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Evaluation of Plasma Lead Levels in Pregnancy and Outcome Implications, Kinshasa, DR Congo

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ABSTRACT

The aim of this work was to evaluate plasma Pb levels in pregnancy and their birth outcomes implications. For analysis (n = 396 pregnant women with 56 fetal-maternal clusters), plasma samples were diluted quantitatively with a matrix modifier solution and Pb levels were measured using an atomic absorption spectrophotometer (AA500FG). Compared to women with a normal Body Mass Index, underweight, overweight and obese women group had increased levels of plasma Pb (t-test, p=0.0395). Levels of plasma Pb were also observed in women with a family history of preeclampsia and diabetes mellitus (t-test, p=0.0050 and 0.0312, respectively). At delivery, plasma Pb levels were significantly higher in women as compared to prenatal period [means (±SD), 3.387 µg/L (± 0.965) in 37-42 weeks, 2.060 µg/L (± 0.980) in 20-36 weeks and 1.543 µg/L (± 0.709) in 10-19 weeks, ANOVA, p < 0.0001] and newborns showed higher plasma Pb levels than their mothers [means (±SD), 2.304 µg/L (± 0.644) versus 2.067 µg/L (± 1.067), t-test, p < 0.0001]. Globally, plasma Pb levels show no significant linear negative correlation to all of the birth outcomes (weight, height, ponderal index, Apgar score, gestational age, head circumference).

Keywords: Plasma Lead, Birth Outcomes, Maternal Outcomes, Prenatal Exposure, Kinshasa.

BACKGROUND

Pb is one of the most widespread toxicants in the world, and although its uses have been progressively prohibited by rules and regulations resulting in a dramatic decline of Pb exposure in many countries, it remains a matter of public health concern, especially for pregnant women and children [1,2]. Prenatal exposure to Pb has been shown to be associated with neurological dysfunctions, stillbirths, hypertension, spontaneous abortions, preterm birth, reduced birth weight and birth size [3-8].

It is also well established that blood Pb levels increase during pregnancy, from 24 weeks of gestation until delivery, because of increased

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gastrointestinal absorption and because of an increase in bone turnover in this period [9,10]; and cord and maternal blood Pb levels had a good relationship [8] confirming that Pb easily crosses the placental barrier [11]. At delivery, Pb levels in maternal blood were strong predictors of cord blood levels [8].

In DRC, blood Pb levels measured after phasing out of leaded gasoline continue to constitute a major public health concern for pregnant women and children in Kinshasa [12-16], increased urinary excretion of toxic metals, especially Pb, was observed in preeclampsia [17]. In line with these results, exposure levels to metals including Pb are connected to negative effects such as, preeclampsia, birth defects, children's temperament difficulties, and holoprosencephaly [18].

Although plasma Pb represents a more relevant index of exposure to, distribution of, and health risks associated with Pb than does blood Pb [19-22], most research on associations between maternal Pb levels and adverse birth outcomes have been reported for whole blood levels of Pb. In this work, the plasma Pb levels in pregnancy and their birth outcomes was evaluated. A conclusion will be given by providing recommendations to create a local Pb screening committee during pregnancy and lactating as suggested by committee opinion of the American College of Obstetricians and Gynecologists.

METHODS

Study population and Data collection

Pregnant women were recruited at the maternity hospitals [Kinshasa General Reference Hospital (Gombe), Delvaux Maternity Hospital (Binza), Saint-Christophe Health Center (Binza); Saint-Raymond Health and Maternity Center (Matete), Esengo Maternity Hospital (Kisenso), Lisanga Maternity Hospital (Lemba); Bomoyi Health and Maternity Center (Tshangu)]. Enrolment was implemented between June 2019 and June 2020 during the pregnancy visits. A kohort of 400 eligible women received a detailed explanation of study procedures before consenting to participate [living in Kinshasa ≥ 6 months, amenorrhea period ≥ 10 weeks, not planning to move out of the city before delivery]. Positive responses were obtained from 396 pregnant women, more than 95 % of those approached. The research protocol was approved by the Bio-ethics Committee of the School of Public Health at the University of Kinshasa.

Data collection

During the pregnancy visit women provided venous blood samples in 10 mL metal free tubes containing lithium heparin as described elsewhere [23]. At delivery, both maternal venous blood and umbilical cord blood samples were collected. All blood was immediately centrifuged (10 minutes, 3000 g) and the plasma fraction was transferred into 2.5 mL pre-cleaned glass vials (Supelco®) and stored at -80°C for Pb analysis. The plasma samples were transported to the Analytical Chemistry and Environmental Toxicology laboratory of the University of Kinshasa. Pregnancy and delivery information collected in the questionnaires were clinics, socio-demographics, anthropometrics, current and previous pregnancies, current and previous preeclampsia or diabetes mellitus, smoking during pregnancy, and lifestyle.

Analytical methods

The samples were brought to room temperature and vortexed after thawing. Pb was measured by atomic absorption (AA500FG, PG Instruments, and Wibtoft, LE17 5BH, UK) [24]. Aliquots of 100 µL plasma were diluted (1+10 by volume) with a matrix modifier solution containing 0.5 % Triton X-100 (Sigma-Aldrich, St. Louis, MO, USA), 0.2 % nitric acid (65 % pure, Carl Roth, Karlsruhe, Germany) and 0.1 % ammonium phosphate (0.1 mg/mL PO43-, Sigma-Aldrich). Determinations were calibrated with Pb solutions prepared from Pb standard solution suitable for atomic spectrometry [1000 ppm Pb, 1 mg/mL Pb-Sigma-Aldric]. Because the plasma Pb levels were low, triplicate samples were analyzed, repeated for each sample with a coefficient of variation less than 10 %, and the detection limit (LOD) was 0.5 µg/L. Analytical validity was confirmed using commercial standard serum (Seronorm L1 and L2) at the beginning of the run and the end of each run of 20 samples, as previously described [25-27].

Statistical analysis

Statistical data analysis was completed using Prism Graph Pad 9.41 (Graph Pad Soft-ware, San Diego, CA, USA). The normality of residuals was evaluated using Kolmogorov-Smirnov test for continuous variables. For the descriptive statistics, results are presented as percentage for categorical variables and as means (± standard deviation), percentiles (P25, P50, P75, P95) and minimum-maximum for continuous variables. Differences between groups were analyzed with analysis of variance (ANOVA), t-test, and trend test after log transformation of skewed variables. Differences in proportions were analyzed with chi-square test. A multiple linear regression was used to estimate the association between log-transformed continuous plasma Pb and other continuous or categorial variables. Two-sided $p < 0.05$ was considered statistically significant. Pb levels below the LOD were assigned a value of LOD/2 for statistical calculations [28,29].

RESULTS

Of the 396 women included in this study, 177(45 %) had 30

years of age or more, 306(77 %) had lower or middle school degree, 81(20 %) were unmarried, 186 (47 %) earned less than $100 USD monthly, 212(54 %) were multiparous, 69(17 %) had diabetes mellitus, 142(36 %) had history of preeclampsia and 243(62 %) were underweight, overweight or obese women; 40(10 %) consumed alcohol during pregnancy. None of them smoked during pregnancy (Table 1). Among the 56 births occurred, 11(20%) were pre-term or post-term, 35(63%) were female, 1(2%) was under 7 Apgar score in 5 minutes, 7(12%) were underweight or overweight newborns (Table 1).

Table 1. Sociodemographic characteristics of the study subjects (2019 - 2020, Kinshasa, n = 396).

		n (%)
	Maternal characteristics	396(100)
Age (years)	<18	36(9)
	18-29	163(41)
	≥ 30	177(45)
Education	Lower school or none	20(5)
	Middle school	286(72)
	High school or university degree	90(23)
Marital status	Married or living as married	315(80)
	Unmarried	81(20)
Family income (month)	None	86(22)
	<100 $ USD	100(25)
	100-500	196(49)
	≥ 500$	14(4)
Smoking during pregnancy	Yes	0
	No	396(100)
Alcohol use during pregnancy	Yes	40(10)
	No	356(90)
Parity	0 (primiparous)	184(46)
	≥1 (multiparous)	212(54)
BMI	≤18.5 (underweight)	5
	18.5-24 (normal)	149(38)
	25-29 (overweight)	141(36)
	≥30 (Obese)	97(26)
Diabetes mellitus	Yes	69(17)
	No	327(83)
Family history of preeclampsia	Yes	142(36)
	No	254(64)
Newborn characteristics		56(100)
Sex	Female	35(63)
	Male	31(47)
Birth weight (g)	<2500 (underweight)	3(5)
	2500 - 4000 (normal)	49(88)
	> 4000 (overweight)	4(7)

Ponderal Index (g/cm3)(63)	≤ 2.49 (Low ponderal index)	56(100)
	2.50-3.16 (Normal Ponderal index)	0
	≥ 3.17 (high ponderal index)	0
Gestational age (weeks)	<37 (pre-term)	6(11)
	37 - 41 (normal)	45(80)
	>42 (post-term)	5(9)
Delivery method (n)	Vaginal	56(100)
	Caesarean section	0
Apgar score	5 min <7	1(2)
	5 min ≥7	55(98)

BMI: Body Mass Index

Table 2 lists the means (±SD), percentiles (P25, P50, P75 and P95) and minimum as well maximum of the continuous variables: maternal parameters including plasma Pb (µg/L), age (years), weight (kg), height (m), amenorrhea period (weeks), BMI (kg/m2), SBP (mm Hg), DBP (mm Hg), and newborn parameters containing foetal plasma Pb, birth weight (g), birth height (cm), ponderal index (g/cm3), gestational age at birth (years), head circumference at birth (cm) and Apgar score. The plasma Pb means (±SD) were respectively 2.067 µg/L (± 1.067) in maternal and 2.304 µg/L (± 0.644) in newborns.

Table 2. Association between maternal-child parameters and plasma Pb levels.

Variables	Mean ±SD	Percentiles				Min - Max
		P25	P50	P75	P95	
	Mothers					
Pb (µg/L)	2.067 ± 1.067	1.605	1.994	2.329	4.021	0.250 - 4.630
Age (years)	26.57 ± 4.70	23.00	26.00	29.50	35.00	16.00- 45.00
Weight (kg)	68 ± 12	59	66	75	91	40 - 116
Height (m)	1.60 ± 0.07	1.60	1.60	1.70	1.7	1.00 - 1.80
Amenorrhea period	26.0 ± 8.5	19	26	32	39	10 - 42
BMI (kg/m²)	27 ± 5	23	26	30	35	16 - 45
Systolic blood pressure (mm Hg)	107 ± 15	100	110	110	113	69 - 221
Diastolic blood pressure (mmHg)	66 ± 10	60	60	70	80	55 - 126
	Newborns					
Pb (µg/L)	2.304 ± 0.644	2.025	2.282	2.836	3.227	0.245 - 4.911
Birth weight (g)	3190 ± 530	2820	3200	3543	4215	1500 - 4340
Birth height (cm)	49.0 ± 3.8	46	48	50	56	38 - 59
Ponderal Index (g/cm³)	1.393 ± 0.284	1.173	1.400	1.580	1.985	0.679 - 2.008
Gestational age at birth (weeks)	38.38 ± 1.53	33.00	38.50	39.00	40.45	33.00 - 42.00
Head circumference at birth (cm)	34 ± 2	33	34	36	37	29 - 38
Apgar Score	9 ± 1	9	10	10	10	5 - 10

AM: Arithmetic means, SD: Standard deviation, Percentiles (P25, P50, P75, P95), Min: Minimum and Max: Maximum, BMI: Body Mass Index

Regarding differences between groups, multiparous women had high levels of plasma Pb as compared to nulliparous (t-test, p =0.0072) (Figure 1). Compared to women with a normal BMI, underweight, overweight and obese women group had increased levels of plasma Pb (t-test, p=0.0395). Levels of plasma Pb were also observed in women with a family history of preeclampsia and diabetes mellitus (t-test, p=0.0050 and 0.0312, respectively). At delivery, plasma Pb levels were significantly higher in women as compared to prenatal period [means (±SD), 3.387 µg/L (± 0.965) in 37-42 weeks, 2.060 µg/L (± 0.980) in 20-36 weeks and 1.543 µg/L (± 0.709) in 10-19 weeks, ANOVA, p < 0.0001] and newborns showed higher plasma Pb levels than their mothers [means (±SD), 2.304 µg/L (± 0.644) versus 2.067 µg/L (± 1.067), t-test, p < 0.0001]. No significant associations were observed between maternal plasma Pb and birth weight (g), birth height (cm), ponderal index (g/cm3), gestational age at birth (weeks), head circumference at birth (cm) or Apgar score (Figure 2).

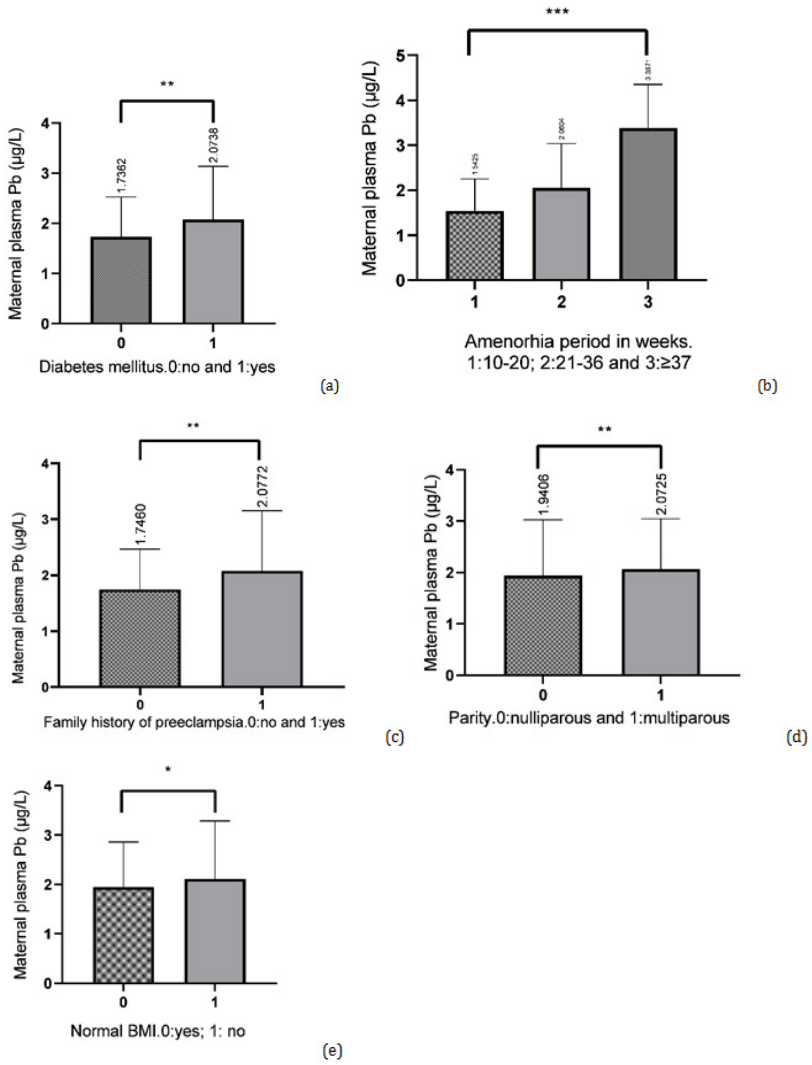

Figure 1. Comparison between plasma Pb levels and maternal outcomes (t-test or ANOVA). Maternal plasma Mn levels (µg/L) against (a) Diabetes mellitus, Amenorrhea period in weeks, (b) (c) Family history of preeclampsia, (d) Parity and (e) BMI.

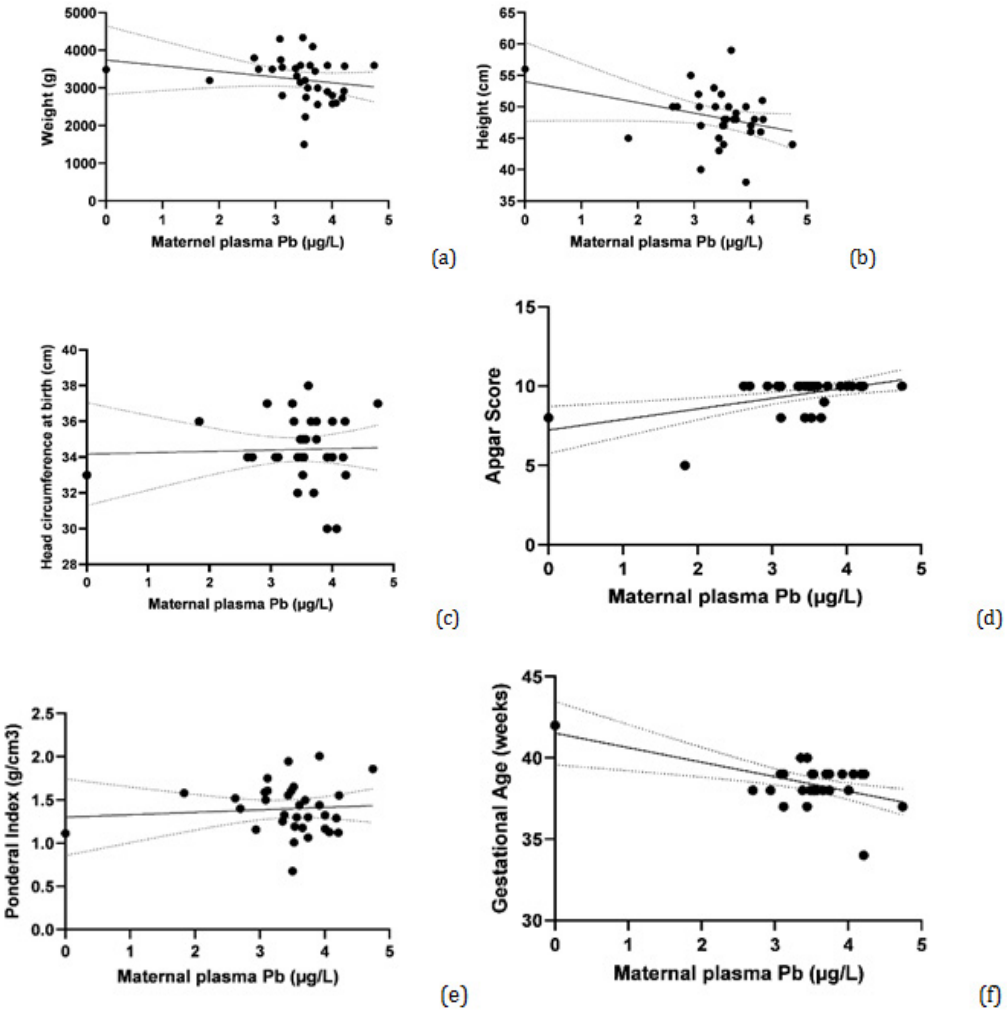

Figure 2. Scatter Plot of Maternal plasma Pb levels (µg/L) against birth outcomes. Maternal plasma Pb levels (µg/L) against (a) Birth weight (g), (b) Birth height (cm), (c) Head circumference at birth (cm), (d) Apgar Score and (e) Ponderal Index (g/cm3) and Gestational Age (weeks).

DISCUSSION

Most Pb in whole blood is bound to red blood cells [30,31], and the remaining Pb in the plasma which is bound with proteins such as albumin and globulin [32-34]. For a given whole-blood Pb, the plasmatic fraction [usually below 1 %, with < 0.5 % as median level)] represents the toxicologically active fraction for exchange with target tissues, including the developing fetus and the relevant index of health risks of Pb exposure [21,30,35-38]. Moreover, a strong curvilinear relationship was observed between Pb blood and Pb plasm (r = 0.75-0.97, Spearman's coefficient) [22,38,39]. On the other hand, more than in Pb blood, some studies observed a stronger correlation between plasma Pb with bone Pb suggesting that bone Pb contributes to the higher fraction of Pb in plasma [22,40,41]. In pregnant women, a high fraction of Pb plasma in whole blood implies more circulating Pb is free to cross the placenta increasing risk of Pb exposition and toxicity in fetus [42,43]. Nevertheless, laborious methods, specialized equipment and ultra-clean techniques are required for measuring Pb plasma accurately [44]. Consequently, the interest in using Pb plasma measures during pregnancy is modest [45].

The overall mean and range values of plasma Pb levels (2.067 µg/L; 0.250 - 4.630 µg/L, n = 396) in this study were higher than those reported in the literature: 0.42 µg/L (range 0.02-1.5) (22); 0.317 µg/L (range 0.060-2.65) [44] and 0.62 µg/L (range 0.55-0.69) [45]. The traditional use of fired clay for the treatment of gastritis by pregnant women, food habits and car battery recycling in certain residences appear to constitute the main sources of exposure in the city of Kinshasa [13,46].

Blood Pb levels have been linked with hypertension [47]. Principal risk factors for preeclampsia (≥ 140 mm Hg

systolic pressure and/or ≥ 90 mm Hg diastolic pressure after week 20) include multiple pregnancy, nulliparity, family history of preeclampsia and obesity, as previously reported [48,49]. Moreover, a meta-analysis reported a strong and reliable association between maternal blood Pb levels and preeclampsia [50]. In light of the above results, multiparous women with a family history of preeclampsia, diabetes mellitus and an anormal BMI had significantly higher plasma Pb levels in this study. However, most of these women had a normal systolic blood pressure with the 95th percentile of 113 mmHg for systolic pressure and 90 mmHg for diastolic pressure (Table 3). Consequently, pressure has not been found to correlate with maternal plasma Pb levels (Figure 2) as previously shown [47,51]. Otherwise, no significant difference was observed in plasma Pb levels as compared to certain characteristics such as marital status, family income, education and alcohol use during pregnancy. These results were consistent with certain studies [52,53].

Table 3. Multiple regression analysis model.

Parameter (Dependent Variable)	Partial R^2 (Independent Variables)				Total R^2
	BMI	multiparous	Family history of preeclampsia	Amenorrhea period	
Log (maternal plasma Pb levels)	0.02018	0.02425	0.02019	0.02418	0.0888

In pregnancy, elevated blood Pb levels have been associated with several adverse outcomes, including spontaneous abortion, gestational hypertension, abnormal fetal neurodevelopment, and low birthweight [50,54,55]. This study reported a good relationship between plasma Pb levels and amenorrhea periods (Pearson r = 0.549, p<0.001). High levels were also observed at delivery as compared to other amenorrhea periods (p<0.001) and Pb levels in fetal plasma were higher than those reported in maternal plasma (p<0.001). This is consistent with previous data in the literature reported increasing Pb levels during pregnancy, from 24 weeks of gestation until delivery [17,45, 56-60].

Although the evidence of associations between elevated Pb levels and several adverse outcomes reported in whole blood [3,5,6,7,18,40,45,60,61], the findings of this work indicate there was no significant linear negative correlation between maternal plasma Pb and all of these outcomes (birth weight, birth height, Apgar score, head circumference at delivery, ponderal index, gestational age at birth). The Possible reasons for this might be that the relatively small number of birth cohort studied and research on associations between plasma-Pb and adverse outcomes is still sparse in literature [22]. Nevertheless, despite this gap in knowledge, it is clear that the plasma Pb levels measured in this study constitute a major public health concern for pregnant women and newborns [18]. Moreover, CDC updated the blood Pb reference value to 3.5 µg/dL which provides an opportunity for additional progress in addressing longstanding disparities in lead exposure and BLLs in children [62]. Risk assessment of Pb exposure should take place at the earliest contact with pregnant and lactating women as recommended by committee opinion of the American College of Obstetricians and Gynaecologists [49].

A major limitation should be considered in evaluating present results. With regard to study population, data collection and analytical methods, the relatively small number of birth cohort studied. The sample collection methods used here were not robust but by chance, which were practically inevitable under present survey conditions and susceptible to errors associated with sample collection. Analytical problems at the low levels of Pb found in plasma are major reasons that plasm Pb should be measured routinely with much lower detection limits and with better accuracy by ICP-MS without advanced clean room facilities [27,37]. Moreover, potential contamination by analysis of plasma Fe and free hemoglobin was not assessed [30,38,39,44].

CONCLUSIONS AND RECOMMENDATIONS

Although no significant linear negative correlation between maternal plasma Pb and all of these outcomes (birth weight, birth height, Apgar score, head circumference at delivery, ponderal index and gestational age at birth) has been found in this study, possibly due to small number of birth cohort studied and scarce relevant data on associations between plasma-Pb and adverse outcomes, multiparous women with a family history of preeclampsia, diabetes mellitus and an anormal BMI had significantly higher plasma Pb levels in this study. Furthermore, plasma Pb levels reported in Kinshasa constitute a major public health concern for pregnant women and newborns. Risk assessment of Pb exposure should take place at the earliest contact with pregnant and lactating women as recommended by committee opinion of the American College of Obstetricians and Gynecologists.

DECLARATIONS

ETHICAL APPROVAL

The research protocol was approved by the Bio-ethics Committee of the School of Public Health at the University of Kinshasa. Kinshasa, DR Congo.

COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR'S CONTRIBUTIONS

The first draft of this manuscript has been written by the first author Y. M. T. The co-authors H.N. and M.M. prepared Tables 1, 2 and 3, and Figures 1 and 2. The co-authors D.M., C.M., J.P. and A.M. reviewed equally the manuscript. The J.K. contributed to supervise all the work and to correspond with the Journal.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable. However, the study results will report to individuals sample donors with proper explanations.

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