cases comparison to non-PROM mothers; although, increased in the blood pressure is small and may not be clinically important. Elevated lead levels may increase the risk of pregnancy-induced hypertension [3,44]. Thus, elevated diastolic blood pressures in the PROM patients may be related to their higher lead levels. Nevertheless, a causal relationship between PROM risk and elevated diastolic blood pressure cannot be proven by the current study.

In summary, the present study found a statistically significant association between 1st trimester maternal lead levels and subsequent risk of PROM. Elevated risk was found at lead levels below 10 μg/dl which is the current level considered to be “safe”. While a causal link between lead levels and PROM cannot be proven, this report is consistent with previous works which suggest lead levels as low as 5 μg/dl may contribute to the risk of PROM and other adverse pregnancy outcomes.

Conflict of interest statement

The authors declare that there are no conflicts of interest in this survey.

Acknowledgements

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