Fetal Lead Exposure at Each Stage of Pregnancy as a Predictor of Infant Mental Development

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<table>
<thead>
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<th>Citation</th>
<th>Hu, Howard, Martha Maria Tellez-Rojo, David Bellinger, Donald Smith, Adrienne S. Ettinger, Hector Lamadrid-Figueroa, Joel Schwartz, Lourdes Schnaas, Adriana Mercado-Garcia, and Mauricio Hernandez-Avila. 2006. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environmental Health Perspectives 114(11): 1730-1735.</th>
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</table>
The findings of a wide variety of international studies on the impacts of lead exposure on mental development persuaded many countries to progressively reduce the amount of lead exposure deemed safe during childhood. Since 1991, the U.S. Centers for Disease Control and Prevention (CDC) has recommended 10 µg/dL (0.48 µmol/L) as the pediatric blood lead level as the index of prenatal exposure (Bellinger et al. 1989), whereas others took measures in the first or second trimester (Dietrich et al. 1987), in mid-pregnancy and at delivery (Wasserman et al. 1997), or at delivery only (Cooney et al. 1989; Ernhart et al. 1986). Some studies relied solely on umbilical cord blood lead level as the index of prenatal exposure (Bellinger et al. 1987). One study measured perinatal maternal bone lead level as an index of mobilizable maternal lead burden during the course of pregnancy (Gomaa et al. 2002).

The toxicokinetics of lead in the maternal–fetal unit are poorly understood. Lead levels in different compartments and at different stages of pregnancy are only modestly correlated, suggesting that each measure captures different aspects of fetal exposure (Baghurst et al. 1987). It is well known from the experimental literature that the vulnerability of developing organ systems, including the brain, to environmental toxicants can vary widely over the course of pregnancy (Mendola et al. 2002). Thus, it is plausible that lead exposure may be particularly neurotoxic during a specific trimester.

Recent evidence also suggests that whole blood lead levels in a pregnant woman might not be the optimal marker for lead concentrations in the fetal brain. Over 99% of lead in whole blood is bound to red cells and thus not available for toxicokinetic studies. A related issue that has received less attention is the extent to which prenatal lead exposure may produce adverse outcomes. This study was supported by National Institute of Environmental Health Sciences (NIEHS) grants P42-ES05947, R01-ES07821, Center Grant P30-ES008002, and T32-ES07069, and by Consejo Nacional de Ciencia y Tecnologia (CONACyT) Grant 4150M9405 and CONSERVA, Department of Federal District, Mexico. Additional support for the interpretation of results and authorship of this publication was made possible by NIEHS P01 ES012874, and a STAR Research Assistance Agreement RD-83172501 awarded by the U.S. Environmental Protection Agency (EPA). The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, National Institutes of Health, or the U.S. EPA. The authors declare they have no competing financial interests.
available to cross the placenta (Goyer 1990); instead, it is the < 1% of lead in the plasma compartment of blood that is of greatest interest in terms of fetal exposure. Recent data suggest that there are significant interindividual differences in the ratio of red cell lead to plasma lead (Hu 1998; Lamadrid-Figueroa 2006), making maternal whole blood lead levels potentially unreliable as a proxy for plasma lead and fetal exposure (Chuang et al. 2001; Goyer 1990).

To date, no study of fetal lead neurotoxicity has included the biomarker measurements needed to compare whole blood and plasma lead levels during each trimester of pregnancy as predictors of infant neurodevelopment. It is such a comparison that we report here.

Materials and Methods

Study subjects. Subjects were recruited between May 1997 and July 1999 from 2,273 women approached during prenatal visits at one of three clinics of the Mexican Institute of Social Security (IMSS) in Mexico City. Women were eligible if they had a confirmed positive β-human chorionic gonadotropin test or were trying to become pregnant, lived in Mexico City, and were willing to participate in the 3-year follow-up study protocol. Of the 2,273 women approached, 1,502 (66%) declined to be enrolled. We applied the following exclusion criteria to the 771 (34%) women who were willing to participate (percent excluded in parentheses): having plans to leave the area in the following 5 years (3.7%); having a psychiatric disorder (0%); daily consumption of alcoholic beverages (0%); addiction to illegal drugs (0%); continuous use of prescription drugs (0%); diagnosis of high-risk pregnancy (10.9%), preeclampsia (0.9%), renal or circulatory disease including hypertension (8.4%), or gestational diabetes (0.7%); suffering from seizures that required medical treatment (0.3%); and being pregnant with > 14 weeks of gestation (15.3%). A total of 280 already pregnant women were recruited; 182 women with a negative pregnancy test declared an intention to become pregnant in the near future and were also recruited. Of the latter group, 47 became pregnant, agreed to participate, and were enrolled in the cohort comprising a total of 327 pregnant women.

Of these 327 women, 216 continued the full follow-up and bore children who were evaluated for the Bayley Mental Development Index (MDI) (Bayley 1993) at 24 months of age. Of these 216 mother–infant pairs, 146 met the following inclusion criteria: child born with at least 37 weeks of gestational age; at least one valid measurement of plasma lead during any of the three visits made during pregnancy; complete information on maternal age and IQ; and child’s blood lead level at 24 months of age, sex, weight, and height.

All mothers were informed about the study; those who agreed to participate read and signed a letter of informed consent. The research protocol was approved by the Ethics Committees of the National Institute of Public Health of Mexico, the Harvard School of Public Health, the Brigham and Women’s Hospital, the University of California, and the participating hospitals.

Blood and plasma lead measurement in mothers. Blood and plasma samples were collected during each prenatal visit of the mothers to the Center for Environmental Health Research of the American British Cowdray (ABC) Hospital in Mexico City. Visits were scheduled at 12, 24, and 34 weeks of pregnancy, and samples were classified as corresponding to first, second, or third trimester according to the timing of these visits. Subjects were instructed to fast overnight before sample collection. Before venipuncture, each subject’s arm was washed with ultrapure water and disinfected with reagent-grade alcohol. Three milliliters of venous whole blood was collected with a butterfly catheter (19 gauge) into a low-leak container (Vacutainer B-D 367734; Becton-Dickinson, Franklin Lakes, NJ, USA) for blood lead analysis, and 13 cm³ venous blood was then collected into a polyethylene tube containing 100 ISP (international units) sodium heparin (H-3393; Sigma Chemical Company, St. Louis, MO, USA), processed, and shipped to the trace metal facility at the University of California, Santa Cruz, for measurement of whole blood lead and plasma lead using ultra-clean methods detailed elsewhere (Hernandez-Avilà et al. 1998; Smith et al. 1998). All samples were analyzed using inductively coupled plasma mass spectrometry (ICP-MS; Thermo Finnigan, Bremen, Germany).

Potential contamination by lead from hemozytized red cells was assessed by measuring levels of plasma iron and free hemoglobin using sensitive methods previously described in detail (Smith et al. 1998). Accordingly, 18 samples were determined to be contaminated and excluded from further analyses.

Children’s blood lead measurement. Umbilical cord and infant venous blood samples at 24 months were collected in trace-metal–free tubes. Due to the logistical constraints posed by the collection of samples during birth from multiple hospitals and at unpredictable hours, we obtained data on cord blood on only 57% of the mothers participating in this study. Samples were analyzed for lead using an atomic absorption spectrometry (AAS) instrument (model 3000; PerkinElmer, Chelmsford, MA, USA) at the metals laboratory of the ABC Hospital, which participates in the external validation protocol of the Wisconsin Laboratory of Hygiene. The Pearson correlation coefficient between all available measurements by AAS and those by ICP-MS was 0.93 (in mothers). Precision was similar using either measuring technique; standard deviations were not significantly different (p = 0.32); and accuracy was comparable (with difference in means < 1.0 μg/dl).

Measurement of child development and potential confounders. Infant development at 24 months was assessed by trained personnel using the Bayley Scales of Infant Development II–Spanish version (BSID-IIS) (Bayley 1993) using a standardized protocol described in a previous study by our research group (Gomaa et al. 2002). All assessors were blind to the children’s in utero and postnatal lead measurements. MDI scores at 24 months of age were considered the primary outcome. Information on demographic, socioeconomic, and other factors that could confound the relationship between lead and child development was collected. Maternal IQ was assessed using the Information, Comprehension, Similarities, and Block Design subtests of the Wechsler Adult Intelligence Score (Wechsler 1968).

Statistical analysis. Descriptive statistics and appropriate transformations were performed before bivariate analyses. Outliers were identified using the ESD (Extreme Studentized Deviate) Many-Outlier procedure (Rosner 1983). We calculated Spearman correlation coefficients among the lead measurements. Height and weight data were transformed into Z-scores by using World Health Organization (WHO)/National Center for Health Statistics/CDC reference data (WHO 1979) and interpreted as indices of a child’s nutritional status. Variables considered to be potential confounders based on biologic plausibility, regardless of statistical significance, and those significantly (p < 0.1) associated with MDI scores in bivariate analyses were included in multiple linear regression models; given these criteria, confounders included were child’s sex, blood lead at 24 months of age, height for age z-score and weight, as well as maternal age and intelligence quotient. All models featured log-transformed lead measures because this procedure provided the best fit. We first generated “single-trimester” models, in which we evaluated the associations between MDI score and log-transformed plasma and whole blood lead levels during each trimester of pregnancy adjusting for potential confounders. We generated “multitrimester” models, incorporating, in each model, the data from either plasma or whole blood lead concentrations from all three trimesters. We also ran models using maternal plasma lead or whole blood lead, averaged over all three trimesters. Infant lead measurements containing multiple lead measures for the mother and child were used in a separate model to enable better comparability of the relative effects of plasma lead and blood lead, we compared effect estimates for a 1-SD change in each exposure metric. We carried out a similar analysis using log-transformed cord blood lead levels as a proxy variable for prenatal lead.
Pregnancy a current weight, height-for-age Z-score, and maternal IQ. Logarithmically transformed lead concentrations were used. CI, confidence interval. Each model is adjusted for infant’s concurrent blood lead (24 months of age), sex, maternal age, number of years in school, IQ, and children’s hemoglobin, height, weight, and MDI when compared with mother–child pairs who participated but who did not meet the inclusion criteria for this analysis (n = 70; data not shown). Circulating levels of lead in the included mothers were moderately high, with mean (± SD) values for first-trimester whole blood lead of 70.7 ± 51.0 µg/L and 14% of values ≥ 10 µg/L (Table 1). (Whole blood lead values are expressed in this article as micrograms per liter for ease of comparison with plasma levels.) Both maternal plasma and whole blood lead followed a U-shaped pattern over the course of pregnancy, reaching their lowest points during the second trimester and rising during the third trimester.

Table 2. Single-trimester multivariate linear regression models for MDI of offspring (at 24 months of age) comparing markers of lead exposure at different times for blood lead and plasma lead.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>β</th>
<th>p-Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>119</td>
<td>–4.13</td>
<td>0.04</td>
<td>–8.10 to –0.17</td>
</tr>
<tr>
<td>Second trimester</td>
<td>136</td>
<td>–4.08</td>
<td>0.06</td>
<td>–8.29 to –0.12</td>
</tr>
<tr>
<td>Third trimester</td>
<td>132</td>
<td>–2.42</td>
<td>0.23</td>
<td>–6.38 to 1.54</td>
</tr>
<tr>
<td>Average</td>
<td>146</td>
<td>–3.52</td>
<td>0.10</td>
<td>–7.66 to 0.63</td>
</tr>
<tr>
<td>Plasma lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>119</td>
<td>–3.77</td>
<td>0.03</td>
<td>–7.12 to –0.42</td>
</tr>
<tr>
<td>Second trimester</td>
<td>136</td>
<td>–2.48</td>
<td>0.13</td>
<td>–5.74 to 0.77</td>
</tr>
<tr>
<td>Third trimester</td>
<td>132</td>
<td>–0.32</td>
<td>0.83</td>
<td>–3.38 to 2.74</td>
</tr>
<tr>
<td>Average</td>
<td>146</td>
<td>–3.11</td>
<td>0.07</td>
<td>–6.53 to 0.31</td>
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<tr>
<td>Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood lead (µg/L)</td>
<td>83</td>
<td>–0.35</td>
<td>0.88</td>
<td>–4.72 to 4.03</td>
</tr>
<tr>
<td>Postnatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child blood lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>125</td>
<td>–2.38</td>
<td>0.23</td>
<td>–6.24 to 1.49</td>
</tr>
<tr>
<td>24 months</td>
<td>146</td>
<td>–1.00</td>
<td>0.50</td>
<td>–3.33 to 1.34</td>
</tr>
</tbody>
</table>

CI, confidence interval. Each model is adjusted for infant’s concurrent blood lead (24 months of age), sex, maternal age, number of years in school, IQ, and children’s hemoglobin, height, weight, and MDI when compared with mother–child pairs who participated but who did not meet the inclusion criteria for this analysis (n = 70; data not shown). Circulating levels of lead in the included mothers were moderately high, with mean (± SD) values for first-trimester whole blood lead of 70.7 ± 51.0 µg/L and 14% of values ≥ 10 µg/L (Table 1). (Whole blood lead values are expressed in this article as micrograms per liter for ease of comparison with plasma levels.) Both maternal plasma and whole blood lead followed a U-shaped pattern over the course of pregnancy, reaching their lowest points during the second trimester and rising during the third trimester.

As expected, measurements of lead biomarkers in the three stages of pregnancy were moderately well correlated (all p < 0.05); Spearman correlations between blood lead measurements at different stages of pregnancy (mean = 0.72; range, 0.67–0.81) were, on average, higher than their plasma lead counterparts (mean = 0.62; range, 0.55–0.69). Cord blood lead was most highly correlated with maternal whole blood lead measured during the third trimester of pregnancy (r = 0.5436, p < 0.001). Cord blood lead concentrations were 10.6 µg/L lower, on average, than maternal whole blood lead levels at delivery. Children’s whole blood lead levels at 12 and 24 months of age were correlated (r = 0.58, p < 0.01) and lower, on average, than their cord blood lead levels.

Figure 1. Plasma lead levels during pregnancy according to gestational age. Plasma lead measurements were taken at what were intended to be the first, second, and third trimesters. Dotted lines mark the 13th and 26th weeks of gestation.

Table 1. Characteristics of the study population of mother–infant pairs.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>Mean ± SD</th>
<th>Range</th>
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<td>Mothers</td>
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<tr>
<td>Age (years)</td>
<td>146</td>
<td>27.1 ± 5.3</td>
<td>15–43</td>
</tr>
<tr>
<td>IQ</td>
<td>146</td>
<td>89.1 ± 12.9</td>
<td>55–120</td>
</tr>
<tr>
<td>Whole blood lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>119</td>
<td>70.7 ± 51.0</td>
<td>14.9–435.9</td>
</tr>
<tr>
<td>Second trimester</td>
<td>136</td>
<td>60.8 ± 31.5</td>
<td>15.8–224.4</td>
</tr>
<tr>
<td>Third trimester</td>
<td>132</td>
<td>68.6 ± 42.3</td>
<td>15.3–330.8</td>
</tr>
<tr>
<td>Delivery</td>
<td>111</td>
<td>72.6 ± 43.3</td>
<td>15–324</td>
</tr>
<tr>
<td>Plasma lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>119</td>
<td>0.16 ± 0.14</td>
<td>0.04–0.99</td>
</tr>
<tr>
<td>Second trimester</td>
<td>136</td>
<td>0.14 ± 0.11</td>
<td>0.03–0.67</td>
</tr>
<tr>
<td>Third trimester</td>
<td>132</td>
<td>0.16 ± 0.24</td>
<td>0.03–2.63</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>146</td>
<td>3,144 ± 359</td>
<td>2,125–4,000</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>76</td>
<td>52.05</td>
<td></td>
</tr>
<tr>
<td>Blood lead (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>83</td>
<td>62.0 ± 38.8</td>
<td>9–200</td>
</tr>
<tr>
<td>12 months</td>
<td>125</td>
<td>52.2 ± 34.1</td>
<td>9–204</td>
</tr>
<tr>
<td>24 months</td>
<td>146</td>
<td>47.9 ± 37.1</td>
<td>8–368</td>
</tr>
<tr>
<td>Height at 24 months (cm)</td>
<td>146</td>
<td>86.1 ± 3.0</td>
<td>74–93</td>
</tr>
<tr>
<td>Weight at 24 months (kg)</td>
<td>146</td>
<td>11.98 ± 1.55</td>
<td>9.4–13.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>135</td>
<td>12.4 ± 1.2</td>
<td>7.1–14.8</td>
</tr>
<tr>
<td>MDI score (at 24 months)</td>
<td>146</td>
<td>91.5 ± 11.6</td>
<td>68–122</td>
</tr>
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</table>
Single-trimester models of MDI scores (Table 2) suggested a negative relationship between circulating lead in each trimester of pregnancy and MDI scores at 24 months of age, adjusting for maternal age and IQ and child’s concurrent blood lead, sex, weight and height-for-age Z-score. MDI was most strongly associated with lead concentrations during the first trimester for both plasma (standardized coefficient, –4.13; \( p = 0.03 \)) and whole blood lead (standardized coefficient, –3.77; \( p = 0.04 \)). Both maternal plasma and whole blood lead averaged over all three trimesters had associations with MDI of borderline significance (standardized coefficients of –3.52, \( p = 0.07 \); and –3.11, \( p = -0.10 \), respectively).

When we repeated the analysis using only those measurements correctly classified in each trimester of pregnancy, we found that lead concentrations during the first trimester were significantly associated with a decrease in MDI at 24 months of age. The estimated coefficients in the first trimester (\( n = 56 \)) were –6.39 (\( p = 0.04 \)) and –6.94 (\( p = 0.04 \)) points per log micrograms per liter of plasma and whole blood lead, respectively. The coefficients for the second trimester plasma and whole blood lead levels (\( n = 102 \)) were much smaller (–1.73, \( p = 0.38 \); and –3.66, \( p = 0.16 \), respectively). Umbilical cord lead at birth and infant whole blood lead at 12 and 24 months were inversely but weakly (\( p > 0.20 \)) associated with MDI at 24 months.

In multitrimester models (Table 3), the plasma lead model predicts that an increase of 1 SD in \( \log e \) transformed plasma lead in the first trimester is associated with a 15-point decline in MDI score at 24 months of age, in contrast to a 4-point decline per 0.1-µg/L increase in plasma lead for observations above the median plasma lead—confirming that the nonlinear pattern is not an artifact of our transformation of the variable.

**Discussion**

This study is the first of which we are aware that attempted to compare the relative influence on neurodevelopmental toxicity of two different biomarkers of fetal lead exposure at each stage of pregnancy. We found that both maternal blood lead and maternal plasma lead vary considerably over pregnancy; first-trimester levels of either measures were better than second- or third-trimester levels or levels averaged over all three trimesters at predicting infant neurobehavioral performance at age 24 months; and first-trimester maternal plasma lead levels were somewhat better than first-trimester maternal whole blood lead levels at predicting infant neurobehavioral performance at 24 months of age.

Our study had several limitations. Our sample size was modest, a reflection of the labor- and cost-intensive nature of collecting plasma samples using a rigorous protocol. Nevertheless, we were able to successfully distinguish and compare the relative contributions to neurodevelopment of trimester- and biomarker-specific measures of exposure. Our subjects were a small subset of women who had been initially approached in the clinics (\( n = 2,273 \)), raising the issue of the generalizability of our study. However, the women included in our final sample did not differ significantly from other eligible subjects on key covariates, suggesting that our sample was quite representative of all eligible women.

Table 3. Multivariate models of MDI of offspring (at 24 months of age) using either whole blood or plasma lead concentrations as markers of prenatal lead exposure at different trimesters of pregnancy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma model (( R^2 = 0.22 ))</th>
<th>Blood model (( R^2 = 0.21 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )</td>
<td>( p )-Value</td>
<td>( \beta )</td>
</tr>
<tr>
<td>Pb first trimester( a )</td>
<td>–3.54</td>
<td>0.03</td>
</tr>
<tr>
<td>Pb second trimester( a )</td>
<td>0.80</td>
<td>0.65</td>
</tr>
<tr>
<td>Pb third trimester( a )</td>
<td>1.18</td>
<td>0.44</td>
</tr>
<tr>
<td>Current blood lead( b )</td>
<td>–0.01</td>
<td>0.62</td>
</tr>
<tr>
<td>Sex( c )</td>
<td>3.64</td>
<td>0.13</td>
</tr>
<tr>
<td>Height-for-age Z-score</td>
<td>2.87</td>
<td>0.06</td>
</tr>
<tr>
<td>Current weight (kg)</td>
<td>–1.70</td>
<td>0.06</td>
</tr>
<tr>
<td>Mother’s IQ</td>
<td>0.08</td>
<td>0.40</td>
</tr>
<tr>
<td>Mother’s age (years)</td>
<td>0.59</td>
<td>0.01</td>
</tr>
<tr>
<td>Intercept</td>
<td>84.25</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

These are the results of two multivariate regression models with either plasma lead or whole blood concentrations in different trimesters of pregnancy simultaneously included in each of the two models. Coefficients are mean change in MDI per increase of 1 SD in \( \log e \) lead concentrations, which allows for direct comparisons between the beta-coefficients of plasma lead versus blood lead.

*Plasma lead concentration (µg/L) in corresponding trimester. \( a \) Infant whole blood lead (µg/L) at 24 months of age. \( a \) Infant sex: 1 = male, 2 = female.
representative of the women serviced by our participating clinics. Some of our observations were misclassified with respect to trimester; however, our results were very similar in the reanalysis using classification corrections. Indeed, the association between first-trimester lead exposure and infant neurodevelopment appeared to be even greater, a finding that sug-
gests that there was downward bias due to
improper assignment of second-trimester
women to the first trimester category. We did not control for a summary measure of home
conditions, such as the Home Observation for Measurement of the Environment (HOME) score; however, the absence of this covariate is unlikely to explain differences in effects
among the three trimesters of lead exposure.
Finally, offspring blood lead levels at 24 months did not significantly predict lower
MDI score; on the other hand, our sample
size, again, was modest, and in a separate
analysis of the larger group of mother–infant
pairs participating in this research (n = 294) that was not confined to women who had
plasma lead levels, we found an important
surrogate impact of offspring blood lead levels at 24 months of age on 24-month MDI score (Tellez-Rojo et al. 2006).

The best-fitting model relating first-
trimester plasma lead to 24-month MDI scores was one in which lead level was expressed as
the natural logarithm of the measured value.
This suggests that the shape of the dose–effect
relationship is supralinear, with a steeper slope
at lower plasma lead levels. This is consistent
with the blood lead–IQ relationships in chil-
dren reported by Canfield et al. (2003), in
reanalyses of the Boston prospective study of
children (Bellinger and Needleman 2003), and in pooled analyses that included several addi-
tional prospective studies (Lanphear et al. 2005).
In quantitative terms, however, the
rates of change over both ranges of plasma lead
level were approximately twice as great as those
reported by Canfield et al. (2003). Meta-anal-
yses of multiple studies have converged on an
estimate of a 2–3 IQ point decrement for each
10-μg/dL increase in postnatal blood lead level
(International Program on Chemical Safety
1995; Pocock et al. 1994; Schwartz 1994), but
these estimates might reflect mostly the region
of the dose–effect relationship in which the
slope is shallower. Moreover, blood lead is a
surrogate measured with error for toxicologi-
cally available lead, and the larger effect size
estimates for plasma lead suggest that many
previous studies may have had effect estimates
downwardly biased by measurement error.

We are not aware of previous studies for
comparison that have included maternal mea-
ures of circulating lead at each stage of preg-
nancy. Although Schnaas et al. (2006) also
studied lead exposure and neurobehavior in a
cohort of Mexico City children from the
in utero period to childhood (and found a
significant adverse impact of in utero lead
exposure), their observations began after the
12th week of pregnancy and thus precluded
examination of the direct effects of first-
trimester lead exposure.

In experimental studies, lead is known to
affect a wide range of processes critical to
central nervous system development, including
differentiation (Alfano and Petit 1982; Petit and LeBoullier 1979; Petit et al. 1983), myelina-
tion (Mendola et al. 2002), and synaptogenesis
(Johnston and Goldstein 1998). Of these, differ-
entiation is primarily a first-trimester event,
making a targeting of this process as a possible explanation for our finding of a first-trimester
dominant effect.

Mobilization of maternal bone lead stores has been clearly identified as a major source of
fetal lead exposure (Gulson et al. 2003; Hu and
Hernandez-Avila 2002), and elevated maternal
bone lead can be expected to trans- 
fer to women with ongoing environmental or occu-
pational exposures and in women who have
retained bone lead burdens from earlier lead
exposures. The women in our study fell into
the latter category, having lived in Mexico
City, where leaded gasoline was combusted
until 1997. Some have suggested that fetal lead
exposure resulting from the mobilization of
maternal bone lead stores during pregnancy
can be reduced by calcium supplementation
(Gulson et al. 2004; Janakiraman et al. 2003).
Our study suggests that if such a strategy were
to prove useful in reducing lead exposure to
the fetus, it would have to be implemented
very early in pregnancy to maximize the benefit
to fetal neurodevelopment.

Our findings do not mean that measure-
ment of maternal plasma lead is likely to
become a clinically useful environmental
health tool. The methods required to measure
plasma lead are laborious and require special and expensive equipment. However, this bio-
marker is a useful research tool in efforts to
understand and detect the health impacts of
environmental lead exposure.

In conclusion, we found that first-trimester
measures of fetal lead exposure—particularly
levels of lead in maternal plasma, but also levels of lead in maternal whole blood—were predic-
tive of adverse neurodevelopment later in life,
with an effect that was independent from that
of postnatal lead exposure and that was stronger
than the effects associated with second- or
third-trimester measures. This is of major
potential public health concern because lead
remains a widespread environmental health
hazard and current efforts at primary preven-
tion have focused almost entirely on childhood
rather than fetal exposure. If future research
confirms this finding, ascertaining women at
risk and identifying effective strategies for pre-
vention of fetal lead exposure may become an
important public health priority; moreover, it
can be necessary to consider prepregnancy
interventions, because our research suggests that
screening and intervention any later than the
first trimester may be too late to prevent the
greatest fetal neurotoxic effects.
Fetal lead exposure and infant mental development


