Effect of lead exposure on the development of polycystic ovary syndrome

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Abstract:

Background

The effects of Lead and other essential metal like zinc and copper on the reproductive system have been previously reviewed.

Objective

Our goal in this study was to estimate the levels of Lead, Zinc and Copper in patients with polycystic ovary syndrome and to confirm the effect of such metals on the female reproductive system at environmental exposure

Materials and Method

Fifty two women in their reproductive age (20-40) years old, which had been diagnosed as PCOS. Venous blood sample were taken from each patient and control, blood lead, zinc and copper were determined by atomic absorption spectrophotometer.
Hormone assay were determined by ELISA (Enzyme Linked Immune Sorbet Assay) technique.

Results

This study showed a significant increase of blood lead and serum zinc, copper ($p<0.01$),in addition to testosterone, lutenizing hormone, LH/FSH ratio and body mass index (BMI) ($p<0.05$) in patients with polycystic ovary syndrome when compared with control.

Conclusions

On the basis of the observations of the present study, it can conclude that the increased levels of Lead as a result of the exposure to this metal may be a risk factor for the development of polycystic ovary syndrome in women and has adverse effects on female endocrine and reproductive function.

Key Words: **Infertility, PCOS, Lead, Zinc, Copper.**

Introduction

Polycystic ovary syndrome (PCOS) is a common condition affecting approximately 5-8%reproductive aged women (1). It is characterized by chronic anovulation and hyperandrogenism with variable clinical manifestations that include oligomenorrhea, infertility, hirsutism, and acne (2). Although these manifestations typically provide the impetus to seek medical evaluation, it is the associated complications of PCOS, namely obesity, dyslipidemia, insulin resistance (3). The combination of elevated levels of adrenal androgens and obesity leads to increased formation of

extraglandular estrogen. This estrogen exerts a positive feedback on LH secretion and negative feedback on FSH secretion, resulting in a ratio of LH to FSH levels in plasma greater than 2.These features are associated with hypersecretion of LH and androgens but with normal or low serum concentration of FSH(4)

All living and even beings are exposed to numerous chemicals persisting in the environment. The scope of the reproductive disorders thus caused in the general population is becoming widely documented, and the possible role of these agents present in the environment on the incidence of these disorders has renewed worldwide attention to review the problem (5). There is concern in the scientific community and the public about commonly used chemicals that are hormonally active and potentially toxic to reproductive systems. There has been growing apprehension that synthetic chemicals released into the environment have affected the development and/or function of the reproductive,endocrine,immune and nervous systems of different species(6). Although many environmental contaminants can affect reproductive health there is an important class of chemicals called endocrine disrupting chemicals(EDCs)that interfere with the production, release, transport, metabolism binding action or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis and regulation of developmental process,(5).

Lead is a soft, malleable metal, that is also considered to be one of the heavy metals. Lead has the highest atomic number of all stable elements, has a half-life so long, it can be considered stable. Like mercury, another heavy metal, lead is a potent neurotoxin that accumulates in soft tissues and bone over time (7).Lead entering the respiratory and digestive systems is released to the blood and distributed through the body.More than 90 percent of total body burden of lead is accumulated in the bones, where it is stored for decades. Lead poisoning was documented in ancient Rome, Greece, and China (7). It is widely used in the production of batteries, ammunition and devices to shield X-rays leading to its exposure to the people working in these industries. Lead used in gasoline, paints and ceramic products, caulking, and pipe solder. Ingestion of contaminated food and drinking water is the most common source of lead exposure in humans. Exposure can also occur via inadvertent ingestion of contaminated soil/dust or lead-based paint, smelling of burning of leaded gasoline (8).Most common source of exposure in Iraq is leaded benzen and leaded gasolin which were used in large and small generators. Several other metals, such as copper (Cu), manganese (Mn), selenium (Se), and zinc (Zn), are essential for good health but may be harmful above certain levels (9,10). For example Mn and Cu, which act as cofactors for a variety of important enzymes, have been associated with reduced semen quality in rodents and in humans (11). Because the potential exists for a number of metals to positively or negatively affect reproduction either individually or together, we also included these metals (zinc and copper) in our analysis. This work represents the study of metal exposures at environmental levels and PCOS.

Materials & Methods:

Fifty two women in their reproductive age (20-40) years old, who had been diagnosed as PCOS, were recruited from IVF Institute of Embryo Research & Infertility Treatment,Al-Nahrain University , Baghdad. They were seen in time period from August 2008 till March 2009.

PCOS was defined as anovulatory infertility and patients matched to the revised 2003 criteria in which PCOS is

diagnosed if there are any two of the following: (2 out of 3)

1- Female with irregular menstrual cycle.

2- Clinical (hirsute, acne, alopecia) or biochemical hyperandrogenism.

3- Presence of polycystic ovaries on ultrasound examination (12).

Twenty apparently healthy fertile women were served as control, which were matched for age and with regular menstrual cycle and normal ultrasound. Both patients and control are neither occupationally exposed to Pb, nor smokers.

Two venous blood sample were taken from each patient. One sample was collected in an EDTA coated tube and refrigerated until analyzed for blood lead using atomic absorption spectrophotometer. Serum was collected from the second sample for measurement of testosterone, follicle stimulating hormone (FSH), lutenising hormone (LH), zinc (Zn) and copper (Cu). Endocrine evaluation and lead, zinc and copper assays were performed in both cases and controls.

Hormone assay were determined by ELISA (Enzyme Linked Immune Sorbet Assay) technique (13). Pb, Zn and Cu were determined by atomic absorption.

Statistical Analysis:

Statistical analyses were done using student t- test .The statistical significance and strength of linear correlation between two continuous variables was assessed by Pearson's correlation coefficient.P value less than 0.01and 0.05was considered statistically significant.

Results:

The results in Table-1 showed that: the mean Body Mass Index (BMI) in patients with PCOS was equal to (29.3 ±7.3) kg/m^2 which was significantly elevated when compared to the normal control group (22.6± 2.7) kg/m^2 and $P<0.05$.

The mean serum levels of FSH in patients with PCOS was equal to (5.4 ±1.5) mIU/ml which is within the normal range with no significantly different when compared with the normal control group (5.8±0.5) mIU/ml and P value > 0.05 .The mean serum levels of LH in patients with PCOS was equal to (11.9±5.4), which is significantly elevated when compared with normal controls group (7±0.6) m IU/ml. and $P<0.05$.

The mean serum levels of LH to FSH ratio in patients with PCOS was found to be equal to (2.3±1.1) which was also significant elevated when compared with the normal controls group (1.2±0.1). and $P<0.05$.

The mean serum levels of total testosterone in patients with PCOS were equal to (50 ±9.6) ng/dl which was significantly elevated when compared with normal controls group (24±3.4) ng/dl. and $P<0.05$.

In Figure (1), the mean blood levels of lead in patients with PCOS was found to be equal to (26.22 ±3.07)µg/dl which was significantly elevated when compared with the normal controls group (15.46±1.47) µg/d. And $P<0.01$.In Figure(2),the mean serum levels of zinc in patients with PCOS was found to be equal to (90.4±13.39) µg/dl which was significant elevated when compared with the normal controls group (79.28±7.62) µg/dl.and$P<0.01$.In Figure(3),the mean serum levels of copper in patient with PCOS was found to be equal to (172.4± 33.23) µg/dl which was significant elevated when compared with the normal controls group (93.09±14.70) µg /dl.and $P<0.01$.

Table (1)BMI and Endocrine parameters of PCOS and Healthy control subjects

Characteristics	PCOS	Control	P value
Number	52	20	
BMI (kg/m2)	29.3±7.3	22.6±2.7	< 0.05
FSH (mIU/ml)	5.4±1.5	5.8±0.5	>0.05
LH (mIU/ml)	11.9±5.4	7.0±0.6	<0.05
LH/FSH ratio	2.3±1.1	1.2±0.1	<0.05
Testosterone (ng/ml)	50±9.6	24±3.4	<0.05

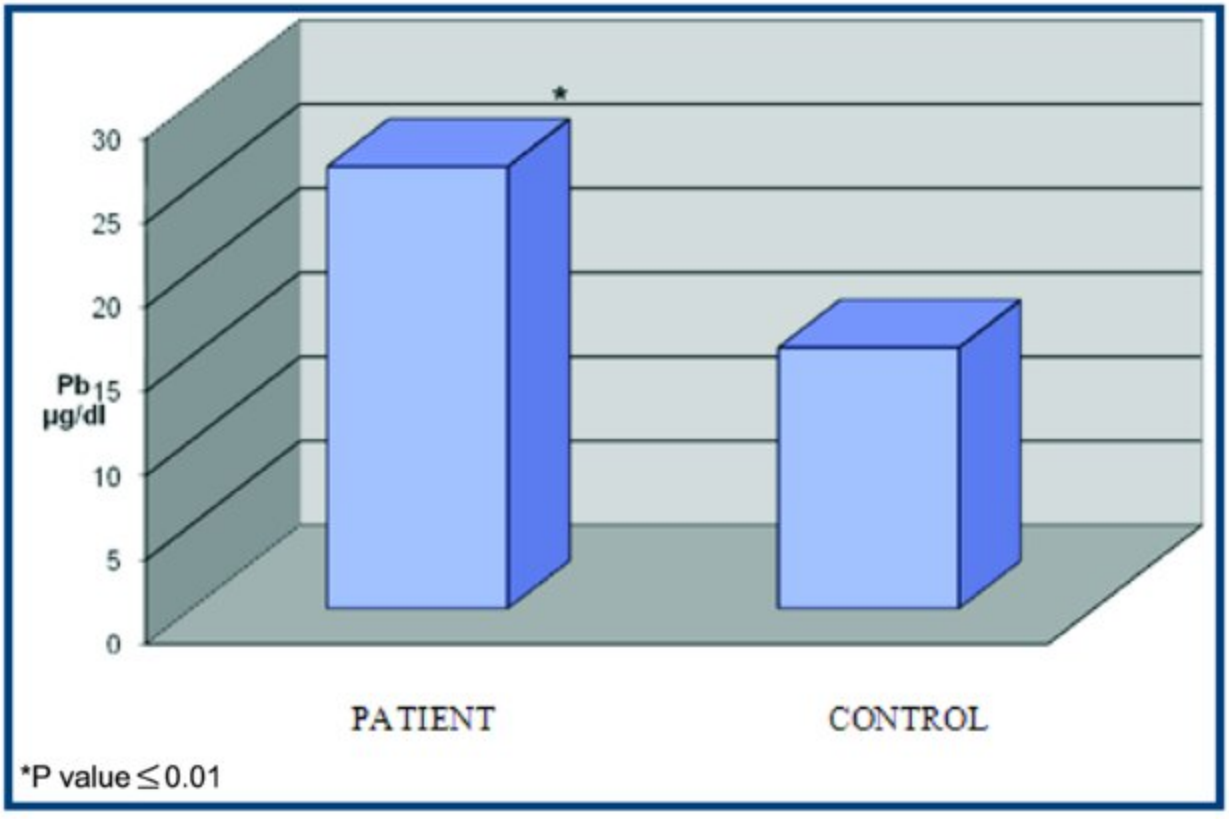

Figure (1) A diagram showing the distribution of mean of blood Lead level in PCOS patients and control.

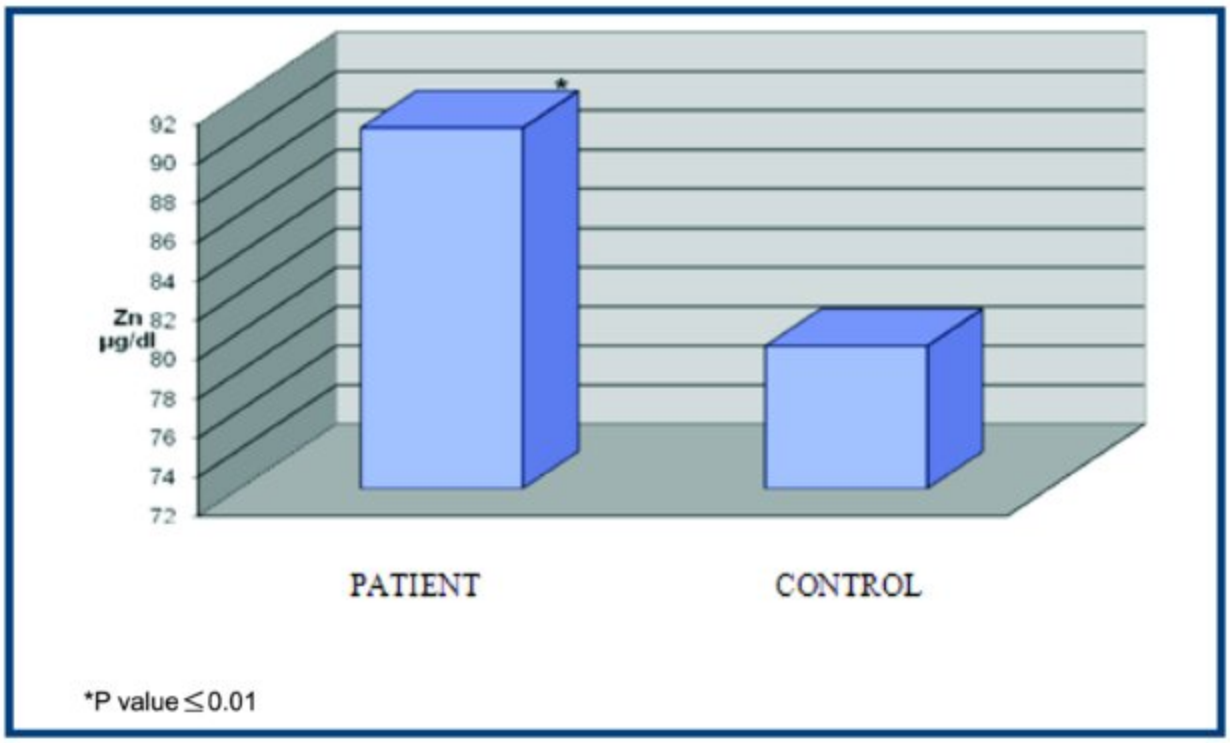

Figure (2) A diagram showing the distribution of the mean of serum Zinc level in PCOS patients and control.

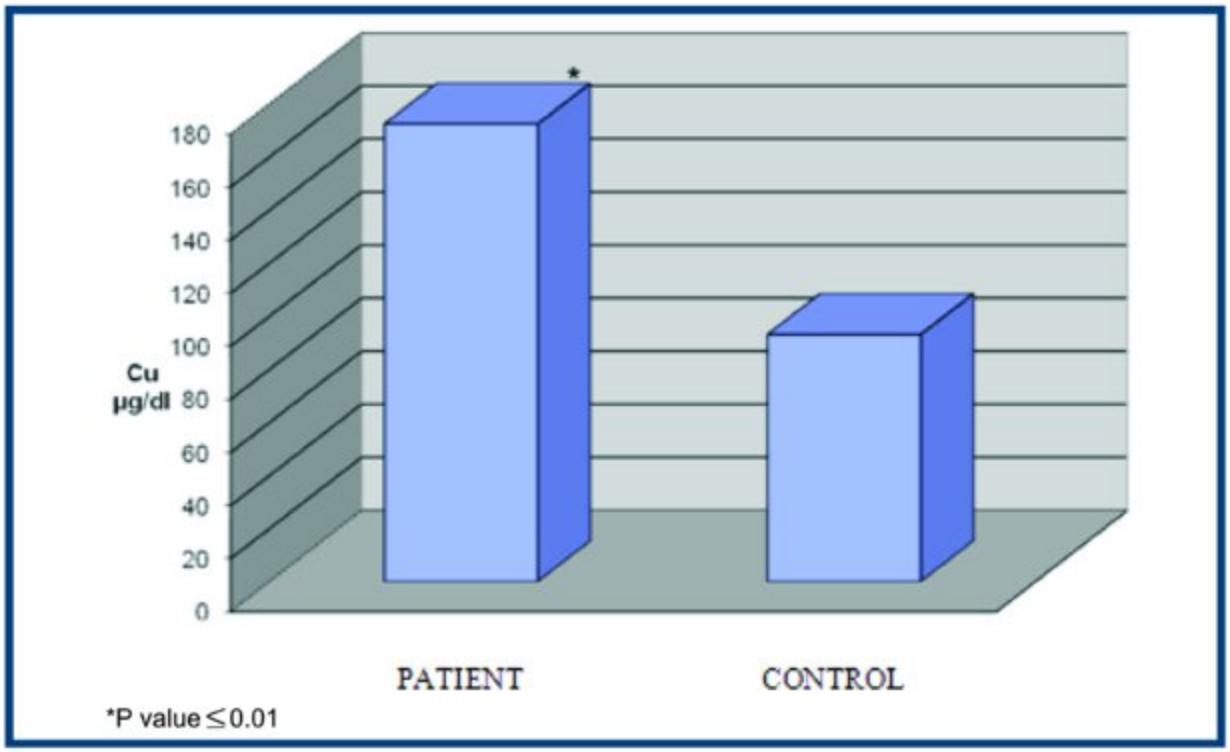

Figure (3) A diagram showing the distribution of the mean of serum Copper level in PCOS patients and control.

Discussion:

To our knowledge, the distribution of blood lead in PCOS patients has not been reported in the literatures. There was a significant elevation in Pb, Zn and Cu in patients with PCOS when compared with control as shown in Fig (1, 2 3). PCOS is a complex clinical picture and presents a multifaceted etiology related to imbalance of the hypothalamic-pituitary-adrenal (HPA) axis, thyroid involvement and metabolic syndrome (insulin resistance) (14). Heavy metals such as lead were among the first recognized human reproductive toxicant(15). Animal, clinical ,and epidemiologic studies have demonstrated that exposure to lead disrupt all level of the reproductive axis, with the central nervous system (16). By binding to steroid hormone receptors, these compounds can impact female fertility by altering ovarian development and function, purportedly through estrogenic, anti-estrogenic, and/or anti-androgenic effects (17). Based upon the evidence from studies involving long-term exposure to the endocrine disruptors, it is clear that adult ovarian function, and thus female fertility, are affected by this endocrine disruptors(18,19). Hildebrand, et al (20) observed that sexually mature female rats exposed to lead acetate exhibited irregularity of the estrous cycle and ovarian cysts. Lead is consistently observed to be a reproductive toxicant, causing decreased fertility and increased pregnancy loss (6).Craft et al(21) suggested that environmental exposure may be co-factor in determining disease outcomes related to obesity because it has the potential to exacerbate medical conditions, so environmental exposure of PCOS women to Pb, lead to deteriorate their health. On the other hand we thought that PCOS women are susceptible to Pb. Environmental chemicals can cause a broad spectrum of effects, which depends not only on route of exposure and dose, but on the susceptibility of the individual to the compound. Age ,gender, and genotype can influence susceptibility to disorders, anatomic abnormalities, and Diseases From exposure(6). Susceptibility to any agent results from the interaction between genetics (enzyme polymorphisms, for example) and environment (fitness, nutrition, past or concurrent exposures, etc.(22) Genetic factors may influence the availability of sulfhydryl-containing compounds such as glutathione and metallothionein, which modify the distribution and toxicity of certain metals (23).Factors influencing susceptibility may act at the site of exposure (usually by increasing or decreasing uptake), may effect the toxicodynamics of a metal (usually by complexing or covalent binding), may influence the transport to a target organ, or (theoretically at least) may influence some immunologic, biochemical, or cytologic functional response at the target organ (22). Although there have been many publications on risk factors for disease, as well as on the phenotypic variation of various hematologic or biochemical markers in populations, relatively few studies have combined these studies to focus on susceptibility per se (24).

Certain chronic neoplastic or metabolic diseases produce changes in one or more body systems which should, indirectly at least, render those systems more susceptible to metal toxicity (25). Although Pb and other heavy metals usually inhibit enzymes by binding -SH groups and distorting structure, Pb enhances gluconeogenesis at several enzymatic steps. Some schools of medicine emphasize the role of metals like lead, copper, gold, iron, mercury, silver, tin and zinc in the proper functions of the human body. Any imbalance in the composition of these metals is thought to cause diseases, and the equilibrium of these metals is seen as a requirement of normal immune defenses and general health (26). Since metals are not themselves metabolized, the opportunities for influencing toxicity are more restricted than for many organics, in which the availability of alternative

metabolic pathways may profoundly influence an organism's response (23).
Another possible explanation for the elevation of Pb in the serum of the patients with PCOS is because of the increase Pb mobilization from bone ; bone-to-blood lead mobilization increases during periods of pregnancy, lactation, menopause, physiologic stress, chronic disease, hyperthyroidism, kidney disease, broken bones, and advanced age, all which
are exacerbated by calcium deficiency(27), Dimitrios et al (28),find an elevation of parathyroid hormone concentrations in serum of women with PCOS, and as we know parathyroid glands stimulated by fall in plasma calcium ion. Moreover, treatment with calcium (1,500mg/day) and vitamin D reversed abnormalities in the calcium economy and led to remission of symptoms in the majority of the women with PCOS after 2 months (29). Many studies show that metals behave differently in males and females of various animals. Female rabbits showed an earlier and higher rise in Zn protoporphyrin after lead exposure than males (30). Annapoorna (31), notice the elevation of zinc in lead poisoning. Falnoga et al (32) found that: exposure to toxic metal lead to increased tissue levels of essential Cu and Zn, and this in turn can alter the blood levels Cu and Zn .In this work there was an increase in blood levels of Zn and Cu in PCOS patients that associated with an elevation of Pb

Conclusion:

On the basis of the observations of the present study, it can concluded that the increased level of lead as a result of exposure to this heavy metal may be a risk factor for the development of PCOS in women and has adverse effects on female endocrine and reproductive function.

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