Maternal serum lead levels and risk of preeclampsia in pregnant women: a cohort study in a maternity hospital, Riyadh, Saudi Arabia

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Abstract: Preeclampsia is one of the major cause of maternal morbidity and mortality. Despite numerous studies, the etiology of preeclampsia has not yet been fully elucidated. There has been confliction in results on the role of maternal lead in preeclampsia. Keeping in view with the scarcity of data on role of lead in preeclamptic women of Saudi Arabia and the disparity in earlier findings, the present study was carried out to determine the levels of maternal serum lead in patients with preeclampsia in comparison to normal pregnancy. The study consisted of 120 pregnant women divided into three groups of 40 each, control, HR group and PET group. The serum levels of lead were estimated by Inductively coupled plasma optical emission spectrometry. We found that the mean value of serum lead was 18.23 ± 2.34, 20.08 ± 2.15 and 27.18 ± 2.13 µg/dl in control, high risk group and preeclamptic group respectively. The levels of Pb were found to decrease significantly (P < 0.05) in preeclamptic group compared to control. However, there was no significant change in levels of Pb when HR group was compared to Control and preeclamptic group. In the present study, we observed that serum levels of lead were positively correlated with systolic and diastolic blood pressure and were statistically significant (P < 0.05). However, negative correlation was observed between Pb and BMI ruling out the association of BMI with preeclampsia. It is thus concluded that preeclampsia is associated with significant increase in maternal lead and these increasing levels of serum lead pose a significant risk in pregnant women to preeclampsia.

Keywords: Lead poisoning, serum lead, blood pressure, BMI, preeclampsia

Introduction

Lead is a well known industrial and environmental toxin with a wide range of acute and chronic toxic effects [1]. It is known to induce broad range of harmful effects on various organs including the reproductive system. Lead poisoning remains an urgent public health problem in both developed and developing countries. It is considered to be one of the most difficult health issues during pregnancy and cause number of adverse outcomes in women like hypertension, infertility, miscarriage, premature membrane rupture and premature delivery [2]. Long-term exposure during pregnancy to even low concentrations of toxic metals, which have the ability to accumulate, often leads to irreversible damage to fetal developments and maternal morbidities including preeclampsia [3].

Preeclampsia, the most common medical complication of pregnancy, is associated with oxidative stress. Oxidative stress is a condition of oxidant/antioxidant disequilibrium, in which increased reactive oxygen species (ROS) generate overwhelms antioxidant defense mechanisms that lead to oxidative damage of cellular molecules. One of the important contributors to the state of oxidative stress is exposure to excess toxic metals in the environment and the deficiency of trace elements like copper, manganese and zinc which are necessary for antioxidant defense mechanisms [4]. In Saudi Arabia the incidence of preeclampsia is extrapolated to 13,876 out of a population of 25,795,938 [5]. It is characterized by development of high blood pressure (hypertension) and proteinuria after 20 weeks of gestation and affects about 5-8% of all pregnancies [6].
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Lead is ubiquitous in environment due to mining and industrialization. It is found in air, water, soil and as a contaminant in humans and has no known physiological function [7]. There are innumerable sources of lead in our environment such as paint, plumbing and water supplies from lead pipes or lead-soldered joints, dust and paint chips from older houses having lead paints, air and soil pollution from leaded gasoline, cooking in leaded pots, newsprint and many other sources. It is hard to avoid exposure to lead due to its widespread distribution in the environment. Environmental lead is absorbed either through the gastrointestinal tract or through the lungs into the blood. Recently, the center for disease control (CDC) has cut down the lead allowable threshold level from 25 µg/dL of blood to 10 µg/dL [8]. Some studies reported that maternal blood Pb levels ≥ 10 µg/dL may cause complications during pregnancy including increased risk of gestational hypertension, reduced length of gestation, miscarriage, spontaneous abortion and preterm delivery, others reported lack of association between maternal Pb level and some adverse pregnancy outcomes [9]. Lead was observed to damage the vascular endothelium and endothelial dysfunction is an important mediator of gestational hypertension [10].

Pregnancy is a state of high sensitivity to toxic substances. Blood lead levels increases during pregnancy either from endogenous source (bone saved) or from ambient pollution and affects health in pregnancy and could be extremely harmful to mother and the growing fetus [10]. Bone lead stores are mobilized during periods of increased bone turnover such as pregnancy and lactation for women with prior lead exposure. Chronic exposure to low levels of lead has been shown to increase arterial blood pressure in humans and in experimental animals and may result in pregnancy induced hypertension or preeclampsia, cognitive decline, defects in hematopoietic and renal impairment, spontaneous abortion, alteration of fetal anthropometric characteristics, birth weight and preterm labor [11, 12]. Blood lead concentration is the primary biomarker used for monitoring exposure levels, and reflects an individual’s current body lead burden [13]. 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. During pregnancy, there is increase in bone resorption to accommodate the mineral needs of the fetus, which may lead to transient increases in endogenous serum lead levels [14].

There has been conflicting results concerning the role of lead in elevation of blood pressure. A few hospital-based studies found that bone and blood lead levels during pregnancy are associated with increased maternal blood pressure [15, 16]. Due to the scarcity of data on Saudi Arabian population and due to confliction of results concerning role of maternal Pb, we conducted a hospital-based case-control study including patients of Riyadh, Saudi Arabia to assess the risk of preeclampsia in relation to concentrations of maternal lead in serum. The present study was designed to a) analyze the serum level of maternal Pb that could contribute to a better understanding of the potential role of Pb in etiology of preeclampsia and b) to study the inter element relationship of Pb with other trace elements of antioxidant system like copper, manganese and zinc. The present study is an extension of our previous work in which we reported an abnormal kidney function tests in preeclamptic women [17]. Recently we communicated decreased serum levels of Cu, Mn and Zn in preeclamptic pregnancies compared to normal pregnant women (Unpublished data). This study was carried out to add to better understanding of the role of Pb and its correlation with basic clinical characteristics and other trace elements like Cu, Mn and Zn in normal, high risk group and preeclamptic patients.

Materials and methods

Study population

This case controlled study was conducted as joint research of Department of Clinical Laboratory Sciences, King Saud University and Section of Obstetrics and Gynecology, King Saud Medical City Hospital, Riyadh from September 2012 to February 2014. The study was approved by hospital’s ethics committee. Informed consent was obtained from patients before blood sampling.

A total of 120 pregnant women were enrolled in this study and divided into three groups of 40 each healthy normotensive pregnant women (Control group), pregnant women at high risk of
preeclampsia (HR group) and women with pre-eclampsia (PET group). All the study subjects were attending antenatal OPD or labor room in their third trimester of pregnancy.

**Inclusion criteria**

**Control group:** Pregnant women with normal BP, absence of proteinuria and without any other systemic or endocrine disorder. All subjects included were in their third trimester (gestational age of ≥ 24 weeks).

**High risk group:** Women in high risk group were included based on the following criteria: pregnant women with body mass index (BMI) of 35 or more, with mild hypertension, gestational diabetes, IUGR (intrauterine growth restriction) or pre-term delivery in previous pregnancies and those with family history of preeclampsia.

**PET group:** Selection and diagnosis of preeclamptic group was based on the definition of American College of Obstetrics and Gynecologists [18].

**Analysis of trace elements in serum by ICP-OES**

Serum trace elements were determined by ICP-OES (Inductively coupled plasma optical emission spectrometer, ACTIVA-S, HORIBA JOBIN, France) Serum samples were filtered prior to analysis in ICP-OES. 300 µl of serum was appropriately diluted with 1% HNO₃ and 0.01% Triton X 100 (HPLC grade, Sigma Aldrich) as diluents. Different concentrations of standards (50,100 and 500 ppb) of lead were prepared from a stock solution of 1000 ppm lead for calibration of standard graphs. Absorbances were taken at 220.35 nm in ICP-OES. All measurements were conducted in duplicate. The concentrations of serum Pb were expressed in µg/dl.

**Statistical analysis**

The results were expressed as mean ± SD/SE. Statistical analyses were performed using

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**Table 1. Anthropometric data and serum levels of lead in study groups**

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 40)</th>
<th>High risk (HR) group (n = 40)</th>
<th>Preeclamptic group (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>31.20 ± 5.84</td>
<td>34.26 ± 6.69</td>
<td>31.55 ± 6.14</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>29.94 ± 6.05</td>
<td>37.36 ± 9.00</td>
<td>35.12 ± 6.06</td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td>31.17 ± 5.33</td>
<td>30.55 ± 6.33</td>
<td>33.72 ± 3.70</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>34.75 ± 4.30</td>
<td>34.48 ± 3.55</td>
<td>32.76 ± 3.71</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>113.56 ± 13.93</td>
<td>124.7 ± 16.21</td>
<td>167.0 ± 24.43</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>67.66 ± 9.38</td>
<td>74.45 ± 19.14</td>
<td>98.51 ± 11.16</td>
</tr>
<tr>
<td><strong>Serum lead (µg/dl)</strong></td>
<td>18.23 ± 2.34*</td>
<td>20.08 ± 2.15*</td>
<td>27.18 ± 2.13*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, *mean ± SE.

**Table 2. Comparison of the clinical characteristics between control and cases**

<table>
<thead>
<tr>
<th></th>
<th>Control with high risk group</th>
<th>High risk group with Preeclampsia</th>
<th>Control group with Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>4.66 &lt; 0.001*</td>
<td>3.23 0.003**</td>
<td>1.395 0.16</td>
</tr>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td>0.68 0.48</td>
<td>2.85 &lt; 0.05**</td>
<td>2.15 0.06</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>0.31 0.75</td>
<td>1.98 0.096</td>
<td>2.30 0.06</td>
</tr>
<tr>
<td><strong>Platelet count (10^3/µl)</strong></td>
<td>3.94 &lt; 0.001*</td>
<td>3.71 &lt; 0.001</td>
<td>7.705 &lt; 0.001</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>2.63 0.01**</td>
<td>10.7 &lt; 0.001</td>
<td>12.64 &lt; 0.001</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>2.16 0.033**</td>
<td>7.66 &lt; 0.001</td>
<td>9.762 &lt; 0.001</td>
</tr>
<tr>
<td><strong>Serum albumin (g/l)</strong></td>
<td>4.04 &lt; 0.001*</td>
<td>3.94 &lt; 0.001</td>
<td>7.96 &lt; 0.001</td>
</tr>
<tr>
<td><strong>Serum lead (µg/dl)</strong></td>
<td>0.54 0.58</td>
<td>2.10 0.07</td>
<td>2.65 0.029**</td>
</tr>
</tbody>
</table>

*P < 0.001 and **P < 0.05.
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Figure 1. Comparison of serum lead in all the groups.

Table 3. Correlation of lead with gestational age, BMI, systolic and diastolic blood pressure by Pearsons correlation

<table>
<thead>
<tr>
<th>Serum lead in PET</th>
<th>Control group</th>
<th>PET group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.007 (0.96)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.09 (0.54)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.35 (0.02)**</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.103 (0.01)**</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.21 (0.014)**</td>
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</tbody>
</table>

(-) indicates negative correlation; **P < 0.05.

Table 4. Inter-element relationship between lead and other trace elements in control and PET groups

<table>
<thead>
<tr>
<th>Correlation parameters</th>
<th>Control group</th>
<th>PET group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pb and Cu</td>
<td>-0.11</td>
<td>0.016</td>
</tr>
<tr>
<td>Pb and Mn</td>
<td>-0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Pb and Zn</td>
<td>0.04</td>
<td>-0.047</td>
</tr>
</tbody>
</table>

(-) indicates negative correlation.

Results

Analysis of lead in serum

Demographic and clinical characteristics along with the levels of serum lead in control, HR and preeclamptic group and comparison between the groups was performed by one way ANOVA following Holm-Sidak test. Pearsons correlation was performed to determine the relation of lead with maternal age, gestational age, BMI, systolic and diastolic blood pressure in control and preeclamptic group. Inter element relationship was performed between the Pb and other trace elements (Cu, Mn and Zn) in control and PET group by pearsons correlation.

Table 3. Correlation of lead with gestational age, BMI, systolic and diastolic blood pressure by Pearsons correlation

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SPSS software. Comparison of clinical characteristics and biochemical parameters, levels of trace elements between cases and control and among the groups was performed by one way ANOVA following Holm-Sidak test. Pearsons correlation was performed to determine the relation of lead with maternal age, gestational age, BMI, systolic and diastolic blood pressure in control and preeclamptic group. Inter element relationship was performed between the Pb and other trace elements (Cu, Mn and Zn) in control and PET group by pearsons correlation.

In order to study the effect of maternal age, gestational age, BMI, systolic and diastolic blood pressure on serum levels of lead in preeclamptic group, the data was further analyzed by Pearsons correlation. Gestational age was positively correlated with levels of serum Pb in preeclampsia patients. In women with preeclampsia, the serum Pb was significantly correlated (P < 0.05) with systolic and diastolic blood pressure (Table 3). We observed negative correlation between, BMI and the levels of lead (r, -0.35 and P < 0.05).

Inter-element correlations in control and preeclamptic group

To know how the other trace elements like Cu, Mn and Zn are related to levels of lead in serum...
of preeclamptic group, pearsons correlation was performed and represented in Table 4. There was positive association between Cu and Pb and between Pb and Mn in PET group. Zinc was negatively correlated with Pb. The results were reciprocally observed in control. The regression graphs showing the correlation of lead with the other trace elements are shown in Figures 2 and 3.

Discussion

Preeclampsia is a multi factorial disease that may result on account of generation of oxidative stress in pregnant women. One of the important contributors to the state of oxidative stress is exposure to excess toxic metals in the environment that increases the production of free radicals and decreases the availability of bioelements necessary for antioxidant defense mechanisms. Lead is one of the most extensively studied reproductive toxicants to living things. There is increasing awareness that unintended exposure to environmental or occupational contaminants may adversely affect maternal and fetal morbidity and mortality. Acute and chronic low-level lead exposure has been shown to result in adverse health effects [19]. As per the public health regulations, pregnant women should not be exposed to occupational sources. Moreover the local customs in Kingdom of Saudi Arabia does not accept women to work in industries. Therefore they are either exposed to lead due to rapid industrialization and the continued use of leaded gasoline or lead pollution from cosmetics (including Kohl, eye cosmetic, lip glosses), herbal products and the use of canned food and canned juices could also be other sources to increase maternal blood lead concentration. The frequent prevalence of sand storm in Riyadh region (which carries dust) may also be one of source of lead exposure to pregnant women. The major source of lead toxicity in pregnant women is the presence of lead stores in bone. Bone is one of the reservoir of lead in the body. Additionally, the lead stored in its metabolically inactive form in bones for decades, could be released during
conditions of increased bone turnover, such as pregnancy [20]. Gulson et al., have shown that bone lead is the source of more than 30% of blood lead in pregnant women. Because lead stays in women’s bone for years to decades, its mobilization during pregnancy may pose a significant fetal exposure risk long after maternal lead exposure has ceased [21].

In the present study, serum lead levels were measured and compared between the three groups-control, high risk (HR) and the preeclamptic (PET) group. We observed a significant increase (P < 0.05) in levels of lead in PET group compared to control and HR group. There was no significant change between HR and PET group. The remarkably increased serum Pb found in this study may be due to the high prevalence of environmental pollution or the sources of lead discussed above. Also, mobilization of lead from bone during pregnancy results in a significant gestational increase in maternal Pb. Dawson et al., showed that the levels of Pb increases in the amniotic fluid of preeclamptic women [15].

When SBP and DBP were correlated with levels of increased levels of lead, we observed significant correlation between SBP and DBP with levels of lead in PET group. Our results are similar to Kasperczyk et al., where they found that the Pb level in blood were positively associated with both systolic and diastolic blood pressure [22]. The increased systolic and diastolic blood pressure observed in hypertensive women with elevated serum lead levels recorded in the present study is in agreement with previous finding. The levels of lead (27.18 ± 2.13 vs 18.23 ± 2.34 µg/dl in the preeclamptic group vs control respectively) observed in the present study are nearly similar to that obtained by Motawei et al., (37.68 ± 9.17 in preeclamptic women vs 14.5 ± 3.18 µg/dL in normotensive control) [23]. In contrast, Angell and Lavery recorded no relationship between concentrations of lead in cord blood and the incidence of preeclampsia [24]. These differences in findings could be due to differences in the sample used.

Several mechanisms may contribute to the pathogenesis of lead-induced hypertension. It induces hypertension by vascular and nephrotoxic mechanisms. Lead may be involved with vasoconstriction through the inhibition of the Na-K ATPase pump or by enhancing the synthesis of vasoconstrictors and reducing the synthesis of vasodilators (increases endothelin and thromboxane production, inhibition of vascular smooth muscle ATPase). Lead was found to reduce nitric oxide levels which are needed to maintain the vasodilation in pregnancy [16]. Lead directly interrupts enzyme activation, competitively inhibits trace mineral absorption, cause reduction in glomerular filtration rate of the kidneys with increase in the rennin-angiotensin II-aldosterone activity [1].

Women with greater BMI in pregnancy are more likely to become hypertensive than those with lower BMI. But the BMI observed in PET and the Control group in our earlier study ruled out the influence of this parameter on the aetiology or severity of preeclampsia [17]. In the present study, we observed negative correlation between Pb and BMI ruling out the association of BMI with preeclampsia. Hence, BMI was shown to be independent of lead effect. Similar to our finding, Kasperczyk et al., did not find any correlation between Pb and BMI or age [22]. Interactions between lead and other elements are possible because oxidative stress produced by lead or cadmium may be counterbalanced by the antioxidative properties of manganese or zinc. Afridi et al., reported higher levels of blood lead as well as a lower level of Zn, correlated well with the consequences of hypertension [25]. Recently, we observed decrease levels of manganese and zinc (Unpublished data) in preeclamptic women. Lead is also known to decrease the trace mineral absorption that may be responsible for decrease levels of Cu, Mn and Zn in our earlier report. Deficiency of these metals (acting as antioxidants) along with increase levels of lead may be responsible for oxidative stress leading to preeclampsia. However, when Pb was correlated with other trace elements, we did not found any significant correlation. Pb was observed to be independent of other trace elements.

Hypertension causes reduction in renal function that in turn results in retention of lead [11]. In our earlier study, we observed abnormal renal function tests in preeclamptic women [17]. Impaired renal function could also contribute to increase levels of Pb in preeclamptic women observed in this study.
In conclusion, our data suggests that pre-eclamptic pregnant women of Riyadh region of KSA, have higher levels of serum lead compared to healthy pregnant females. Through our study, we conclude that the lead exposure is an important risk factor to pregnant women. It is hoped that this study will contribute in clear understanding of the role of lead and the etiology of preeclampsia. Also, pregnant women should be highly concerned about staying in endemic areas of lead contamination to protect their reproductive health and the development of fetus.

However, limitation of this study is that we did not attempt to ascertain exposures to potential sources of lead such as consumption level of canned food and drinks, contaminated food and contaminated beverages. Future studies should attempt to ascertain the importance of these exposures.

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Disclosure of conflict of interest
None.

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