

Measurement of Blood Lead in Patients with First Trimester Abortion

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Abstract

Background: Blood lead has been associated with an elevated risk of miscarriage. The plasma fraction of lead represents the toxicologically active fraction of lead. Women with a tendency to have a higher plasma lead to a given whole blood lead ratio could tend toward an elevated risk of miscarriage and would consequently have a history of spontaneous abortion.

Objectives : The main objective of this study is to evaluate the role of plasma / whole blood lead ratio as a cause of abortion in the first trimester.

Patients and Methods: We studied 50 pregnant women in the first trimester who developed spontaneous abortion and 50 women with normal pregnancy as a control with matching in gestational age taken between from January 2014 to September 2014. All studied women were taken from Baghdad hospital in Medical City. Criteria for inclusion in this study were patient with spontaneous abortion, and measured their plasma and whole blood lead ratio by inductively coupled plasma mass spectrometry. The study excluded any woman with risk of spontaneous abortion for another cause or any pregnant woman with gestational age more than 14 weeks G.A

Results: There was a significant correlation between plasma whole blood lead ratio and risk of abortion ($P= 0.003$) which is highly significant and the result divided into 3 tertiles according to level of plasma / whole blood lead ratio. Also it found a significant relationship with plasma lead and the risk of abortion ($P= 0.009$) with no significant correlation with whole blood lead ($P= 0.284$).

Conclusions : Women with a large plasma/whole blood lead ratio may be at higher risk of miscarriage, which could be due to a greater availability of placental barrier-crossing lead.

Keywords: bortion , plasma lead , whole blood lead , plasma / whol

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I .Introduction

Lead is a heavy metal used in many materials and products. It is a neurotoxin environmental contaminant and when absorbed in the body, it can be highly poisonous. (1,2) The reproductive effects may be observed from lead exposure include:- Increase risk of spontaneous abortion , Developmental toxicity in the offspring , stillbirth. Prenatal lead exposure increases the risk of preterm delivery and low birth weight and neural tube defect (1,3) Four main sources of lead exposure are occupational , paint , Soil , water and lead containing products like Kohl , same toys and smoking. (2,4,5,6,7) After exposure the main body compartments that store lead are: blood, soft tissues, and bones. The half-life of lead in the blood in men is about 40 days, but it may be longer in children and pregnant women whose bones are undergoing remodeling, which allow the lead to be continuously re-introduced into the blood stream. (8,9) Adverse effects of lead on pregnancy outcome have been well documented over the past century. (4) Indeed lead has been used as an abortifacient agent. (3) Lead concentration in umbilical cord blood has been reported to be positively correlated with an increased risk of minor congenital anomalies. (5) There are many reports demonstrating that lead especially in the first trimester of pregnancy can have a very profound effect upon fetal development. Lead and other heavy metals create reactive radicals which damage cell structures including DNA and cell membranes (10). Lead also interferes with DNA transcription, enzymes that help in the synthesis of vitamin D, and enzymes that maintain the integrity of the cell membrane (11) However, few of these effects are demonstrable in experimental animal models at levels of lead uptake considered equivalent to those in environmentally exposed human population. (12) Few studies have been done to evaluate the effect of lead on the outcome of pregnancy in environmentally exposed human population i.e pregnant women with no direct exposure to lead. In one cohort study done in Australia which indicates that there is a small to moderate increase in blood lead within women who are exposed to lead and this modestly elevated blood lead is associated with an increase in the risk of any of the adverse outcomes of pregnancy. (12) Another

Cohort prospective study done in Yugoslavia which study the effect of lead on pregnancy outcome and shows no positive association between lead level and spontaneous abortion.(13)The aims of this study is to evaluate the role of plasma/whole blood lead ratio as a cause of abortion in the first trimester

II .Patients And Methods

This cross sectional study has been carried in Baghdad teaching hospital , fourth floor , labor ward for a period of nine months from January 2014 to September 2014. This study had included 50 pregnant women who developed spontaneous abortion in the first trimester of pregnancy and were living in Baghdad city with 50 pregnant women who taken as control group where had been seen and interview during their consultation for antenatal care. All patients and controls underwent complete general questionnaire , patients with renal diseases , hypertension , diabetes mellitus , pregnancy more than 14 weeks , psychotic diseases and certain drugs used such as anticonvulsants and continuous use of cytotoxic drugs were excluded from the study . Lead was measured in whole blood and plasma by inductively coupled plasma mass spectrometry using ultra clean techniques. Data were analyzed featuring the incidence rate of spontaneous abortion as the outcome and categorized plasma/blood lead as predictor variables. Method to estimate lead is chemical method .This is a standard method to estimate lead in the atmospheric or biological samples, the lead is extracted with successive portions of dithizone in chloroform, and the optical density of lead dithizonate solution was measured spectrophotometrically at 520 nm. Lead may adsorb on the wall of an ordinary glass or Pyrex glass or polythene should be used. This method is available, so it's used in this study. Procedure: Five milliliters of blood obtained by venous puncture and kept in the refrigerator in a special bottle coated with EDTA. An aqueous standard was used to calibrate the machine in order to determine blood lead using 50 µl of blood sample. Reagent:-a. Nitric acid lead free - b. Triton x-100 - c. Lead standard as $Pb(NO_3)_2$ (1 µg/ml). Standard solution: 3 standard solutions containing 1 µg/ml, 2 µg/ml and 5 µg/ml were used to calibrate the apparatus.

III .Statistical Analysis

Because of their skew distribution (i.e. data not normally distributed in which mean not equal to median) plasma lead, whole/ blood lead and plasma /whole blood lead ratio presented as median and tertiles. For plasma/whole blood lead ratio take an arbitrary cut off points of 0.4 and 0.52 which correspond approximately to the median and to upper 20% distribution of 80th centile to divided the sample into 3 groups namely 1st, 2nd, and 3rd tertiles where the first tertile from lowest value to 50%, second tertile from 51% to 80% and third tertile from 81% to upper value. Correlation between categorized variables such as plasma lead, whole blood lead and plasma/ whole blood lead ratio and women who have abortion and the control were assessed by using chi square Mann Whitney test use to assess the correlation between the age of the women “continue distributed variables which is normally distributed” and the presence or absence of abortion “categorized variables” P.value of 0.05 or less was considered significant. Statistical analysis was performed using SPSS version 17.

IV .Results

This study take in our research 50 pregnant women who developed spontaneous abortion in the first trimester of pregnancy and 50 women with normal first trimester pregnancy as a control as it explained in table 1. Table 2 showed the correlation between the plasma/whole blood ratio tertiles of controls and abortions groups and risk of abortion were in the 1st tertile there was 17(34%) of abortions and 33(66%) of controls women and the total number (no.) was 50. In the 2nd tertile there was 18(60%) of abortion and 12 (40%) and the total no. was 30 women. In 3rd tertile the total no. was 20 divided into 15(75%) abortions and 5(25%) controls. it noticed that increase the percentage of abortions from the 1st to 3rd tertile with corresponding decreasing in the percentage of controls associated with increase the ratio of plasma lead to blood lead ($P=0.003$). The odds ratio for abortion was 4.053 for each 0.2 increase in ratio with p value for odds ratio =0.000 and 95% confidence interval between 1.948_8.434 that was mean there was 4 times increase in the abortion for each 0.2 increase in the plasma lead and blood lead ratio. Table 3, and 4 explained the relation of plasma lead and whole blood lead to risk of abortion respectively where every table also divided into 3 tertile .In tables 3 the 1st tertile total no. was 50 divided into 20(40%) abortion and 30(60%) control where in 2nd tertile the total no. was 30 divided into 14(46.66%) abortion and 16(53.33%) of control and in 3rd tertile there was 16(80%) of abortion and 4(20%) control with total no. of 20 . Also we found there was increasing in the percentage of abortion from the 1st tertile to 3rd one and corresponding decreasing in the percentage of the control from the 1st to 3rd tertile with significant p value =0.009. In table 4 showed decreasing in the percentage of abortion with tertile where the abortion was 28(56%), 15(50%), 7(35%) in the 1st, 2nd and 3rd tertile respectively while there was increasing in the percentage of control with tertile where the control was 22(44%) in 1st tertile, 15(50%) in 2nd tertile, and 16(65%) in the 3rd tertile with insignificant p value of =0.284. In result the median of plasma lead, whole blood lead and their ratio was explained in the table 5 which showed that the median of plasma lead 9 for abortion group and 7 for the control group and that of whole blood lead were 18.5 .for the abortion group and 21 for control group. The median of plasma lead /whole blood ratio was 0.5 in the abortion group and 0.365 in the

control group. So we noticed the median of the plasma lead and that for plasma lead /whole blood ratio higher in the abortion group and low for control group while the median of whole blood was higher in control than abortion group .

Tables 1 : The numbers and percentage of abortion and controls

Groups	No.	Percentage
Abortion	50	50%
Control	50	50%
Total	100	100%

Table2: Correlation between Plasma lead/Blood lead ratio and risk of abortion

Groups	1st Tertile	2nd Tertile	3rd Tertile	Total
Abortion	17(34%)	18(60%)	15(75%)	50
Control	33(66%)	12(40%)	5(25%)	50
Total	50	30	20	100

P= (0.003)

Odds ratio for abortion is 4.053with p value 0.000 and confidence interval 1.948_8.434

Table3 : Correlation Between Plasma Lead And Risk Of Abortion

Groups	1st Tertile	2nd Tertile	3rd Tertile	Total
Abortion	20(40%)	14(46.66%)	16(80%)	50
Control	30(60%)	16(53.33%)	4(20%)	50
Total	50	30	20	100

P=0.009

Table4 : Correlation Between Whole Blood Lead And Risk Of Abortion

Groups	1st Tertile	2nd Tertile	3rd Tertile	Total
Abortion	28(56%)	15(50%)	7(35%)	50
Control	22(44%)	15(50%)	13(65%)	50
Total	50	30	20	100

P=0.284

Table5: Descriptive Table For The Median Of The Plasma, Whole Blood And Their Ratio

	Abortion	Control
Total	50	50
Plasma Lead Median	9	7
Whole Blood Median	18.5	21
Plasma Lead/Whole Blood L Ratio Median	0.5	0.365

V .Discussion

In this study the occurrence of abortion highly associated with the plasma /blood lead ratio where its percentage increased with increased the ratio as explained in table 2where the abortion was increase from34%in the 1sttertile to 60%in 2ndtertile to 75% in 3rdtertile and the control group percentage decreased from 66% in the 1sttertile to 40% in 2ndtertile and to 25% in 3rdtertile The p value for the this relation of plasma / whole blood ratio and abortion was 0.003 which was highly significant. And this table also showed that the increasing in ratio 0.2 associated with increased the abortion about 4 times explained in odds ratio with significant p value for odds ratio 0.000. The results obtained by this study suggest that the plasma /whole blood lead ratio could be viewed as a marker of susceptibility for lead toxicity. Findings are consistent with studies relating blood lead and risk of spontaneous abortion (14). High plasma /blood lead ratio implies more circulating lead is free to cross the placenta at a given blood lead level. If inter individual factors such as polymorphism of the ALAD gene determine the plasma / whole blood lead ratio(15),then some women ,if exposed to lead during pregnancy, would be at increased risk of fetal lead exposure. The rational for the latter idea is that if a pregnant woman is acutely exposed to lead from, for example, eating from a lead-glazed pot, her erythrocytes lead binding capacity will determine how much lead remains free in plasma and potentially reaches the fetus. (16). At same time table 3 showed that the plasma level of lead also highly significant associated with risk of abortion where the p value for this association was 0.009 where the percentage of abortion increased from 1st to 2nd and 3rdtertile from 40% to 46.66%and to 80% respectively while the control group percentage decreased from 60% in 1sttertile to 53.33% in 2ndtertile and to 20% in 3rdtertile. But the table 4 showed insignificant association between the whole blood lead level and risk of abortion where the reverses thing to table 3and 2 occur and the percentage of the abortion decrease with tertile with a p value=0.284where the percentage of abortion decreased from56% in

the 1st tertile to 50% in the 2nd tertile and to 35% in the 3rd tertile while the control percentage increased from 44% in the 1st tertile to 50% in the 2nd tertile and to 65% in the 3rd tertile. However, several studies have reported a positive association between maternal blood lead concentration and the risk of spontaneous abortion (14). This is of concern since one of these studies showed an important increase in the risk of miscarriage even among women with low to moderate blood lead level (15). However, previous studies were not conclusive, which could be attributed to methodological problems in study designs (11).

An additional explanation for the inconclusive results is that blood lead may not be the optimal biomarker to assess lead exposure. Over 99% of blood lead is bound to erythrocytes which cannot cross the placental barrier, thus, plasma lead concentration has been suggested as a better surrogate for the toxicologically active fraction of lead in the blood (15). This has been substantiated by the finding that plasma lead was a greater predictor of toxicity on hematopoiesis than blood lead, and of delay in neurobehavioral after fetal exposure to lead. To our knowledge only Savan. Ketala study assessed whether plasma lead concentration was associated to the occurrence of miscarriage, and also the author could not find an association (17), their study had a rather small sample size (n=40), and plasma lead has a large inter-individual variability (10). The latter could make it difficult to find association if the time between the exposure measurement and the event is relatively large. Hector Lamadrid-Figueroa et al. relates the plasma/whole blood lead ratio with adverse health effect and pregnancy outcome where it was shown significant relationship (16). Smith D et al. shown that the plasma/whole lead ratio was highly influenced by inter-individual factors (18). Such factor could be polymorphic alleles of gene coding for protein involved in partitioning of circulating lead, the most important being aminolevulinic acid dehydratase (ALAD), among other unidentified binding sites for lead (19,20). A recent contribution described that polymorphism in the ALAD gene are strongly associated to plasma/whole blood lead ratio (21). This finding raises the possibility that fetuses of women with tendency to have a lower erythrocytic lead binding capacity, reflected in higher plasma/whole blood lead ratio, and consequently greater plasma lead level to a given whole blood lead concentration would be more exposed to lead and at a greater risk of reproductive toxicity (10). Bergdahl IAGrubbet al. suggest that current blood and plasma lead would not necessarily be strongly associated to history of miscarriage, since blood or plasma lead concentration are more dependent on inter-individual variation than plasma/whole blood lead ratio and would therefore be less correlated between pregnancies (19). If this hypothesis is true then the plasma/whole blood ratio could be viewed as a marker of susceptibility for the toxic effect of lead. The median of the plasma/whole blood ratio was higher in the abortion group than control group which explained in the table 5 where the median in abortion group 0.5 and in the control group 0.35. Table 5 also showed that the median of plasma lead was higher in the abortion group where it was 9 while in the control group was 7. The opposite thing present in the whole blood lead where the median of whole blood lead was low in abortion group which was 18.5 and that of the control group was 21.

Vi. Conclusions

Our results constitute evidence that the history of spontaneous abortion is related to the plasma lead/whole blood lead ratio, which could be due to a greater availability of placental barrier-crossing lead for a given blood lead concentration in some women. Nevertheless, specifically designed longitudinal studies on this issue will be necessary to verify this hypothesis. Assessing the influence of genetic polymorphisms of lead binding protein on the probability of suffering from miscarriage or other reproductive outcome will be very important to identify groups particularly susceptible to the effect of lead exposure during pregnancy.

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