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Lead exposure and association with angiogenic factors and hypertensive disorders of pregnancy

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ABSTRACT

Objectives: Lead exposure has been associated with hypertensive disorders of pregnancy. Angiogenic factors, including soluble fms-like tyrosine kinase 1 (sFlt1) and placental growth factor (PlGF), are aberrant in pre-eclampsia, but have not been correlated with lead levels. We evaluated the association of lead exposure with angiogenic factors.

Study design: This cross sectional study utilized a convenience sample of singleton pregnancies ≥34 weeks' gestation. Blood lead and angiogenic factors were measured before delivery; bone lead was measured post-partum. We dichotomized bone and blood lead into the top tertile versus the bottom tertiles and used log-binomial regression to assess the association between lead and a high angiogenic ratio.

Main outcome measures: The outcomes were high sFlt1 to PlGF ratio and development of a hypertensive disorder of pregnancy.

Results: We enrolled 102 participants, of whom 98 had at least one lead measurement and an angiogenic factor result. Median bone lead was 3.8 ug/g (2.0 – 6.6) and median blood lead was 0.2 ug/dL (0.2 – 0.4). Incidence of hypertensive disorders of pregnancy was 31%. When comparing the highest tertile of bone lead to the bottom two tertiles, there was no association with a high sFlt1/PlGF ratio or hypertensive disorders of pregnancy. Similar results were observed for the exposure of blood lead.

Conclusions: Lead exposure was not an important contributor to an elevated angiogenic factor ratio or hypertensive disorders of pregnancy in our U.S. population. However, lead exposure was modest in our population and we cannot exclude a relationship with hypertensive disorders of pregnancy.

1. Introduction

While human exposure to lead has been linked to adverse pregnancy outcomes, including low birth weight, gestational hypertension, and preeclampsia [1–3], studies are limited, particularly with respect to maternal disease. Angiogenic factors, such as soluble fms tyrosine kinase-1 (sFlt1) and placental growth factor (PlGF), are aberrant in certain types of preeclampsia [4–6], but no published studies have evaluated the association between lead and these angiogenic factors. Quantifying the association between lead and angiogenic factors would strengthen the understanding of the pathophysiologic link between lead and hypertensive disorders of pregnancy.

Most studies evaluating the association of lead and hypertensive disorders of pregnancy have utilized blood lead as a biomarker for lead exposure [1,7]. While blood lead is easy to measure, blood lead levels vary significantly throughout gestation, likely due to increased bone

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turnover [8]. Bone is the primary long-term storage compartment for lead with greater than 90% of the total body lead stored in bone; thus, bone lead levels are relatively stable, despite the turnover that occurs during gestation [9,10]. Since lead is stored in bone, it could serve as a source of endogenous lead exposure from a historic source [11], even as population-wide lead exposure has decreased [12]. Given these properties, bone lead may be a more relevant measure to assess lead exposure during pregnancy and evaluate associations with adverse maternal outcomes, such as hypertensive disorders of pregnancy. While bone lead has historically been measured with a K-shell X-ray fluorescence system which restricted measurement to laboratories due to its size and 30 minute measurement time, portable measurement of bone lead has been validated [13,14] and uniquely allows for improvements in access to and usability of these bone lead measurements in studies.

In this study, we evaluated the association of bone lead with clinically diagnosed hypertensive disorders of pregnancy and levels of angiogenic factors, hypothesizing that higher levels of lead would be associated with both hypertensive disorders of pregnancy and a higher ratio of sFlt1 to PlGF. We also evaluated the correlation of third-trimester blood and bone lead concentrations, as well as the association of blood lead with clinically diagnosed hypertensive disorders of pregnancy and levels of angiogenic factors, given that blood lead has been studied more frequently in prior literature.

2. Methods

2.1. Enrollment

This was a cross-sectional study in which we recruited a convenience sample of parturients who presented for antepartum admission, triage of an acute issue, or scheduled delivery over 6 months from 2018 to 2019 at a single institution. We chose this recruitment approach in order to enrich our population with participants with a hypertensive disorder of pregnancy. Parturients were recruited prior to delivery and were approached if they were at least 34 weeks' gestation, had a singleton pregnancy, and planned delivery at the study site. Parturients were not approached if they were actively laboring or if there were no planned blood draws prior to delivery, given the plan for collection of blood for study purposes at the time of a clinical blood draw. Participants provided written informed consent. We utilized trained medical interpreters to approach and consent participants whose preferred language was not English.

2.2. Bone lead measurements

Within four days of delivery, while the participants were still hospitalized, X-ray fluorescence (XRF) was performed at the bedside by a co-investigator (AJS), using a portable XRF scanner (Thermo Scientific Niton XL3t GOLDD + XRF Analyzer, Thermo Fisher Scientific, Waltham, MA) with special permissions in the software to set the current and voltage to ensure a standard measurement and minimal radiation dose for all participants, as optimized in previous studies using this same device [14–18]. The measurement was performed over the tibia for three minutes while the participant was asked to remain still. Postpartum measurement was performed to eliminate any safety concerns regarding the minimal radiation exposure to the fetus for this exploratory study, and has been performed postpartum in other studies to reflect exposure to lead accrued over decades [19,20]. Bone lead measurements represent a point estimate, which can be negative if the true values are close to zero, because the instrument produces a continuous unbiased point estimate that fluctuates around the true bone lead value. These values were left as negative in descriptive statistics and any continuous variable measures to reduce bias from artificial variance reduction, as has been done in previous studies [19,21].

2.3. Blood lead and angiogenic factor measurements

A nurse or phlebotomist collected 5 mL of venous blood in a royal blue EDTA tube at the time of a clinical blood draw or placement of an intravenous line before delivery. An aliquot of 100 μl of whole blood was stored at −80 °C for later blood lead testing, performed at a CLIA-certified clinical laboratory. The remaining blood was centrifuged at 3000 RPM for 8 min. The plasma was then aliquoted and stored at −80 °C for later measurement of angiogenic factors with manual ELISA. Discarded blood samples were used for angiogenic factor measurements if there was insufficient plasma. Discarded samples originated from clinical blood draws on admission to labor and delivery and were retrieved from the institution's laboratory within 48 h of collection after all clinical tests were completed. Plasma sFlt1 and PlGF were measured using commercially available manual ELISA kits (R and D systems, MN) as described elsewhere [4,22]. Prior work has established the stability of angiogenic factors in plasma when whole blood samples have been stored for up to 48 h at 4 °C prior to processing [23]. If neither venous blood nor discarded blood were available, the participant was excluded from the analysis.

2.4. Hypertensive disorder of pregnancy

Hypertensive disorder of pregnancy was defined as development of *de novo* hypertension after 20 weeks, and included gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension, but not solely chronic hypertension, which was treated as a baseline characteristic. Diagnosis was verified by medical record review according to standard definitions for these disorders [24].

2.5. Covariates

The participant was asked to fill out a brief questionnaire at the time of the bone lead measurement. The questionnaire included a screening for lead, modified from the New York City Department of Health Lead Risk Assessment Questions for Pregnant Women [25]. Participants were also asked to identify their race, ethnicity, place of birth, and occupation. A medical record review was performed to ascertain medical and surgical history, obstetrical history, medication use, delivery outcomes, and neonatal outcomes. All data were stored in REDCap [26].

2.6. Statistical analysis

This was an exploratory study and thus a formal sample size calculation was not conducted. Based on available resources, we aimed to enroll 100 participants, with a plan to enroll up to 105 to account for withdrawals or loss to follow-up.

Though this study was cross-sectional, the cumulative lead exposure reflected in bone lead levels would have preceded the hypertension diagnosis. Thus, we modeled bone lead as an exposure and hypertensive disorder of pregnancy and angiogenic factors as outcomes. Measurement of bone lead produces an uncertainty value, and this uncertainty was incorporated into analyses whenever bone lead was treated as a continuous variable [27,28]. Weights were calculated based on $1/\text{uncertainty}^2$, and then normalized so that all weights summed to 1.

Descriptive data were reported as proportion or median (interquartile range, IQR). Differences between groups were analyzed using Fisher's exact test for categorical variables and nonparametric tests for continuous variables. We used the Spearman correlation coefficient to quantify the relationship between bone and blood lead.

Given non-normal data distributions and for ease of interpretation, we dichotomized bone lead, blood lead and angiogenic factors based on tertiles. For the exposures of bone lead and blood lead, the top tertile was considered exposed and the bottom two tertiles considered unexposed. For the outcomes of sFlt1 and the sFlt1/PlGF ratio, the top

tertile was considered to be the adverse outcome as high levels of each are pathologic [4]. A specific cut-off was not pre-determined due to the use of a manual ELISA, for which cut-offs have not been defined. Given that an sFlt1/PlGF ratio of ≥85 has been established as high in commercial assays, a sensitivity analysis was performed in which we defined a high ratio using this value as well. Lower levels of PlGF are pathologic; thus, when analyzing PlGF as an outcome, the bottom tertile of PlGF was considered to be the adverse outcome. We used log-binomial regression to estimate risk ratios (RR) and 95% confidence intervals (CI) for the associations of high bone or blood lead with the adverse outcomes of hypertensive disorder of pregnancy, high sFlt1, low PlGF and high sFlt1/PlGF ratio. Based on existing literature, maternal age [29,30], race [31], and parity were considered as potential confounders. Final models were adjusted for maternal age and covariates that changed the effect estimate by at least 10%. When modeling angiogenic factors as outcomes, we also adjusted for gestational age at the blood draw.

All data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC). All tests were two sided and p-values < 0.05 were considered statistically significant.

The institutional review board at Beth Israel Deaconess Medical Center approved this study. The institutional review board at the Harvard T. H. Chan School of Public Health ceded review.

3. Results

Over 6 months, we approached 144 parturients and enrolled 102 (71%). Two participants did not have blood collected after enrollment and we could not obtain discarded blood. One participant withdrew her consent prior to any study procedures. Most blood samples (90%) were collected within 3 days before delivery, and all were within 3 weeks before delivery. One additional participant did not have a bone lead measurement performed due to timing of delivery and availability of the portable XRF scanner. Thus, we included 98 participants who had at least a bone lead measurement (n = 98 bone, n = 91 blood) and an angiogenic factor result. Participant characteristics are shown in Table 1. Most participants were Caucasian, 11% were Asian, and 6% were African American. Chronic hypertension was present among 18% of the participants and 62% had a BMI > 30 at delivery. The majority of participants had never smoked. Median bone lead was 3.8 μg/g bone material (2.0 – 6.6), with a range of −13.0 to 26.7 μg/g bone material. Median blood lead was 0.2 μg/dL (0.2 – 0.4), with a range of 0 to 6.4 μg/dL. One participant had a blood lead level above 5 μg/dL, which is the CDC actionable blood lead level in pregnancy [25]. Bone and blood lead measurements were not correlated (Spearman's rho 0.02, p = 0.87).

Table 1
Participant Characteristics.

Characteristics	n = 98
Demographics	
Maternal age	34 (31–36)
Race	
Caucasian	68 (69)
African American	7 (7)
Asian	11 (11)
Other	12 (12)
Hispanic	8 (8)
Gravidity	
1	32 (33)
2	44 (45)
3+	22 (22)
Nulliparous	58 (59)
Medical Factors	
Chronic hypertension	18 (18)
Assisted reproduction	13 (14)
BMI > 30 at delivery	61 (62)
Anemia (Hematocrit < 33)	19 (19)
Pre-gestational diabetes	17 (17)
Smoking status	
Never smoker	88 (90)
Ever smoker	10 (10)
Blood lead (μg/dL)	0.2 (0.2 – 0.4)
Bone lead (μg/g)	3.8 (2.0 – 6.6)

Data presented as median (interquartile range) or n (%).

Table 2
Pregnancy and delivery outcomes.

Outcomes	n = 98
Gestational age at delivery (weeks)	38.7 (37.1 – 40.1)
Preterm delivery	27 (28)
Intrauterine fetal demise	0 (0)
Mode of delivery	
Vaginal	57 (58)
Cesarean	41 (42)
Birth weight (grams)	3325 (2895 – 3625)
Small for gestational age	12 (12)
Hypertensive disorder of pregnancy	30 (31)
Angiogenic factor levels	
sFlt1 (pg/dL)	34397 (19992 – 58179)
PlGF (pg/dL)	187 (114 – 360)
sFlt1/PlGF	200 (52 – 504)

Data presented as median (interquartile range) or n (%).

Pregnancy and delivery outcomes are shown in Table 2. Preterm delivery occurred in 28% of the pregnancies, and 12% of infants were small for gestational age. The prevalence of hypertensive disorders of pregnancy was 31%. The ratio of sFlt1/PlGF was relatively high, with a median of 200 (52 – 504). The top tertile of sFlt1/PlGF included values ≥ 376 (median 775, IQR 520 – 5472).

The median bone lead levels were similar for participants with and without each of the four adverse outcomes—high sFlt1/PlGF ratio, high sFlt1, low PlGF, and hypertensive disorder of pregnancy (Fig. 1A-D; all p > 0.15). Findings for blood lead were similar, though evaluation of blood lead as an exposure was limited by low levels (Supplemental Fig. 1).

When comparing the highest tertile of bone lead (median 7.5 μg/g bone material, IQR 6.3 – 11.5) to the bottom two tertiles, there was no association with a high sFlt1/PlGF ratio, high sFlt1, low PlGF or hypertensive disorders of pregnancy (Table 3) in either the crude or adjusted models. Similarly, there was no significant association observed between the highest tertile of blood lead (median 0.5 μg/dL, IQR 0.4 – 0.7) and the four adverse outcomes (Supplementary Table 1). Results were similar when a high sFlt1/PlGF ratio was defined as ≥ 85 (data not shown).

Pregnancy outcomes for the participants with the top 10% of bone lead levels are shown in Table 4. Among the 10 participants with the highest bone lead levels, there were two participants (20%) who developed hypertensive disorders of pregnancy. There was one participant with a blood lead level > 5 μg/dL, which is considered clinically elevated in a prenatal population. This participant developed pre-eclampsia with severe features. Her sFlt1/PlGF ratio was 1061, which was in the top tertile.

4. Discussion

We did not find an association between bone lead and either hypertensive disorders of pregnancy or third trimester angiogenic factors among a convenience sample of parturients at a single institution in Boston, Massachusetts, despite a wide distribution of bone lead values, a high incidence of hypertensive disorders of pregnancy, and relatively high levels of angiogenic factors. Overall, blood lead levels were low, which limited our ability to assess associations of blood lead with hypertensive disorders of pregnancy or angiogenic factors.

Several studies have evaluated the association between bone lead

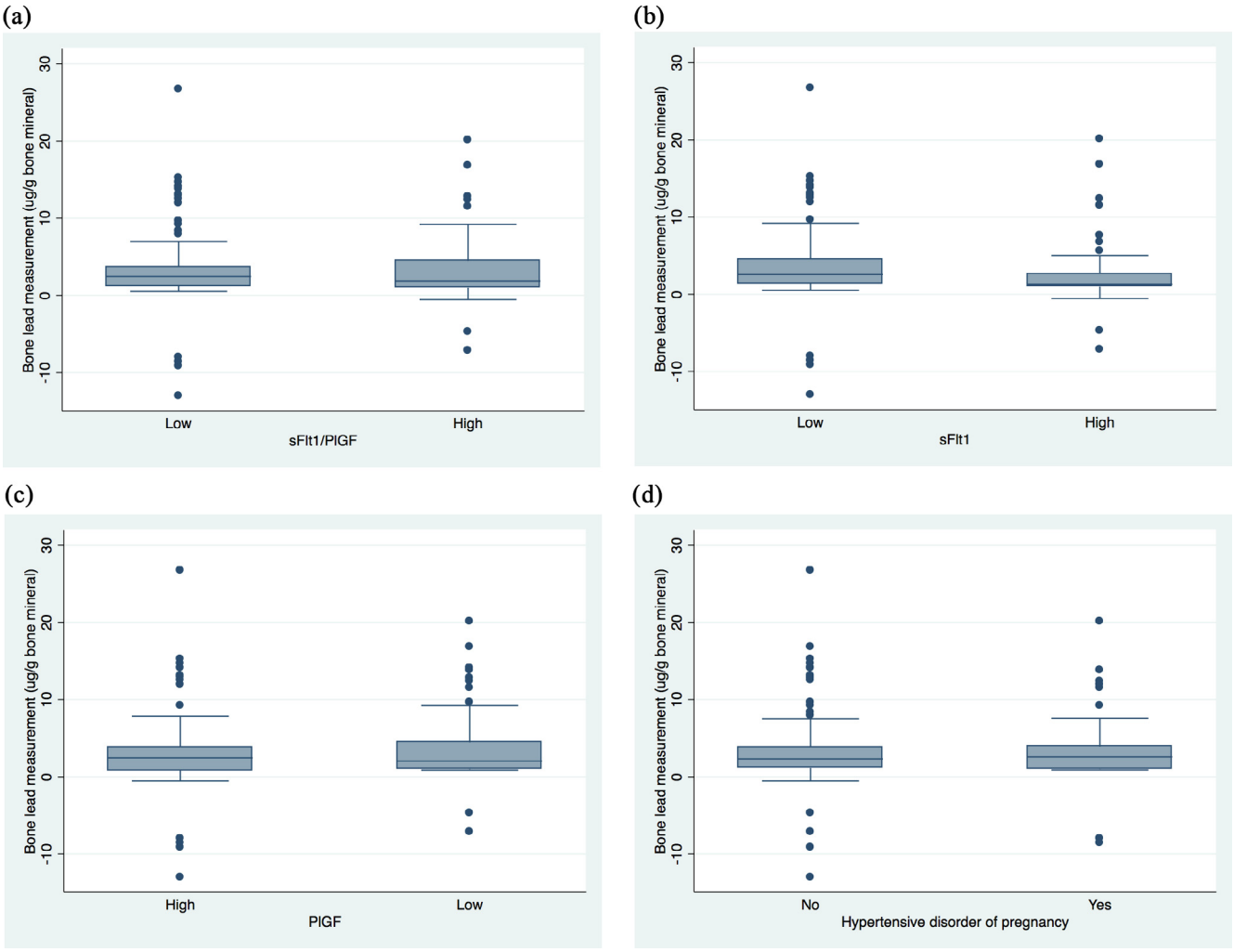

Fig. 1. Bone lead values, stratified by (A) low and high sFlt1/PlGF ratio, (B) low and high sFlt1, (C) high and low PlGF, and (D) presence or absence of hypertensive disorder of pregnancy.

and perinatal outcomes, focusing primarily on birth weight [19,20], but less is known about the association between bone lead and hypertensive disorders of pregnancy. One study [32] identified a modest positive association between bone lead levels and elevated blood pressures in pregnancy, although this finding was limited to trabecular and not cortical bone and included measurement several weeks postpartum. Trabecular bone is more prone to turnover [33], particularly several weeks post-partum [11]. Our study utilized cortical bone lead measurements, which are more stable over time [33] and thus a better proxy for prenatal bone lead levels. While the mean bone lead levels in the study by Rothenberg et al. were higher (8.0 μg/g bone material, standard deviation 11.4) than those measured in our population, this likely reflects the population lead levels at the time of the study (1995 – 2001). The bone lead levels detected among our population were similar to those reported among a postpartum population in Mexico from 2007 to 2011, in which mean bone lead levels were 3.9 μg/g bone material (standard deviation 2.8) [19] and were positively correlated with the clinical outcome of low birth weight. Our negative results are nevertheless reassuring with respect to the outcome of hypertensive disorders of pregnancy.

Our use of angiogenic factors expands the ability to detect a relationship between bone lead and the hypertensive spectrum. In prior work using an automated technique for measurement, sFlt1/PlGF ≥ 85 was associated with increased risk for poor outcomes among participants with suspected preeclampsia [34]. In this study, we defined high sFlt1/PlGF based on the top tertile (≥376), due to the use of a manual ELISA platform for which cut-offs have not been validated. Despite defining the outcome this way, we did not find an association between bone lead and either hypertensive disorders of pregnancy or high levels of angiogenic factors.

In contrast to bone lead, blood lead is better studied with respect to its association with hypertensive disorders of pregnancy [1,7,35]. Our study expands on this prior work by including angiogenic factors. Unlike previous reports, however, we did not find an association between blood lead measured in the third trimester and either angiogenic factors or hypertensive disorders of pregnancy. Our results diverge from a systematic review [1], which found an association between elevated lead and preeclampsia, but agree with a more recent study using a similar source population [7]. Lead levels have steadily declined in the U.S., and studies included in the systematic review were from more than 20 years ago or took place abroad. The mean U.S. blood lead in a 2015–2016 cohort of adults was 0.82 μg/dL (95% CI 0.77–0.87) [12], similar to our study population. The lack of association in our study suggests that lead was not a major contributor to hypertensive disorders of pregnancy in our population. Our results cannot be generalized to other settings where higher levels of lead exposure may be more prevalent. Indeed, the one person with a clinically elevated blood lead level in our study had severe preeclampsia.

Lead remains an important environmental exposure to consider in pregnancy with respect to other outcomes, particularly for those

Table 3
Risk of high vs. low angiogenic factor levels and hypertensive disorder of pregnancy, comparing the top tertile of bone lead to the bottom two tertiles.

	Bone lead	
	Top tertile n = 32	Bottom tertiles n = 66
High sFlt1/PlGF ratio		
Prevalence	10 (30)	22 (34)
Crude risk ratio	0.94 (0.51 – 1.74)	Ref
Adjusted risk ratio*	1.10 (0.65 – 1.87)	Ref
High sFlt1		
Prevalence	7 (21)	25 (38)
Crude risk ratio	0.58 (0.28 – 1.19)	Ref
Adjusted risk ratio**	0.64 (0.31 – 1.35)	Ref
Low PlGF		
Prevalence	13 (39)	22 (34)
Crude risk ratio	1.22 (0.71 – 2.09)	Ref
Adjusted risk ratio*	1.24 (0.74 – 2.09)	Ref
Hypertensive disorders of pregnancy		
Prevalence	8 (24)	22 (33)
Crude risk ratio	0.75 (0.38 – 1.50)	Ref
Adjusted risk ratio***	0.76 (0.39 – 1.50)	Ref

Data presented as n (%) or risk ratio (95% confidence interval).
High sFlt1/PlGF ratio defined by top tertile (≥376).
*Adjusted for gestational age at blood draw, maternal age, parity.
**Adjusted for gestational age at blood draw, maternal age.
***Adjusted for maternal age and parity.

Table 4
Perinatal outcomes for participants with top 10% of bone lead levels.

Participant	Bone Lead Level, μg/g	Mode of Delivery	Gestational age at delivery	Birth weight (g)	Hypertensive disorder of pregnancy?	sFlt1/PlGF ratio
1	26.74	SVD	39w5d	3390	No	43
2	20.10	CD	36w2d	2145	Yes (cHTN, severe PEC)	1007
3	16.74	SVD	41w1d	3910	No	1126
4	15.14	CD	38w4d	3230	No	23
5	14.69	CD	39w1d	3365	No	293
6	14.08	VAVD	41w1d	3130	No	34
7	14.02	SVD	37w3d	2720	No	261
8	13.82	CD	39w6d	3520	Yes (PEC)	300
9	13.11	SVD	41w3d	3980	No	173
10	12.90	VAVD	38w0d	2945	No (cHTN)	51

CD = cesarean delivery, SVD = spontaneous vaginal delivery, VAVD = vacuum-assisted vaginal delivery, cHTN = chronic hypertension, PEC = preeclampsia

parturients with high risk of exposure [25]. Since transplacental passage occurs through the plasma compartment of maternal blood [36], one would postulate that the maternal blood component is most important to measure with respect to perinatal outcomes. Blood lead concentrations can be quite variable, however, depending on degree of mobilization from the maternal skeleton [8], which partially depends on calcium and Vitamin D intake, maternal hematocrit, and acute lead exposure. While we did not observe a correlation between third-trimester lead in blood and bone, this may reflect the overall low exposure in our study population and the coefficient of variation in laboratory procedures. The lack of correlation may support the notion that blood and bone lead reflect acute and chronic exposures, respectively, with an unpredictable relationship during pregnancy. Nevertheless, because of the mobilization of lead from the bone during pregnancy and lactation [37], measuring both blood and bone lead is helpful in understanding the association of lead with perinatal and maternal outcomes, and also for screening for lead exposure.

Strengths of our study include multiple measures of lead exposure, both acute and chronic, as well as both clinical and laboratory outcome measures. In addition, we included a population with a high incidence of hypertensive disorders of pregnancy.

This study is limited by low levels of lead in the population sampled, and thus cannot be generalized to populations with higher levels of lead exposure. Another limitation is that we only captured blood lead at one point in time, but due to bone turnover during pregnancy and lactation, there may be transient increases in blood lead exposure not adequately captured by a single measurement. Finally, our small sample size may have limited the ability to find a statistically significant association between lead and elevated angiogenic factors.

We were unable to find a relationship between lead and angiogenic factors or hypertensive disorders of pregnancy among a population of parturients delivering at an urban tertiary care center in Boston, Massachusetts. Future studies should assess whether higher lead levels are implicated in hypertensive disorders of pregnancy, utilizing both blood and bone measurements as they do not correlate well and reflect different time periods of exposure.

Declaration of 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2020.07.014.

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