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Abbreviations:

BMI: body mass index

Cd: cadmium

CI: confidence interval

DBP: diastolic blood pressure

GM: geometric mean

Mn: manganese

OR: odds ratio

Pb: Lead

PIH: Pregnancy-induced hypertension

SBP: systolic blood pressure

SD: standard deviation

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ABSTRACT:

Background: Prior studies revealed associations of environmental lead exposure with risks of hypertension and elevated blood pressure.

Objectives: To examine the effect of blood lead levels on blood pressure and the incidence of pregnancy-induced hypertension (PIH) in the second and third trimesters of pregnancy.

Methods: One thousand seventeen pregnant women were enrolled in two French municipalities between 2003 and 2005 for the EDEN cohort study. Blood lead concentrations were measured by atomic absorption spectrometry in mothers between 24 and 28 weeks of gestation.

Results: PIH was diagnosed in 106 subjects (10.9%). Age, parity, weight gain, alcohol, smoking habits and calcium supplementation were comparable between hypertensive and non hypertensive women. Lead levels were significantly higher in PIH cases (2.2 µg/dl [0.11 µmol/l] SD 1.4 µg/dl) than in normotensive patients (1.9 µg/dl [0.09 µmol/l] SD 1.2 µg/dl); p=0.02. Adjustment for potential confounders slightly attenuated but did not eliminate the significant association between blood lead levels and the risk of PIH (adjusted OR of PIH= 3.3, 95% CI: 1.1 to 9.7). Geographic differences in lead exposure and in the incidence of PIH were also observed. Significant correlations were found between blood lead levels and unadjusted as well as adjusted systolic and diastolic blood pressures after 24 weeks of gestation.

Conclusions: These findings confirm the relationship between blood lead levels at mid-pregnancy and blood pressure, and suggest that environmental lead exposure may play an etiologic role in PIH.

INTRODUCTION:

Lead (Pb) is one of the most extensively studied reproductive toxicants. Several epidemiologic studies have demonstrated a positive association between blood lead levels and blood pressure among non-pregnant adults (Nawrot et al. 2002; Schwartz 1995). The evidence is sufficient to infer a causal relationship of lead exposure with hypertension (Navas-Acien et al. 2007). However the role of lead in pregnancy induced hypertension (PIH) remains unclear.

PIH is characterized by an increase in systolic blood pressure (SBP ≥ 140 mm Hg) and/or diastolic blood pressure (DBP ≥ 90 mm Hg) after 20 weeks of gestation. This disorder can be complicated by proteinuria, a condition corresponding to preeclampsia. PIH is encountered in 10% of pregnancies and is an important cause of morbidity for both mother and fetus (NHBPEP 2000).

Environmental factors may have a role in this disease occurrence. While some studies failed to find a relationship between lead concentrations in cord blood and preeclampsia (Angell and Lavery 1982), several authors demonstrated higher levels of lead, cadmium (Cd), and manganese (Mn) in blood of hypertensive or preeclampsia patients, compared to normotensive women (Dawson et al. 2000; Kosanovic et al. 2002; Rothenberg et al. 1999; Vigeh et al. 2004). Other elements such as zinc and selenium were reported to be reduced in hypertensive pregnant women (Dawson et al. 1999; Rayman et al. 2003).

Blood lead levels increase during pregnancy, from 24 weeks of gestation until delivery, because of increased gastrointestinal absorption and because of an increase in bone turnover in this period (Hertz-Picciotto et al. 2000; O'Flaherty et al. 1995). Several mechanisms may contribute to the pathogenesis of lead-induced hypertension: increases in endothelin and thromboxane production; inhibition of vascular smooth muscle ATPases; oxidation of endogenous nitric oxide by reactive oxygen species; and decrease in glomerular

filtration rate of the kidneys with increase in the rennin - angiotensin II - aldosterone activity (Gonick and Behari 2002; Vaziri and Khan 2007; Vaziri and Sica 2004). Interactions between lead and other elements are possible since oxidative stress produced by lead, cadmium or manganese may be counterbalanced by the anti oxidative properties of manganese or selenium (Anastasakis et al. 2008; Campagna et al. 2000; Huel et al. 2000; Vaziri and Sica 2004; Verity 1999).

In the current study, we examined the relationship between PIH and circulating blood lead, cadmium, manganese and selenium concentrations in a non-selected population of pregnant women.

METHODS:

The study population included the first 1,017 pregnant women enrolled in the EDEN mother-child cohort study (Drouillet et al. 2008). The number of subjects needed for the study was based on a 10% prevalence of PIH and an estimated relative risk for PIH = 2.0. No other factors influenced the inclusion process.

All women aged from 18 to 45 years who presented before 24 weeks of gestation for prenatal care at two maternity wards in Poitiers (western France) and Nancy (eastern France) were enrolled if they were able to read and write French, and were not planning to move out of the region. We also excluded women who had multiple gestations or a history of diabetes. Among women who fulfilled these criteria, 55% agreed to participate. The study was approved by the Ethic Committee of Bicêtre Hospital (November 2002). All participants provided informed consent consistent with policies of the Institutional Review Board.

We collected maternal blood samples between 24 and 28 weeks of gestation, just after the recruitment was validated by the study midwife. We determined blood lead, cadmium and manganese concentrations by electrothermal atomic-absorption spectrometry (model 4100

ZL, Perkin-Elmer) with Zeeman background correction as previously described (Fréry et al. 1993; Huel et al. 1986; Mergler et al. 1996). We measured selenium by standard fluorometric method as described by Lee et al. (Lee et al. 1995). We calculated values as means of two analyses of each sample expressed in µg/dl. Internal and external quality-control procedures yielded consistently satisfactory results. The limit of detection for the blood lead measurements was 0.5 µg/dl. We assigned a value of 0.5 divided by two for values below the limit of detection. Of the measured values of blood lead, 2.7% were below the limit of detection.

Gestational age was based on last menstrual period and/or ultrasound-based estimated date of conception. We divided pregnancy into three periods: P1 before 24 weeks, P2 between 24 and 36 weeks, and P3 after 36 weeks of gestation. This choice was mainly founded on scientific data regarding the incidence of PIH in second half of pregnancy and its frequency with increasing gestational age (Groom et al. 2007).

We measured maternal blood pressure during routine monthly visits with the subject in supine position, using a standard mercury sphygmomanometer. Measures also were taken by the study midwife between 24 and 28 weeks using a different (semi-automated) device, with two measurements averaged to determine the values for that visit. All measurements taken within each period of gestation (P1, P2, and P3) were averaged to determine the values for SBP and DBP assigned to each period.Women were classified as having PIH based on SBP $\geq$ 140mm Hg or DBP $\geq$ 90mm Hg at two or more visits after the 22nd week of gestation, such that the elevated measures could have occurred during or across any of the three periods, and no diagnosis of PIH was made before 24 weeks.

We gathered medical and reproductive histories, clinical follow-up and delivery data from obstetrical records. Additional risk factors for PIH were obtained using the study questionnaires administered by trained interviewers during a structured interview. These

included basic socio-economic information, educational level, cigarette and alcohol use before and during pregnancy. Dietary information on coffee and tea consumption, and intake of calcium, vitamins or iron supplements was also recorded. We classified socio-economic status based on household monthly income and categorized it into three levels (high if > 3,000 EUR; medium between 1,500 and 3,000 EUR; and low if < 1,500 EUR). We also divided education status into two levels (high if ≥ 12 years, and low if < 12 years). For the analysis of main effects, all variables (except for hematocrit) were categorized.

Statistical data analysis was performed using SAS software v9.1.3 (SAS Institute Inc., Cary, NC, USA). We evaluated variables for normality and for outliers. Because of skewed distributions, lead, cadmium, manganese and selenium blood levels were transformed into their decimal logarithms and subsequent geometric means were calculated. Continuous variables were summarized by calculating the mean and standard deviation. Comparisons of means or proportions were performed by chi-square or Student *t*-test as appropriate. Cochran-Armitage was used for trend analysis. We obtained adjusted odds ratios by means of multivariable logistic regression analysis with PIH as the dependent variable. We based selection criteria for variables on the literature regarding risk factors of PIH. Besides all elements measured, adjustment variables included maternal age, parity, hematocrit, body-mass index, pregnancy weight gain, gestational diabetes, educational level, socio-economic status, geographical residence (maternity ward), smoking status and alcohol consumption before and during pregnancy. Although we used stepwise procedure to ascertain percentage of variance attributable to selected variables, relevant risk factors were forced into the final model. We tested interaction terms between blood lead levels (as a continuous variable) and other maternal variables with a significance level reduced to 0.005 (according to the Bonferroni method). Otherwise, a P value of less than 0.05 was considered to indicate

statistical significance. Pearson partial correlations were calculated between blood lead levels and SBP and DBP during the three periods of pregnancy.

RESULTS:

Among the 1,017 considered women, we excluded 31 records (3.0%) because of insufficient sample volumes or analytical problems in lead measurements and 15 records (1.5%) because of chronic hypertension under treatment before pregnancy. This left a study group of 971 pregnant women. Mothers' mean age was 29.3 ± 4.9 years. PIH occurred in 106 (10.9%) women and was complicated by proteinuria (preeclampsia) in 20 (2.1%) cases.

Table 1 summarizes the characteristics of the cohort in relation to PIH occurrence. When compared with normotensive group, women who developed PIH presented with a higher body mass index before pregnancy (21.9% versus 6.3%, $p<0.001$) and a higher hematocrit (35.2% versus 34.6%, $p=0.02$). They were also more likely to be diagnosed with gestational diabetes (17.0% versus 5.9%, $p<0.001$) and have a premature delivery (prior to completing 36 weeks of gestation, 13.2% versus 5.0%, $p<0.001$). The incidence of PIH was significantly higher in Nancy than in Poitiers (63.2 versus 36.8% of PIH patients, $p<0.001$; respectively). PIH was also negatively associated with birth-weight. There were very few missing covariate data (less than 3.8% in the PIH group and less than 5.2% among women without PIH for most of the variables studied).

Mean blood lead concentration in the PIH group (2.2 ± 1.4 µg/dl; Range: 0.2 – 8.5 µg/dl) was significantly higher than in women without PIH (1.9 ± 1.2 µg/dl; Range: 0.2 – 6.9 µg/dl) ($p=0.02$). Mean manganese concentration was slightly (but not significantly) higher in PIH women. Cadmium and selenium blood concentrations were comparable between groups (Table 2).

The frequency of PIH was lowest among women whose blood lead concentrations were in the lowest quartile (7.7%) and was significantly greater in the second (10.7%), third (11.1%), and fourth exposure quartiles (13.1%) (p=0.03 for trend). The unadjusted odds ratio (OR) of PIH associated with an increase of 1 µg/dl in maternal blood lead was 3.5 (95% CI: 1.4 to 8.9).

Adjustment for a range of characteristics and elements (cadmium, manganese and selenium blood concentrations, hematocrit, maternal age, body-mass index, parity, gestational diabetes, education and socio-economic level, smoking status and geographic residence) slightly attenuated but did not eliminate the significant association between blood lead levels and the risk of PIH (Table 3). Adjusted OR of PIH for an increase of 1 µg/dl in maternal blood lead was estimated at 3.3 (95% CI: 1.1 to 9.7). No significant interactions were observed between blood lead levels and any of the other elements and the maternal characteristics in predicting the risk of PIH (all interaction p-values > 0.05). Furthermore, excluding women with preeclampsia (n=20) did not substantially alter the association between blood lead level and PIH (adjusted OR= 3.1; 95% CI: 1.0 to 10.0).

When stratified by parity (Table 4), blood lead levels were higher in multiparous women than nulliparous women (2.0 ± 1.2 µg/dl versus 1.8 ± 1.3 µg/dl, respectively; p=0.003). The adjusted OR for PIH also was higher in multiparous women (OR= 4.6; 95% CI: 1.0 to 21.6) than nulliparous women (OR= 2.9; 95% CI: 0.6 to 15.7), but there was no interaction between parity and blood lead (p=0.46).

Log-transformed blood lead at mid-pregnancy was significantly correlated with both systolic and diastolic blood pressures at 24 – 36 weeks of gestation (r=+0.08; p=0.03 and r=+0.07; p=0.03, respectively), and after 36 weeks of gestation (r=+0.09; p=0.03 and r=+0.08;

p=0.03, respectively). Figure 1 illustrates correlation between residuals of the linear regression of maternal blood lead and systolic blood pressure at 24 – 36 weeks. Lead concentrations accounted for approximately 5% of the total unexplained variance obtained by linear models. Each decimal-log increase in blood lead was associated with an increase of 3.5 mm Hg in SBP and of 2.5 mm Hg in DBP during the second half of pregnancy.

DISCUSSION:

We found that the adjusted risk of PIH was associated with maternal blood lead levels in mid-pregnancy. This risk was doubled in the highest quartile as compared to the lowest quartile of lead distribution. There was no strong evidence of an interaction between lead and cadmium, manganese, selenium, or other factors associated with the risk of PIH. The risk of PIH increased with increasing absolute values of mid-pregnancy blood lead in a "dose-response" pattern. A positive correlation was particularly found with systolic blood pressure at 24 – 36 weeks that persisted after 36 weeks. All these findings suggest that blood lead level may be one of the causal factors of PIH.

Evidence that lead increases the circulating levels of endothelin, a vaso-active substance secreted by endothelial cells has been reported (Gonick and Behari 2002). Lead is also reported to reduce levels of vasodilator substances such as plasma nitric oxide and endothelial-derived relaxation factor; this reduction is due to a lead-mediated increase in reactive oxygen species (Carmignani et al. 2000; Gonick and Behari 2002; Gonick et al. 1997). Inhibition of membrane ATPases by this metal also leads to increased intracellular calcium ions and vasoconstriction (Moreau et al. 1988). Furthermore, a demonstrable inhibitory effect of lead on blood enzymes such as delta-aminolevulinic acid dehydratase activity was found at a low threshold of lead exposure, ranging from 3.2 to 4.8 µg/dl (Campagna et al. 1999; Telisman et al. 2004). From the above arguments, it may be

hypothesized that environmental exposure to lead increases the risk of PIH by inducing vasoconstriction and placental ischemia or by a direct toxicity on the endothelial cell and the renal function.

Our findings are consistent with those from previous studies showing a relationship between blood lead levels and PIH. However, most of these reports analysed lead concentrations late in pregnancy, either from maternal prenatal red blood cells (Dawson et al. 2000), from umbilical cord (Rabinowitz et al. 1987), amniotic fluid (Dawson et al. 1999), or even from maternal blood within 24 hours after the delivery (Vigeh et al. 2004; Vigeh et al. 2006). Our study did not involve serial measurements of blood lead levels throughout pregnancy. However, the optimal period for such measurement would be in the second trimester (24 weeks of gestation), at the beginning of a potential pathological change in blood pressure. Moreover, models on lead variation during pregnancy described a constant increase in blood lead levels from 24 weeks of gestation until delivery (O'Flaherty et al. 1995). Indeed, longitudinal analyses showed that maternal blood lead concentrations upon entering prenatal care (average of 13.5 weeks) were not associated with PIH, whereas higher lead levels during the second trimester were related to PIH (Sowers et al. 2002).

Our analysis of correlations between blood lead concentrations and SBP and DBP at 24 – 36 weeks and after 36 weeks of gestation was consistent with previous studies on essential hypertension (Batuman et al. 1983). Recent reviews suggest a weak but dependable association between lead levels and blood pressure. The increase in SBP is estimated between 0.8 and 2.0 mm Hg for each 1 µg/dl increase in blood lead (Hertz-Picciotto and Croft 1993; U.S.EPA 2006). Women with chronic hypertension were excluded from our study because of risks of bias associated to prior treatment with anti hypertensive drugs. This exclusion might have attenuated the correlation between blood lead and blood pressure.

Manganese blood level was not significantly associated with PIH in this study, although there was some evidence of a possible weak association. The underlying mechanisms of manganese-induced hypertension are probably independent from gestational age. The decrease in blood manganese with intrauterine growth restriction might obscure any other pathological effect (Vigeh et al. 2008). Cadmium also was not significantly associated with PIH in the present model. This finding may be related to relatively low levels of cadmium observed in this cohort. These reduced levels were probably due to the low prevalence of smoking, which is the main environmental source of cadmium (Bonithon-Kopp et al. 1986). Interaction between selenium and lead concentrations were not significant and the putative protective effect of selenium through anti-oxidative properties was not confirmed in this study.

Hematocrit levels are usually elevated in pregnancy hypertensive disorders (Goldstein et al. 2000). This may be due to a lower water balance index correlated to stroke volume or to a lower venous capacitance in hypertensive patients (Aardenburg et al. 2005). Hematocrit increases automatically increase blood lead which is concentrated in red blood cells. No statistical interaction was found between blood lead and hematocrit, but confounding can not be ruled out.

Body-mass index was strongly associated with PIH. This finding is consistent with previous reports (Hrazdilova et al. 2001; Vigeh et al. 2006). A “dose-response” relationship has also been observed, thus body-mass index before pregnancy should be considered in all models including PIH. Gestational diabetes effect on PIH was limited in the multivariate regression analysis probably because of its association with increased body-mass index. Age and parity were not significant covariates in this study. A trend of increasing blood pressure with age is usually reported for diastolic blood pressure, but the restricted age range (i.e., 18 – 45 yr) and

limited number of women above 40 years in the present study may have reduced our ability to highlight an age effect on PIH.

As to parity, high levels of blood lead observed in multiparous women of this study may have contributed to an increase in the frequency of PIH in this group, thus reducing the difference usually observed in the incidence of PIH and preeclampsia depending on parity. Moreover, data obtained from systematic ambulatory monitoring in a large sample of normotensive pregnant women indicate the lack of differences in blood pressure according to parity (Ayala and Hermida 2001)

Finally, PIH frequency was higher in Nancy than in Poitiers. A separate analysis (not shown) revealed higher blood lead levels in Nancy (2.0 ± 1.3 µg/dl) than in Poitiers (1.8 ± 1.1 µg/dl); $p<0.001$. Thus a major difference in the incidence of PIH between these two regions might have been their history of environmental exposure to chemical pollutants. Blood lead level primarily reflects recent exposure, although a part of lead in blood may originate from lead stored in bone, particularly during pregnancy (Gulson et al. 1997). Since bone lead has a half-life of years to decades, the higher blood lead levels observed in eastern versus western region reflect differences in current exposure, but may also reflect some differences in past exposure, or both. Hence, the relationship between blood lead and blood pressure may be mediated by the contribution of bone lead to blood lead, placing a larger amount of bioavailable lead into tissues and organs that affect blood pressure (Rothenberg et al. 1999).

The main sources of measurements errors of blood pressure are the inaccuracy of measurement methods and the intra-individual variability of blood pressure. We attempted to minimize these effects by averaging all blood pressure measurements available in the obstetrical files.

Although the association between blood lead levels and PIH persisted in the multivariate analysis, it is also possible that it reflects residual confounding due to

unmeasured confounders. The geographic residence is a general covariate and residual confounding by this variable cannot be ruled out. However, if this residual confounding explained the association found in the multivariate analysis, it is likely that an interaction between geographic residence and blood lead levels would have been observed. Moreover, blood lead concentration may be a better estimate of maternal environmental exposure than external indicators, and its use as a continuous variable in the regression model limits the risk of residual confounding.

Pregnancy-induced hypertension remains a multifactorial disease with unclear aetiology, which could compromise maternal and newborn reproductive outcomes. We identified a significant association between maternal blood lead levels in mid-pregnancy and blood pressure. Our findings that lead may have an etiologic role in PIH, even at low levels of environmental exposure, suggest that it may be appropriate for public health organizations to consider lowering the upper limit of “acceptable” blood lead levels in pregnant women, which is currently at 10 µg/dl.

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Tables

Table 1. Baseline characteristics according to PIH occurrence among 971 pregnant women with no history of chronic hypertension.

	PIH (mean or %)	No PIH (mean or %)	P Value
Maternal age – yr			0.70
< 25	19.8	17.6	
25 – 34	64.2	68.2	
≥ 35	16.0	14.2	
N	106	865	
Years of education			0.87
≥ 12 yr	64.2	66.2	
< 12 yr	30.2	29.0	
Unknown	5.7	4.7	
N	106	865	
Socio-economic status			0.76
High	25.7	25.5	
Medium	52.4	55.5	
Low	21.9	19.0	
N	105	851	
Geographic residence			< 0.001
Poitiers (Western)	36.8	58.6	
Nancy (Eastern)	63.2	41.4	
N	106	865	
Hematocrit – % [a,b]	35.2 (2.5)	34.6 (2.6)	0.02
N	105	842	
BMI before pregnancy – Kg/m^2			< 0.001
< 25	53.3	76.2	
25 – 29.9	24.8	17.5	
≥ 30	21.9	6.3	
N	105	835	
Weight gain during pregnancy – kg [a]	13.4 (6.5)	13.4 (4.6)	0.92
N	104	834	
Gestational diabetes			< 0.001
No	83.0	94.1	
Yes	17.0	5.9	
N	106	851	
Parity			0.71
Nulliparous	42.5	44.3	
Multiparous	57.5	55.7	
N	106	848	
Smoking during pregnancy – cig/day			0.86
0	72.6	71.7	
≥ 1	27.4	28.3	
1 – 9	19.6	22.2	
≥ 10	7.8	6.1	

N	102	820	
Alcohol consumption before pregnancy			0.90
No	28.2	28.7	
Yes	71.8	71.3	
N	103	849	
Iron/calcium supplementation			0.95
No	2.8	3.9	
Yes	61.3	60.1	
Unknown	35.9	36.0	
N	106	865	
Premature delivery (before 37 wk)			<0.001
No	86.8	95.1	
Yes	13.2	5.0	
N	106	851	
Neonate weight – gr [a]	3126.7 (719.9)	3299.0 (493.6)	0.02
N	106	844	
Neonate gender			0.28
Male	58.5	52.9	
Female	41.5	47.1	
N	106	849	

[a] values are means (SD).

[b]Hematocrit levels were measured concomitantly with metals between 24 and 28 gestational weeks

Table 2. Distribution of elements levels in maternal blood at mid-pregnancy, according to PIH occurrence.

	PIH (n=106)		No PIH (n=865)		P Value[a]
	Mean (SD)	GM	Mean (SD)	GM	
Lead (µg/dl)	2.2 (1.4)[b]	1.9	1.9 (1.2)	1.6	0.02
Cadmium (µg/l)	0.9 (0.5)	0.8	0.9 (0.6)	0.7	0.08
Manganese (µg/l)	11.8 (6.3)	10.6	10.6 (4.5)	9.6	0.06
Selenium (µg/l)	98.8 (29.0)	93.3	98.6 (26.2)	95.5	0.76

[a] *t*-test on the log transformed variables

[b] To convert values for lead to micromoles per liter, multiply by 0.0483.

Table 3. Odds ratios for PIH, according to maternal blood lead distribution and overall outcome characteristics.

	Unadjusted Analysis		Adjusted Analysis[a]	
	OR (95% CI)	P value	OR (95% CI)	P value
Log (Pb)[b]	3.49 (1.37 – 8.87)	0.009	3.29 (1.11 – 9.74)	0.03
- Q1[c] (referent)	1.0		1.0	
- Q2	1.55 (0.78 – 3.11)	0.94	1.84 (0.77 – 4.41)	0.84
- Q3	1.61 (0.78 – 3.31)	0.81	2.07 (0.83 – 5.13)	0.50
- Q4	2.19 (1.09 – 4.41)	0.06	2.56 (1.05 – 6.22)	0.09
Number of observations used in adjusted analysis: 720; Convergence criterion satisfied; R^2=15.7%				

[a] Adjusted for maternal age, cadmium, manganese and selenium blood levels, hematocrit, parity, body-mass index, gestational diabetes, educational level, socio-economic status, geographical residence, and smoking status during pregnancy.

[b] Log-transformed maternal blood lead used as a continuous variable

[c] Quartiles of maternal blood lead distribution: Q1 (< 1.20 µg/dl); Q2 (1.20 – 1.70 µg/dl); Q3 (1.71 – 2.30 µg/dl); and Q4 (> 2.30 µg/dl).

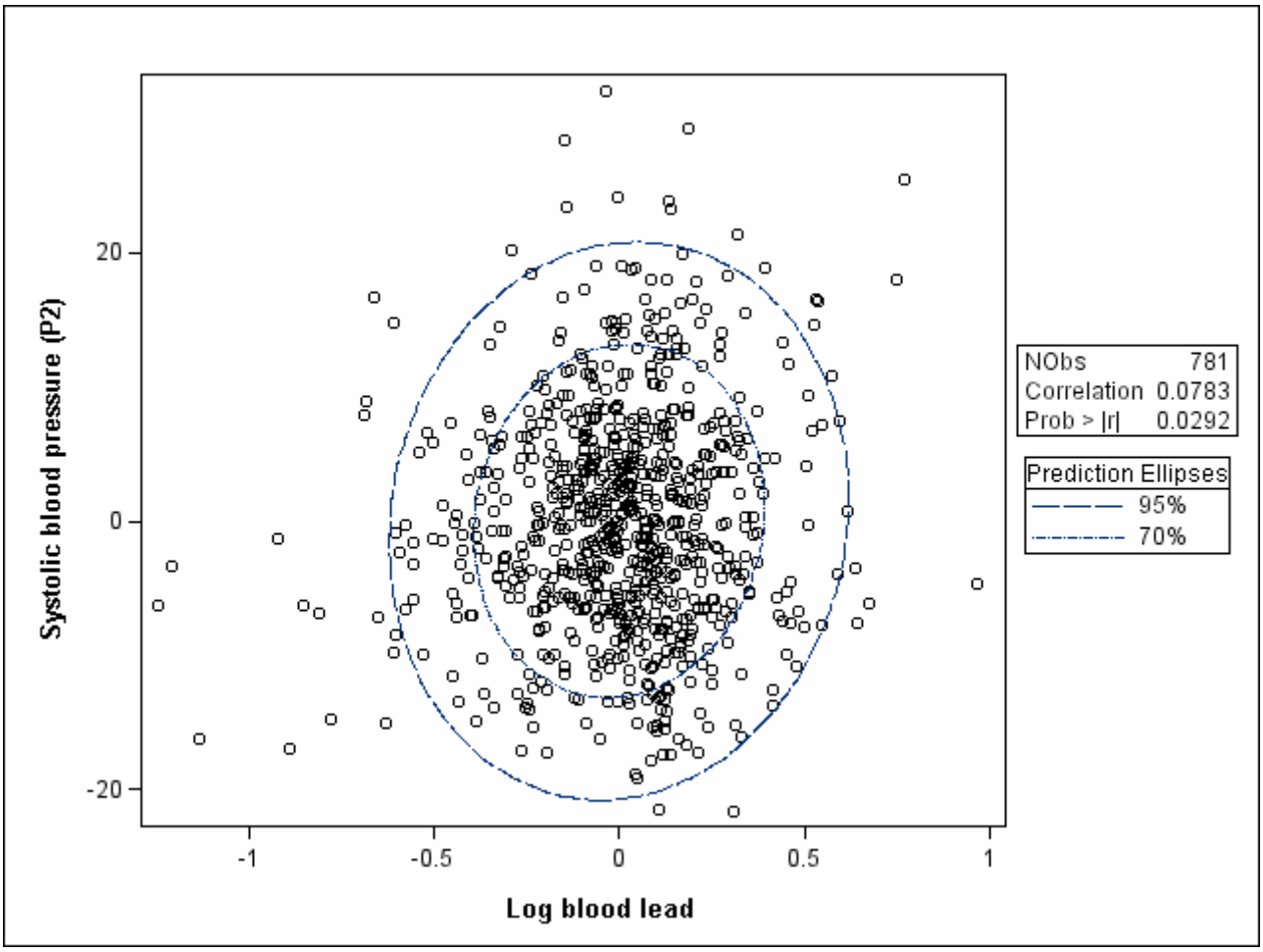
Table 4. Odds Ratios for PIH according to parity, per unit increase in blood lead level.

	PIH incidence	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Nulliparous	10.7 %	1.8 (0.5 – 6.6)	2.9 (0.6 – 15.7)
Multiparous	11.4 %	3.7 (1.1 – 12.3)	4.6 (1.0 – 21.6)

[a] Adjusted for maternal age, cadmium, manganese and selenium blood levels, hematocrit, body-mass index, gestational diabetes, educational level, socio-economic status, geographical residence, smoking status and alcohol consumption before pregnancy.

Figures

Figure 1. Scatter plot of the residuals for maternal blood Lead and systolic blood pressure between 24 and 36 weeks (SBP2) after controlling for the effect of variables listed in the logistic model in table 3.



This figure illustrates the correlation between residuals of the linear regression of the two variables on the partialled variables. In the 95% and 70% prediction ellipses, the major axis length is significantly larger than the minor axis length, indicating a partial correlation between maternal blood lead and SBP2.