

## RESEARCH ARTICLE

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## Environmental exposure to lead and cadmium in patients with preeclampsia; A case-control study

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### ABSTRACT

#### Objectives:

High blood lead and cadmium levels were associated with adverse pregnancy outcomes including preeclampsia. The aim of the current study was to evaluate the relationship between blood lead and cadmium levels in pregnant females and preeclampsia.

#### Methods:

A total of 130 pregnant women were enrolled in the study; 80 of them were suffering from preeclampsia (preeclampsia group) and 50 healthy pregnant women taken as (control group).

#### Results:

There was significant increase in blood lead level among the preeclampsia group (p value=0.001) when compared with the control group. Also, cadmium level was significantly higher in the preeclampsia group (p value=0.017) when compared with the control group.

#### Conclusion:

The results of this study revealed that high blood lead and cadmium levels were significant risk factors for development of preeclampsia

#### Keywords:

Preeclampsia, environmental toxins, cadmium, lead.

### Introduction

Preeclampsia (PE) is a multisystem disorder of pregnancy which affects more than 8 million pregnancies worldwide annually (1). Affecting about 5% of all pregnancies, preeclampsia is the most common cause of maternal and perinatal mortality and morbidity (2).

Endothelial cell dysfunction appears to be a central feature in the pathophysiology of preeclampsia (3). At present, the etiology of preeclampsia remains unknown. As a result, preventative measures and screening tools are lacking, treatment is directed at the management of overt clinical manifestations and delivery remains the only definitive cure (4).

Lead (pb) is one of the most extensively studied reproductive toxicants. Blood lead levels increase during pregnancy, from 24 weeks of gestation until delivery, because of increased gastrointestinal absorption and an increase in bone turnover in this period (5). Placental blood lead levels at or even

below 10 µg/dL were associated with adverse pregnancy outcomes (6).

Human exposure to lead occurs through various sources like leaded gasoline, industrial processes such as lead smelting and coal combustion, lead-based paints, lead containing pipes or lead-based solder in water supply systems, battery recycling, grids and bearings (7).

Cadmium (Cd) is used industrially to manufacture electro-plates, batteries, alloys and fuels. The increasing industrial use of Cd causes soil, air and water contamination (8). Kulusari et al (9) reported that the level of serum cadmium significantly increased in women suffering from preeclampsia. The current study aims to demonstrate the pattern and relationship between blood lead and cadmium levels in pregnant women and preeclampsia.

## METHODS

The current study was a prospective case control study conducted in Assiut Women Health Hospital, Egypt in the period from March 2014 through August 2014. The study was approved from the Assiut Medical School Ethical Review Board and a written informed consent was obtained from all study participants.

All pregnant women attended the reception unit in Women Health Hospital during the study period were clinically examined and those diagnosed as preeclampsia after 20 weeks of gestation were approached for participation in the study (preeclampsia group).

Preeclampsia was diagnosed as elevation of blood pressure above 140/90 mmHg with proteinuria (10). Proteinuria was diagnosed if there was excretion of  $\geq 300$  mg of protein in a 24-hour urine collection (10). We excluded pregnant patients with previous history of metabolic disorders, renal diseases or diabetes mellitus. Age, parity and gestational age matched women without any complications during pregnancy had approached to participate in the study as (control group).

A full history had been taken from each participant including age, BMI, residence, educational level, active or passive smoking, food habits (eating canned food or seafood), past history and family history of preeclampsia. The patient considered passive smoker if her spouse is smoking at home or she was working in an office shared with an active smoker.

### **Samples collection and laboratory analysis**

Trained nurses of the labor ward collected the blood samples. Six milliliters of maternal blood was collected in plastic tubes containing K3EDTA as anticoagulant. Two milliliters of them were collected as whole blood and the remaining 4 ml was centrifuged at 4000 rpm for 10 min and its RBCs were collected and washed three times with saline. The whole blood and RBCs were digested using the same method described by Marouf, 2011 (11) stored at 70° refrigerator were used for measurement of lead and cadmium, respectively.

### **Biochemical analysis**

Lead (Pb) and cadmium (Cd) were measured by inductively coupled plasma-optical emission spectrophotometer (Thermo Fisher Scientific, ICP-OES, iCAP 6200 series) using lead and cadmium

standards (5 and 10 ppm, respectively), at wavelengths 220.3 and 139.7 nm, respectively (12).

### **Statistical analysis**

Collected data were reviewed and analyzed using the Statistic Package for Social Science Version 20 (SPSS 20.0) for windows. Qualitative data were expressed as frequency and percentage. Quantitative data were presented in terms of mean and standard deviation. Chi-square test was used to compare the relation between qualitative data and 2-independent samples *t*-test was used to compare two quantitative data. The level of significance was taken at *p*-value of  $\leq 0.05$ .

## RESULTS

One hundred twenty two women were diagnosed to have preeclampsia during the study period. Forty two patients were excluded for various exclusion criteria ends in 80 patients with preeclampsia included in the study group. Fifty pregnant women with matched age, parity and gestational age were recruited as a control group.

There were non-significant differences between both groups as regard maternal age and parity. Statistically significant differences were found as regard to family residence ( $p=0.001$ ). Preeclampsia was more common in women living in urban areas. In addition, women in the preeclampsia group were more illiterate than the control group ( $p=0.012$ ). Women who had previous history of preeclampsia posed an increased risk of recurrence ( $p=0.035$ ). Also, patients with family history of preeclampsia had significant higher risk than the control group ( $p=0.001$ ). The incidence of exposure to passive smoking was significantly higher in the preeclampsia group ( $p=0.042$ ). Patients with history of chronic hypertension had significant higher risk for development of preeclampsia ( $p=0.026$ ). Furthermore, pre-pregnancy maternal body mass indices (BMI) were significantly higher in the preeclampsia group ( $p=0.04$ ). Demographic data and comparison between risk factors in both groups were summarized in Table 1.

**Table 1.** Demographic data and possible predisposing factors in preeclampsia group as compared to control group

Variables		Preeclampsia group (n=80)		Control group (n=50)		p-value
		No.	%	No.	%	
Residence	▪ Rural	28	35.0	27	54.0	0.893
	▪ Urban	52	65.0	23	46.0	<b>0.001</b>
Educational level	▪ Illiterate	71	88.8	40	80.0	<b>0.012</b>
	▪ Primary education	9	11.2	10	20.0	0.096
Family history of preeclampsia	▪ Yes	20	25.0	3	6.0	<b>0.001</b>
	▪ No	60	75.0	47	94.0	
Previous history of preeclampsia	▪ Yes	9	11.2	2	4.0	<b>0.035</b>
	▪ No	71	88.8	48	96.0	
Smoking	▪ Non smokers	32	65.0	23	46.0	<b>0.042</b>
	▪ Passive smokers	48	35.0	27	54.0	
History of chronic hypertension	▪ Yes	8	10.0	1	2.0	<b>0.026</b>
	▪ No	72	90.0	49	98.0	
Maternal age (years)		(23.75±4.16)		(25.11±4.23)		0.093
Maternal BMI (kg/m <sup>2</sup> )		(29.17±4.88)		(25.57±3.56)		<b>0.04</b>

- BMI: body mass index,

- Figures in between brackets represent the mean ±standard deviation.

- No active smokers were detected in the present study.

Table 2 shows the levels (mean ± SD) of whole blood lead and cadmium among the preeclampsia group as compared to the control group. There was a significant increase in blood lead level among the

preeclampsia group ( $p=0.001$ ) when compared with the control group. Moreover cadmium level was significantly higher in the preeclampsia group ( $p=0.017$ ) when compared with the control group.

**Table 2.** The levels of blood lead and cadmium in the preeclampsia and control groups.

	Preeclampsia group (n=80)			Control group (n=50)			p-value
	Mean	SD	95% CI	Mean	SD	95% CI	
Pb (ug/dl)	140.6	60.9	126.5-154.7	103.1	34.4	92.8-113.4	<b>0.001</b>
Cd (ug/dl)	1.132	2.46	1.019-1.245	0.398	0.88	0.358-0.438	<b>0.017</b>

Pb: lead, Cd: cadmium, SD: standard deviation, CI: confidence interval

Table 3 shows the effect of maternal risk factors on lead and cadmium levels in blood in patients with preeclampsia. No significant difference among different age groups. Also no difference as regard place of residence, educational level, smoking status, parity. Women who had history of preeclampsia in previous pregnancy were associated with low level of blood lead in comparison to those who had no history (statistically insignificant  $p=0.935$ ) while blood cadmium was higher in those having history of

preeclampsia in previous pregnancy (statistically insignificant  $p=0.099$ ).

Blood lead level was high in women with family history of preeclampsia but non-significant ( $p=0.155$ ), while blood cadmium was significantly high in women with family history of preeclampsia ( $p=0.001$ ). Also, Blood lead level was high in women without history of chronic hypertension but non-significant ( $p=0.355$ ), while blood cadmium was significantly high in women with history of chronic hypertension ( $p=0.001$ ).

**Table 3.** The effect of maternal risk factors on blood lead and cadmium levels in preeclampsia group

	Pb (ug/dl)				Cd (ug/dl)			
	Mean	SD	p-value	95% CI	Mean	SD	p-value	95% CI
<b>Age</b>								
≤ 19 yrs	152.0	26.5	0.926	136.8-167.2	1.008	1.050	0.257	0.907-1.109
20 - ≤ 29 yrs	138.7	49.2		124.8-152.6	0.761	1.174		0.685-0.837
≥ 30 yrs	142.8	77.5		128.5-157.1	1.703	3.638		1.533-1.873
<b>Residence</b>								
Rural	136.0	78.8	0.621	122.4-149.6	0.858	1.040	0.468	0.772-0.943
Urban	143.1	49.3		128.8-157.4	1.280	2.956		1.152-1.407
<b>Educational level</b>								
Primary	113.8	99.7	0.821	102.4-125.2	0.138	0.159	0.609	0.124-0.151
Illiterate	141.2	62.4		127.1-155.3	1.229	2.593		1.106-1.352
<b>Smoking</b>								
Passive smoker	133.6	36.4	0.204	120.2-146.9	1.225	2.783	0.681	1.103-1.348
Non smoker	151.3	85.1		136.1-166.4	0.992	1.911		0.893-1.091
<b>Parity</b>								
Primipara	137.4	51.6	0.431	123.7-151.1	0.890	1.534	0.063	0.801-0.979
Multipara	135.1	51.5		122.9-151.5	1.85	2.720		1.12-2.43
<b>Previous history of preeclampsia</b>								
Positive	141.6	47.2	0.935	127.5-155.8	2.814	5.646	0.099	2.533-3.096
Negative	143.7	72.9		129.4-158.1	0.948	1.816		0.853-1.043
<b>Family history of preeclampsia</b>								
Positive	157.4	64.4	0.155	141.7-173.2	2.160	4.167	0.003	1.944-2.376
Negative	135.0	59.1		121.5-148.5	0.789	1.427		0.71-0.868
<b>History of chronic hypertension</b>								
Positive	120.8	46.1	0.355	108.8-132.9	4.404	5.778	0.001	3.963-4.844
Negative	142.8	62.2		128.6-157.1	0.768	1.450		0.691-0.845

Pb: lead, Cd: cadmium, SD: standard deviation, CI: confidence interval

## DISCUSSION

Preeclampsia is a multisystem disorder that remains a major cause of maternal and fetal morbidity and death. In developing countries where access to health care is limited, preeclampsia is a leading cause of maternal mortality causing an estimated >60,000 maternal deaths worldwide per year (13). In Egypt, the prevalence of PE is 10.7% in a community based

study while in hospital based studies it ranged from 9.1% to 12.5% of all deliveries (14). In the present work, we provided clues that there is a significant increase in the levels of lead and cadmium in pregnant women suffering from preeclampsia as compared to those with normal pregnancies.

Exposure to environmental pollutants is an important issue as regard to maternal and fetal health. The results of the current study revealed significant increase in blood lead level among the preeclampsia group when compared to the control group ( $p=0.001$ ). These findings were in keeping with the results of Rothenberg, *et al* who found a significant positive association between blood lead and elevated blood pressure in pregnant females (15). These results also agreed with Motawei, *et al* 2013 and EL-Moselhy *et al.*, 2012 who attributed the remarkably high blood lead levels found in their study participants to the high prevalence of environmental pollution in many developing countries including Egypt (6, 14).

Yazbeck *et al* reported that the risk of pregnancy induced hypertension increases with increasing absolute values of mid-pregnancy blood lead in a “dose–response” pattern (5). All these findings suggest that high blood lead level may be one of the causal factors of preeclampsia. Blood lead level has been reported to be increased in pregnant than in non-pregnant women, because of bone remodeling (16). In pregnancy, bone lead released into the blood varies from subject to subject, but there is an estimated 20.0% increase in blood lead (14, 17).

The results of the current study also revealed that cadmium level was significantly higher among the preeclampsia group when compared to the control group ( $p=0.017$ ) and this finding was in agreement with the results of Kulusari *et al* (9).

In the current study, there was variation in blood lead and cadmium level among different age groups with increase in level as age increase but this increase was non-significant, this can be explained by cumulative properties of these metals and this may explain why incidence of preeclampsia increase as age increase. This finding was in agreement with Rabinowitz, 1991 who found that in the case of chronic exposure; elevated blood lead levels might persist for years, with large amounts of lead deposited in bone and so some of lead's toxic effects are proportional to cumulative exposure (18). Also, Silbergeld, 1991 found that women older than 30 years had significantly higher levels of breast milk lead than women between 20 and 30 years of age (19). Schwartz *et al.*, 2003 reported that cadmium levels in the body accumulate with age as only a

minute part of the body burden (0.01–0.02%) is excreted per day (20).

In the current study, urban residence was a significant risk factor for preeclampsia ( $p =0.001$ ) and also associated with high lead and cadmium level in blood (insignificant) in comparison with rural residence and this may explain the high incidence of preeclampsia in urban residence. This finding was in agreement with Semczuk and Semczuk-Sikora, 2001 who found a slight increase of blood lead content in pregnant women from urban areas (21). This also in accordance with EL-Moselhy *et al.*, 2012 who explain this finding by the presence of heavy traffic in urban areas which represents a source of lead exposures beside of using leaded gasoline especially in developing countries (14).

In the current study significant association was found between preeclampsia and illiteracy ( $p=0.012$ ) and this was associated with high blood lead (95% CI=127.1-155.3) and cadmium level (95% CI=1.106-1.352). This finding was in agreement with Tebeu *et al.*, 2011 who reported that illiteracy was associated with about 2-fold risk for presenting hypertensive disorder in pregnancy (22). Also, Silva *et al.*, 2008 reported that women with relatively low levels of education had a higher risk of gestational hypertension than women with a high educational level and explained this by unequal distributions of known risk factors for gestational hypertension across educational levels, particularly by the higher rates of overweight and obesity and the relatively high blood pressure levels at enrolment found in lower educated women (23). In our population the low school level is associated indirectly with precocious marriage and limited access to health care, including family planning.

The present study show a statistical significant difference between preeclampsia and control group as regard to passive smoking ( $p=0.042$ ). This was associated with high blood cadmium level, although it was non-significant, and this may explain the strong association between smoking and cadmium toxicity. This finding was in agreement with Hogervorst *et al.*, 2007 that reported that tobacco smoke and polluted air are additional sources of exposure to cadmium (24). Also, Gallagher and Meliker, 2010 reported that smoking is associated with increased cadmium levels because cigarettes contain cadmium taken up by the tobacco plant and

smokers have approximately twice the cadmium body burden of non-smokers (25).

There was a significant association was found between preeclampsia and increasing body mass index ( $p=0.04$ ) so, obesity is a strong risk factor for preeclampsia. This agreed with the studies of Bhattacharya *et al.*, 2007 and Duckitt and Harrington, 2005 who found a strong association between increasing BMI and pregnancy induced hypertension besides a significantly lower risk of preeclampsia in underweight women (26, 27). Sebire *et al.*, 2001 also found a significantly lower risk of preeclampsia in underweight women (28).

Blood lead level was high in primiparous women when compared to multipara among the preeclampsia group but this increase was non-significant. This finding was in contrast with Yazbeck *et al.*, 2009 who observed high levels of blood lead in multiparous women of their study and so an increase in the frequency of pregnancy induced hypertension in this group (5).

As regard multiparous women, the risk of preeclampsia in this study was found to be significantly increased in women with history of preeclampsia in previous pregnancy in comparison with control ( $p=0.035$ ). This was in agreement with Raijmakers *et al.*, 2004 who found that the risk of preeclampsia markedly increases in women with previous preeclampsia (29). Also, Duckitt and Harrington, 2005 found that women who have preeclampsia in a first pregnancy have seven times the risk of preeclampsia in a second pregnancy (27). The result of this study, however, are in contrast with Li and Wi, 2000 who said that preeclampsia is predominately a condition of the first birth and the risk decreases substantially among multiparous women (30).

In the current study, history of preeclampsia in previous pregnancy was associated with relatively high level of blood lead but non-significant. This finding can be explained according to Brown and Margolis, 2012 by, lead persists in bone for decades, as bone stores are mobilized to meet the increased calcium needs of pregnancy and lactation, women and their infants might be exposed to lead long after external sources have been removed (31).

In the current study, history of preeclampsia in previous pregnancy was associated also with high blood cadmium level but non-significant.

In this study, statistically significant difference was found between the preeclampsia group and control as regard the family history of preeclampsia. This finding was in agreement with Duckitt and Harrington, 2005 who reported that family history of preeclampsia nearly triples the risk of preeclampsia (27). This finding was associated with increase in blood lead and cadmium level ( $p=0.155$ , 0.003 respectively), this may be due to exposure to the same risk factors (e.g. smoking, residence, illiteracy, drinking contaminated water and low educational level).

In conclusion, there is a higher level of hazardous exposure to lead and cadmium in pregnant women with preeclampsia as compared to normal pregnancies. Passive smoking, living in urban areas may be the cause of such increased risk. These results may highlight and increase the awareness of the importance of different environmental pollutants that may contribute to the unknown etiology of preeclampsia.

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