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ABSTRACT. The authors investigated the effect of blood lead (BPb) and its relationship with calcium and phosphorus in the development of preeclampsia in Nigeria. Blood samples were collected from 59 preclamptics, 150 normal pregnant, and 122 nonpregnant women. Blood lead and serum Ca and P were determined. Blood lead was significantly higher ($p < .001$), whereas serum Ca and P were significantly lower ($p < .001$) in preclamptics than in normal pregnant women (60.2 ± 12.8 vs 26.3 ± 8.0 μg/dL for Pb, 1.39 ± 0.33 vs 2.03 ± 0.22 mmol/L for Ca, and 0.76 ± 0.10 vs 0.99 ± 0.13 mmol/L for P, respectively). There was significant increase ($p < .05$) in BPb and decreases ($p < .01$) in serum Ca and P in pregnant women than in nonpregnant women (35.7 ± 18.0 vs 13.1 ± 6.4 μg/dL for Pb, 1.85 ± 0.33 vs 2.33 ± 0.20 mmol/L for Ca, and 0.93 ± 0.38 vs 1.24 ± 0.26 mmol/L for P). Also, BPb was negatively correlated with serum Ca and, P, and positively correlated with systolic and diastolic blood pressures in pregnancy ($r = -.804$ for Ca, $r = -.728$ for P, $r = .908$ for SBP, and $r = .842$ for DBP) and preeclampsia ($p < .01$). It appears that increase in blood lead, which parallels decreases in serum calcium and phosphorus, may be related to the development and progression of preeclampsia in this environment.

KEYWORDS: calcium, lead, phosphorus, preeclampsia, pregnancy

Lead (Pb) is a ubiquitous environmental toxicant, which has been implicated in numerous acute and chronic illnesses. Despite the banning of lead-based gasoline, paint, and solder, as well as passage and enforcement of industrial and environmental regulation in the United States and other developed countries,[1] significant lead exposure continues in countries such as Nigeria, where lead-based gasoline was banned since 2002, but other environmental and industrial regulations, though existing now, are not strictly enforced. Besides, there is poor community awareness campaign on lead exposure in this environment.

Lead is absorbed via the respiratory and gastrointestinal tracts and, occasionally, through the skin.[2] After absorption, lead is distributed in the blood, bone, and soft tissues, with

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over 95% of the total body lead content residing in bones. The half-life of lead in the skeleton is 20–30 years.[3] Gradual release of lead from bone serves as a persistent source of exposure. The rate of release of lead and calcium from bone is increased in conditions associated with heightened bone resorption/turnover, such as pregnancy, lactation, menopause, osteoporosis, immobilization, and hyperthyroidism.[4]

Preeclampsia is the most common medical complication of pregnancy associated with increased maternal and infant mortality and morbidity.[5] However, the exact etiology is not known. Several reports show that various elements might play an important role in etiology of preeclampsia. Despite all indications that lead might be a factor in this, it has not been examined in this environment. This study was conducted to examine this possibility and implications for maternal and fetal health.

METHODS

Sample size calculation

The formula previously described by Araoye[6] was employed for sample size calculation:

$$n = \frac{2z^{2pq}}{d^2}$$

where $n =$ the desired sample size or the desired effect size was calculated as 184 pregnant women. The standard normal deviation is usually set at 1.96 (or more simply at 2.0), which corresponds to the 95% confidence level. What the projected sample size would be to fulfill the study objective was derived by approximating the calculated 184 to 200 pregnant women.

Study population

This study enrolled a cohort of pregnant women who commenced prenatal care at the antenatal clinic and ward of Irrua Specialist Teaching Hospital Irrua, Edo State, Nigeria, between November 2006 and September 2008. The informed consent and approval of all the subjects were obtained. Each participant signed a consent form after the procedure and implications had been explained to the subject in English language or special English. The study was approved by the Research and Ethics Committee of Irrua Specialist Teaching Hospital, Irrua, Edo State.

The inclusion criterion for each subject was that she must be within the age range of 20 to 35 years, whereas the exclusion criterion was history of any chronic disease and glycosuria. Medical and obstetrics histories were obtained from each participant's case note/file by 2 resident doctors who were blinded to the goal of the study. To ensure consistent data abstraction and handling, they filled in a printed form for each participant, which was handed to the principal investigator for data processing.

Maternal systolic blood pressure (SBP) and diastolic blood pressure (DBP) during routine visits to prenatal clinic was measured with the subject in supine position, using a standard mercury sphygmomanometer (Accoson, Essex, UK). The subjects were also tested for presence of protein and glucose in their urine on each visit, using Medi-Test Combi 2 strips (Macherey-Nagel, Duren, Germany.). Those with glycosuria were excluded from the study. Women were classified as having preeclampsia based on SBP $\geq$140 mm Hg and/or DBP $\geq$90 mm Hg and proteinuria,[7] measured during at least 2 visits after the 22nd week of gestation, such that the elevated levels could have occurred during or across any of the weeks, at any point after 22 weeks. Consequently, no diagnosis of preeclampsia was made before 24 weeks. The mean value of the last 2 measurements taken before delivery as recorded in their case note/files was calculated to determine the values for SBP and DBP assigned to each subject.

Blood sample collection

Ten milliliters of venous blood was collected from the antecubital vein of each participant at delivery; 7 mL was dispensed into plain container to obtain serum for calcium and phosphorus determination, whereas the remaining 3 mL was dispensed into an EDTA container and mixed gently for blood lead determination. The serum was stored frozen and analyzed within 24 hours for Ca and P, whereas the whole blood was stored refrigerated at 2°C to 8°C, and were analyzed for blood Pb within 4 days.

Procedures

Atomic absorption spectrophotometer model 200A (Buck Scientific, East Norwalk, UK) with detection limit of 1 μg/dL was employed for blood lead determination, as described by Welz[8]; the digested samples were analyzed in duplicates by the atomic absorption spectrophotometry methodology using wavelength of 283 nm, and the mean value computed. Repeated analyses of standard solutions confirmed the method's precision.

Serum calcium was determined by the cresolphthalein-complexone colorimetric method described by Gitelman.[9] Chemical kits supplied by Human Diagnostica (Wiesbaden, Germany) was employed. Serum phosphorus was determined by the colorimetric method as described by Gomori.[10] Humatrol quality-control samples (Human Diagnostica) were used for assessment of quality assurance. This was included in each batch of the analysis for calcium and phosphorus.

Statistical analysis

All data generated were subjected to statistical analysis. Means, standard deviations, Student's t test, and Pearson correlation were computed using SPSS 16.0 software for Windows (SPSS, Chicago, IL, USA). Results were expressed as mean $\pm$ SD. The 5% ($p < .05$) level of significance was adopted.

Table 1.—Blood Lead, Serum Calcium, Inorganic Phosphorus, BMI, SBP, and DBP Levels in Pregnant and Nonpregnant Women (Controls)

	Pregnant women ($n = 209$)		Nonpregnant women (controls) ($n = 122$)			
Variables	*M*	*SD*	*M*	*SD*	*t* value	*p* value
Age (year)	26.9	3.5	26.8	3.6	0.6773	>.05 (NS)
Lower 95% CI	26.4		26.1			
Upper 95% CI	27.4		27.4			
Gestational age (week)	38.1	2.4	NA		NA	NA
BMI	28.2	4.1	25.5	2.1	8.2983	<.001*
Lower 95% CI	27.6		25.1			
Upper 95% CI	28.8		25.9			
SBP (mm Hg)	131.8	31.5	111.7	9.9	9.0993	<.001*
Lower 95% CI	127.5		110.4			
Upper 95% CI	136.1		114.4			
DBP (mm Hg)	84.0	20.6	67.4	4.3	2.4545	<.05*
Lower 95% CI	81.2		66.5			
Upper 95% CI	86.8		69.2			
Pb (μg/dL)	35.7	18.0	13.1	6.4	2.336	<.05*
Lower 95% CI	33.3		12.0			
Upper 95% CI	38.2		14.3			
Ca (mmol/L)	1.85	0.38	2.33	0.20	2.7172	<.01*
Lower 95% CI	1.80		2.30			
Upper 95% CI	1.90		2.37			
P (mmol/L)	0.93	0.16	1.24	0.26	9.1884	<.001*
Lower 95% CI	0.90		1.19			
Upper 95% CI	0.95		1.28			

*t test significant. NS = nonsignificant; NA = not applicable.

RESULTS

A total of 283 pregnant women were enrolled initially. Of these, 74 were excluded for noncompliance with laid down criteria or did not finally deliver in the hospital of study. Finally, we examined 209 pregnant women with mean age 28.2 ± 4.1 years. The pregnant women consisted of 150 normal pregnant women and 59 women with preeclampsia. The control group (nonpregnant women) totaled 122 in number with mean age 26.8 ± 3.6 years.

Blood lead, serum calcium, inorganic phosphorus, BMI, SBP, and DBP levels in pregnant women versus controls

Blood lead level was significantly higher in pregnant women than in controls (35.7 ± 18.0 vs 13.1 ± 6.4 μg/dL, $p < .05$; Table 1). Systolic and diastolic blood pressures were significantly higher in pregnant women than in controls (131.8 ± 20.6 vs 111.7 ± 9.9 mm Hg, $p < .001$, for SBP and 84.0 ± 20.6 vs 67.4 ± 4.3 mm Hg, $p < .05$, for DBP, respectively; Table 1). Serum calcium and inorganic phosphorus levels were both significantly lower in pregnant women than in the controls (1.85 ± 0.38 vs 2.33 ± 0.20 mmol/L, $p < .01$, for Ca and 0.93 ± 0.16 vs 1.24 ± 0.26 mmol/L for P, $p < .001$, respectively; Table 1). Body mass index (BMI) was significantly higher in pregnant women than in controls (28.2 ± 4.1 vs 25.5 ± 2.1 kg/m^2; $p < .001$).

Blood lead, serum calcium, inorganic phosphorus, BMI, SBP, and DBP levels in women with preeclampsia versus normal pregnant women

Blood lead concentrations in women with preeclampsia were significantly higher than in normal pregnant women (60.2 ± 12.8 vs 26.3 ± 0.22 μg/dL, $p < .001$; Table 2), whereas the serum calcium and inorganic phosphorus were significantly lower in women with preeclampsia compared with normal pregnant women (1.39 ± 0.33 vs 2.03 ± 0.22 mmol/L for Ca and 0.76 ± 0.10 vs 0.99 ± 0.13 mmol/L for P, $p < .001$, respectively; Table 2). BMI was similar in preeclamptics and normal pregnant women (29.4 ± 4.6 vs 27.6 ± 3.7; $p > .05$).

Blood lead, serum calcium, inorganic phosphorus, BMI, SBP, and DBP levels in normal pregnant women versus controls

The normal pregnant women had significantly higher BPb than the control (26 ± 8.0 vs 13.1 ± 6.4 μg/dL, $p < .01$;

Table 2.—Blood Lead, Serum Calcium, Inorganic Phosphorus, BMI, SBP, and DBP Levels in Women With Preeclampsia and Normal Pregnant Women

	Preeclampsia ($n = 59$)		Normal pregnant ($n = 150$)			
Variables	*M*	*SD*	*M*	*SD*	*t* value	*p* value
Age (year)	27.3	3.2	26.7	3.6	0.2327	>.05 (NS)
Lower 95% CI	26.5		26.1			
Upper 95% CI	28.2		27.3			
Gestational age (week)	35.5	2.0	39.0	1.6	6.4226	<.001*
Lower 95% CI	35.0		38.8			
Upper 95% CI	36.0		39.3			
BMI	29.4	4.6	27.6	3.7	0.0103	>.05 (NS)
Lower 95% CI	28.2		27.1			
Upper 95% CI	30.7		28.4			
SBP (mm Hg)	175.2	20.9	114.6	13.1	4.2800	<.001*
Lower 95% CI	169.7		112.4			
Upper 95% CI	180.7		116.7			
DBP (mm Hg)	110.6	15.8	73.3	9.8	1.9678	<.05*
Lower 95% CI	106.4		71.7			
Upper 95% CI	114.8		74.9			
Pb (μg/dL)	60.2	12.8	26.3	0.22	6.3737	<.001*
Lower 95% CI	56.9		25.0			
Upper 95% CI	63.4		27.6			
Ca (mmol/L)	1.39	0.33	2.03	0.22	9.7912	<.001*
Lower 95% CI	1.30		1.99			
Upper 95% CI	1.48		2.06			
P (mmol/L)	0.76	0.10	0.99	0.13	2.6491	<.001*
Lower 95% CI	0.73		0.97			
Upper 95% CI	0.78		1.01			

*t test significant. NS = nonsignificant.

Table 3). Systolic blood pressure was similar in normal pregnant women and controls (114 ± 13.1 vs 117.99 ± 9.9 mm Hg, $p > .05$; Table 3). Diastolic blood pressure was significantly higher in normal pregnant women compared with controls (73.3 ± 9.8 vs 67.4 ± 4.3 mm Hg, $p < .01$; Table 3). Serum calcium and inorganic phosphorus were both significantly reduced in normal pregnant women than in controls (2.03 ± 0.22 vs 2.33 ± 0.20 mmol/L for Ca, $p < .05$, and 0.99 ± 0.13 vs 1.24 ± 0.26 mmol/L, for P, $p < .001$; Table 3). There was no significant difference ($p > .05$) in BMI of normal pregnant women and controls.

Correlations of blood lead with serum calcium, inorganic phosphorus, BMI, SBP, and DBP in pregnant women

Table 4 shows that BPb was positively correlated with SBP and DBP ($r = .908$ and $r = .842$, respectively, $p < .01$ in both cases) in pregnant women. BPb was negatively (inversely) correlated with serum calcium and inorganic phosphorus ($r = -.804$ and $r = -.728$, respectively, $p < .01$ in both cases) in pregnant women. Blood lead was positively correlated with BMI in pregnant women ($r = .228$, $p < .01$).

Correlations of blood lead with serum calcium, inorganic phosphorus, BMI, SBP, and DBP in preeclampsia

Data in Table 5 show that BPb was positively correlated with SBP and DBP in women with preeclampsia ($r = .790$ and $r = .517$, respectively, $p < .01$ in both cases). Also, BPb was negatively correlated with serum calcium and inorganic phosphorus in women with preeclampsia ($r = .629$ and $r = .513$, respectively, $p < .01$ in both cases). Blood lead was not associated with BMI in preeclampsia ($r = .143$, $p > .05$).

COMMENT

This study reveals a significant increase in the blood lead (BPb) level of pregnant women compared with the nonpregnant women (controls) (35.7 ± 18.0 vs 13.1 ± 6.4 μg/dL; $p < .05$). The increase in the BPb observed in the pregnant women most probably results from of mobilization of Pb from the maternal bone. It has been reported that women of childbearing age have bone lead stores due to lead exposure as children.[11] Approximately 15% of all the lead that enters the body is sequestered in the skeleton, where it becomes

Table 3.—Blood Lead, Serum Calcium, Inorganic Phosphorus, BMI, SBP, and DBP Levels in Normal Pregnant Women Versus Nonpregnant Women (Controls)

	Normal pregnant ($n = 150$)		Nonpregnant women (controls) ($n = 122$)			
Variables	*M*	*SD*	*M*	*SD*	*t* value	*p* value
Age (year)	26.7	3.6	26.8	3.6	0.8999	>.05 (NS)
Lower 95% CI	26.1		26.1			
Upper 95% CI	27.3		27.4			
Gestational age (week)	39.0	1.6	NA		NA	NA
Lower 95% CI	38.8					
Upper 95% CI	39.3					
BMI	27.6	3.7	25.5	2.1	1.0952	>.05 (NS)
Lower 95% CI	27.1		25.1			
Upper 95% CI	28.4		25.9			
SBP (mm Hg)	114.6	13.1	111.7	9.9	0.0428	>.05 (NS)
Lower 95% CI	112.4		110.4			
Upper 95% CI	116.7		114.4			
DBP (mm Hg)	73.3	9.8	67.4	4.3	2.9954	<.01*
Lower 95% CI	71.7		66.5			
Upper 95% CI	74.9		69.2			
Pb (μg/dL)	26.3	0.22	13.1	6.4		
Lower 95% CI	25.0		12.0			
Upper 95% CI	27.6		14.3		3.8207	<.01*
Ca (mmol/L)	2.03	0.22	2.33	0.20	1.9818	<.05*
Lower 95% CI	1.99		2.30			
Upper 95% CI	2.06		2.37			
P (mmol/L)	0.99	0.13	1.24	0.26	8.6892	<.001*
Lower 95% CI	0.97		1.19			
Upper 95% CI	1.01		1.28			

*t test significant. NS = t test nonsignificant; NA = not applicable.

incorporated into the hydroxyapatite mineral structure of bone and persists with a half-life of decades.[12,13] Therefore, over 95% of body burden of lead in a typical adult can be found in bone.[14] Pregnancy is associated with some physiological changes. Following deposition in bone, lead can be mobilized in response to both physiologic and pathologic conditions. Both lead and calcium stored in bone can be mobilized into the mother's blood and cross the placenta.[15,16] Also, Gulson et al[17] in their study reported that lead is mobilized from the skeletal stores at an accelerated rate during pregnancy and contributes significantly to blood lead levels during pregnancy. This is consistent with the finding in this report and at least in part explains the higher blood lead concentration observed in pregnant women than in nonpregnant women in the present study.

We observed a statistically significant increase in BPb in women with preeclampsia compared with the normal pregnant women in the present study. A possible mechanism involves the marked increases in mobilization of lead from maternal bone that have been demonstrated to occur during pregnancy.[17] This possibility may have deleterious effect because marked increases in maternal bone lead mobilization

Table 4.—Correlations of Blood Lead With Serum Calcium, Inorganic Phosphorus, BMI, SBP, and DBP in Pregnant Women

Dependent variables	*n*	*r* value	*p* value
SBP	209	.908	<.01
DBP	209	.842	<.01
BMI	209	.228	<.01
Calcium (Ca)	209	−.804	<.01
Phosphorus (P)	209	−.728	<.01

Table 5.—Correlations of Blood Lead With Serum Calcium, Inorganic Phosphorus, BMI, SBP, and DBP in Women With Preeclampsia

Dependent variables	*n*	*r* value	*p* value
SBP	59	.790	<.01
DBP	59	.517	<.01
BMI	59	.143	>.05 (NS)
Calcium (Ca)	59	−.629	<.01
Phosphorus (P)	59	−.513	<.01

result in increased lead exposure not only to maternal but also to the fetal circulation, since the placenta is not a meaningful barrier against the movement of lead from mother to fetus.[17,18]

There is evidence that lead increases the circulating levels of endothelin, a vasoactive substance secreted by endothelial cells.[19] Lead is also reported to reduce the levels of vasodilator substances such as plasma nitric oxide (NO) and endothelial-derived relaxation factor (EDRF); this reduction is due to a lead-mediated increase in reactive oxygen species (ROS).[19–21] Inhibition of membrane adenosine triphosphatases (ATPases) by Pb metal also leads to increased intracellular calcium ions and vasoconstriction.[22] These appear to be the mechanisms of lead increasing the risk of preeclampsia by inducing vasoconstriction and placental ischemia or by a direct toxicity on the endothelial cell and the renal function and thus causing proteinuria, which is a common feature of preeclampsia.

Findings in the present study are consistent with report from a recent study showing a relationship between blood lead levels and pregnancy-induced hypertension.[23] Our observations corroborate an earlier report by Vigeh et al[24] that environmental exposure to lead may increase the risk of preeclampsia in women without occupational exposure. However, the present study is inconsistent with an earlier report that lead appears to have small, but demonstrable association with pregnancy-induced hypertension and blood pressure at the time of delivery, but not with preeclampsia.[25] Environmental, race, and dietary differences may in part be responsible for the difference in results from the Rabinowitz et al[25] study 2 decades before the present study.

Maternal calcium requirements increase in the early stages of pregnancy and continue to rise until delivery.[26] Calcium is actively transferred to the fetus; a full-term infant accumulates over 30 g of calcium during gestation, most of which is assimilated into the fetal skeleton in the third trimester.[27] Besides, low phosphate mobilizes lead from bone and raises the concentrations in soft tissues.[28] These most probably explain the significantly lower concentrations of calcium and phosphorus in the pregnant women than in the controls observed in this present study. It is noteworthy that our study reveals a negative correlation of blood lead with serum calcium and phosphorus in the pregnant women. This appears to buttress that as lead and calcium are mobilized from the bone, calcium and phosphorus are transferred to the fetus to meet the increasing need of the growing fetus, thereby decreasing the maternal serum levels of Ca and P, as observed in the present study. Ikaraoha et al[29] have previously reported a progressive decrease in serum calcium and inorganic phosphate levels in pregnant women in Nigeria.

The preeclamptic patients study maintained negative correlations of BPb with Ca and P. Also, comparison of Ca and P in our study shows significantly lower concentrations in women with preeclampsia than in normal pregnant women. All of the implications are that low serum calcium stimulates bone resorption, which will mobilize lead from bone, leading to increase in BPb, which may lead to the development of preeclampsia. Susceptibility may be related to greater increase in blood lead and decrease in serum calcium. Our findings corroborate a recent report from India that reduction in serum levels of calcium might be possible contributor in the etiology of preeclampsia.[5] Also, lead causes alteration of cellular Ca^{2+} transport and intracellular Ca^{2+} distribution, leading to movement of calcium from the extracellular to the intracellular compartments,[4] thus explaining the observed decrease in serum calcium with increase in BPb of women with preeclampsia in our study.

Other investigators who assessed longitudinal changes in blood lead levels during pregnancy have suggested that calcium intake may provide some protection against lead exposure.[30] Hertz-Picciotto et al[30] reported that a higher calcium intake was inversely associated with blood lead levels in the latter half of pregnancy. The mechanism by which calcium decreases blood lead levels remains to be elucidated. It probably halts or slows down lead mobilization from bone. A recent trial documented that calcium supplements decreased bone resorption in the last trimester of pregnancy.[31] Similarly, studies that evaluated bone mineral density using ultrasonography have demonstrated greater changes among women with a lower calcium intake.[32] Further research in this area should focus on the evaluation of dietary interventions for decreasing prenatal lead exposure in this environment.

BMI was not associated with preclampsia in this study. However, a positive correlation was observed for lead with BMI in pregnant women. The significantly higher value of SBP and DBP in preeclamtic women compared with the normal pregnant women defines preeclampsia. Blood lead was positively correlated with SBP and DBP of pregnant women and women with preeclampsia. It is likely that the higher blood lead level observed in the pregnant population was responsible for the increase in both SBP and DBP. Previous studies have reported increase in blood pressure with lead exposure.[25] A trend of increasing blood pressure with age is usually reported for DBP. The age range (20 to 35 years) in the present study eliminated the effect of age on blood pressure.

A previous report shows that approximately 37,000 Nigerian women die annually because of preeclampsia/eclampsia-related complication.[33] But this present study reveals that elevated blood lead level may in part contribute to the development of preeclampsia in this environment. The importance of this result is that it indicates a public health problem in Nigeria, as lead is a ubiquitous environmental toxicant. This result may be important to other populations with lower blood lead levels and the overall Nigerian population in the prevention of preeclampsia and other lead-related disorders.

The present study has several limitations. A large number of prospective subjects declined to participate due to the relatively large volume (10 mL) of blood sample required for the study, whereas others refused because of their religious and other beliefs. Other study limits are serial blood Pb were not included; blood Pb were not done at the same point of

time of gestational age for all pregnant women; acute/chronic effect was not determined with other biologic testing; and source of exposure was not adequately assessed for these pregnant women: diet versus home distance from Pb source, or occupation of any worker versus other.

Conclusion

Preeclamptics have a higher blood lead concentration when compared with normal pregnant women and controls. The increases in blood Pb concentration appear to parallel decreases in serum calcium and phosphorus in preclamptics. Primary prevention should include enforcement of strict measures to minimize lead exposure to the general populace in this environment.

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