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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2018;7(1):39-42

Evaluation of serum heavy metal levels on primary ovarian insufficiency

Sule Ozel[1], Ayla Aktulay[1], Osman Aykut[2], Hikmet Gulsen Uncu[2], Hatice Kansu Celik[1], Sunullah Soysal[3], Mehmet Cinar[1], Yaprak Engin Ustun[1]

[1] University of Health Sciences, Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey
[2] Public Health Institution of Turkey
[3] Marmara University Faculty of Medicine Department of Obstetrics and Gynecology, Istanbul, Turkey

Received 27 April 2017; Accepted 30 June 2017
Available online 19.07.2017 with doi: 10.5455/medscience.2017.06.8666

Abstract

In this study we aimed to investigate the level of exposure to these toxic heavy metals such as Aluminum (Al), Arsenic (As), Mercury (Hg) ,Manganese (Mn) and Lead (Pb) among Premature Ovarian Insufficiency (POI) patients. This cross-sectional study was performed in 23 women with normal reproductive hormones (control) and 23 women with POI (case). Risk factors evaluated were; age,body mass index(BMI), gravidity and blood serum metal levels (Al,As,Hg,Mn,Pb). Risk factors were compared between groups. Women with history of pelvic surgery, any cancer or autoimmune disease treatment, endometriosis and other chronic systemic diseases were excluded from the study. The Age, BMI and Gravidity were similar between the case and control group ($p > 0.05$). And also the aluminum, arsenic, manganese, mercury and lead serum levels were smilar between the case and control group ($p > 0.05$). Etiology of most POI cases remains undetermined. Early recognition of predisposing factors of POI may help to make prevention about ovarian failure and would offer this patient population the opportunity to preserve fertility. Identifying people with elevated blood heavy metal levels will give chance of avoiding oncoming destructive health effects of heavy metals.

Keywords: Primary ovarian sufficiency, heavy metals, lead, arsenic, mercury

Introduction

Primary Ovarian Insufficiency (POI) is a clinical syndrome defined by the loss of ovarian activity before the age of 40. POI increasing recently can be detected in 2% to 10% of patients with amenorrhea[1]. Diagnostic criteria of POI is amenorrhea for at least four months and follicle-stimulating hormone (FSH) level >25 IU/l on two detection>4 weeks apart [2]. Mechanisms of primary ovarian insufficiency is follicle dysfunction and follicle depletion [3]. POI is different from menopause in case of some individuals with that may ovulatory and even approximately 5–10% of patients with POI are able to conceive spontaneously after the diagnose [4-6].

Testing for caryotype, adrenal antibodies, FMR1 premutation and pelvic ultrasonography must be applied to find out etiologies of primary ovarian insufficiency [7,8]. Pathogenesis of POI is largely unknown and usually classified as idiopathic. Radiation exposure, chemotherapy, extensive surgery, severe PID, mumps, enzyme deficiencies, Turner syndrome, Mosaicism, gene deletions and inversions, gene mutations, autoimmune diseases, environmental toxins can play role in the etiology of POI .

Heavy metal toxicities have been recognized for years. Exposure through occupational, residential, and environmental contamination may lead to heavy metal toxicities. The clinical presentations of metal toxicity is variable in a wide spectra. Many heavy metals can be effect reproduction and growth, and some have carcinogenic potentials [9]. Although many toxic metals can effect multiple organ systems, most metal toxicoses are characterized by involvement of particular organs [10].

Aluminum (Al), Arsenic (As), Mercury (Hg), Manganese (Mn) and Lead (Pb) are environmental pollutants that have wide spread throughout the world. The present study aimed to investigate the level of exposure to these toxic heavy metals among POI patients.

Material and Methods

This cross-sectional study was performed in a six-month period in 2016 in January 5to June at Zekai Tahir Burak Women's Health and Resource Hospital Ankara, Turkey. The study protocol was approved by the Ankara Numune Hospital ethical committee. Women were fully informed about the study and who participated

***Coresponding Author:** Mehmet Cinar, University of Health Sciences, Zekai Tahir Burak Women's Health Education and Research Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey
E-mail: drmcinar@gmail.com

provided written informed consent prior to taking blood sample. All our patients were examined to confirm POI in case of levels of FSH and other hormones, caryotype to determine whether any chromosomal abnormalities existed and antibody measurements to find or exclude any autoimmune causes of ovarian insufficiency. After the full course of evaluation, idiopathic POI was diagnosed. 23 Women with normal reproductive hormones Follicle Stimulant Hormone (FSH), Luteinize Hormone (LH), estradiol (E2) (aged ≤40 years), we examined blood serum heavy metal levels (Al,As,Hg,Mn,Pb). After every POI women with selection criteria, first matched healthy women without any systemic diseases selected as control patient.

Participants and samplings

This study included only healthy women taken POI diagnose (amenorrhea for at least four months and follicle-stimulating hormone (FSH) level >25 IU/l on two detection> 4 weeks apart). Exclusion criteria were as women with, history of pelvic surgery, any cancer or autoimmune disease treatment, endometriosis and other chronic systemic diseases.

In total, 23 eligible POI women diagnosed as case group and 23 matched healthy women diagnosed as control group, agreed to the study.

Before the collection of specimens, subjects fasted overnight. Cd, Al, As, Hg, Mn and Pb levels were measured in serum samples of case and control group blood samples. The levels of aluminum, arsenic, manganese, mercury, lead in serum samples were measured at Redo slab, İstanbul, Turkey. Samples were analyzed via inductively coupled plasma mass spectrometry (ICP-MS) using an Thermo ICAP RQ instrument (THERMO, Waltham,MA-USA). The lowest limit of quantization (LOQ) in serum was Al: 0,3 µg/L, As: 0,3 µg/L, Hg: 0,06 µg/L, Mn: 0,3 µg/L, Pb: 0,06 µg/L, Cd: 0,3 µg/L. Serum samples (2–3 mL) collected in polystyrene tubes were centrifuged at 1500 rpm for 15 min to obtain serum which was transferred in polystyrene tubes and kept at -20 –c until analysis centrifuged and frozen immediately after collection and kept frozen (_20 _C) until analysis. In order to minimize the polyatomic interference, 65% nitric acid (concentrated grade [Merck 452]), reagent water equivalent to ASTM type 1 (ASTM D 1193; N18m_cm resistivity), 0.5% (v/v) nitric acid, a tuning solution (for sensitivity tuning: 10 mgL_1 for each of the metals Li, Y and Tl in 1% HNO3) and a single-element standard stock solution for Al, As, Hg, Mn, Pb and Cd (1000 ppm) were used. Next, 1 g serum samples were accurately weighed placed in a dry Teflon vessel and then 5mL of HNO3 and 5mL of distilled water were added. This mixture was placed in a microwave oven for digestion. Following digestion, the samples were diluted with 25mL of distilled water. The standard working solutions and the biological samples in the polyethylene tubes were placed in an ICP-MS automatic sequencer to measure the concentration of aluminum, arsenic, manganese, mercury and lead.

Statistics

Mean and standard deviation (SD) were calculated for continuous variables. The normality of the variables was analyzed by Kolmogorov Smirnov test. Student's t test and Mann Whitney U test have evaluated associations between the categorical and continuous variables. All variables were included in the backward stepwise procedure. Two-sided p values were considered statistically significant at p<.05. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Table 1 summarizes the demographic, clinical, and laboratory findings of the subjects. The Age, BMI and Gravidity were similar between the case and control group (p > 0.05). And also the aluminum, arsenic, manganese, mercury and lead serum levels were similar between the case and control group (p > 0.05).

Table 1. The demographic characteristics of the groups

	Case n=23	Control n=23	p value
Age (years)	29.2±3.9	28.4±5.3	0.213
Gravida	1.0±1.41	0.7 ±1.17	0.115
BMI (kg/m2)	23.5±3.91	21.6 5±5.7	0.132

BMI: Body mass index.

Table 2. The heavy metal levels of the groups

Heavy metals (µg/dl)*	Case (n=23) (mean ±Standard deviation)	Control (n=23) (mean ±Standard deviation)	p values
Al	4.40±1.16	4.23 ±1.87	0.714
As	3.85 ± 2.15	3.69 ± 2.34	0.814
Hg	2.16 ±1.11	2.01 ±1.55	0.700
Mn	1.17 ±0.32	1.22 ±0.45	0.682
Pb	9.5 ± 4.45	8.82 ± 4.02	0.58

Al:aluminium, As:arsenic, Mn:manganase, Hg:mercury, Pb:lead, p was calculated with Mann Whitney U test

Discussion

Heavy metals' toxicities have diverse clinical presentations. Heavy metals in case of their non-degradable properties can have high toxicity and adverse effects on health [11,12]. Ingestion, inhalation and dermal contact are the ways of taking heavy metals in to human body [13-16]. Toxic effect of metals are shown either by binding of the metals binds to vital enzymes or replace other elements in biochemical reactions. Many heavy metals have adverse effects on reproduction and development, and some are carcinogens [17,18].

Aluminum(Al) is common in the environment [19]. The major route of aluminum exposure is dietary, particularly as food additives [20]. Aluminum cause necrosis of spermatocytes/spermatids in the testes and reduce fertility of various male laboratory animals. In our study serum aluminum levels of POF group were higher than control group but difference between groups was not significant (P≥0.05).

Arsenic (As) one of the most toxic metals derived from the natural environment is associated with natural processes, as weather, volcanic emissions as well as a result of human activities such as mining, metal casting and herbicides and fossil fuel production. Such human processes contaminate soil and water with As [21,22]. Prolonged ingestion of water contaminated with arsenic may result in the manifestations of toxicity in all systems of the body. The most serious hazard of arsenic is its carcinogenic potential [23]. Previous studies have shown that As decreased sperm number

and viability, increased morphological alterations, affecting male fertility [24]. In our study serum As levels of pof patients were higher than control group but difference were not significant (p>0,05).

Manganese is a naturally occurring element and an essential nutrient. Manganese is required for the formation of healthy cartilage and bone and the urea cycle; it aids in the maintenance of mitochondria and the production of glucose. It also plays a key role in wound-healing. Impaired sexual function in men may be one of the earliest clinical manifestations of manganese toxicity. There is a lack of information regarding effects in women since most data are derived from studies of male workers. No direct effect of manganese toxicity has been observed on fertility in women. Although many studies in laboratory mammals have attempted to detect effects of manganese on female fertility, only one study demonstrated the possibility that excess manganese exposure outside of pregnancy may impair future fertility (decreased number of offspring) [25]. Normal ranges of manganese levels in serum are 0.4–0.85 μg/L. In our study serum manganese levels of control group were higher than POF group but difference between groups were not significant statistically.

Cadmium exposure is primarily from cigarette smoke, both active and passive, as well as consumption of green leafy vegetables, liver and kidney meats and shellfish [26]. In the general population, Cd was higher among smokers and in people with environmental exposure from living in industrial areas [27]. Cadmium has been shown to effect reproductive hormone actions and associated with adverse reproductive outcomes in epidemiologic studies.

Mercury exposure is primarily through fish and shellfish consumption (organic), and to a lesser extent air pollution (inorganic) and amalgam tooth fillings. Mercury is associated with adverse reproductive outcomes in epidemiologic studies [28]. In our study serum Hg levels of POF group were higher than control group but difference between groups was not significant (P≥0.05).

Lead exposure can be through (Community, Home, Hobbies, Occupation, Personal habits, Diet and Drugs) occupational (Lead mining and refining, plumbing and pipe fitting, auto repair, glass manufacturing, printers, battery manufacturing and recycling, construction work, firing-range instruction, plastic manufacturing, gas station attendant), environmental (Lead paint, soil or dust near roadways or lead-painted homes, plastic window blinds, plumbing leach ate (from pipes or solder), ceramic ware, lead-core candle wicks) hobbies(Glazed-pottery making, target shooting at firing ranges, lead soldering, preparing lead shot or fishing sinkers, stained-glass making, painting, car or boat repair), Other(Folk remedies, gasoline sniffing, costume jeweler, cosmetics) [29].

There is no evidence for a threshold below which lead has no adverse health effects. The health effects of lead exposure include developmental neurotoxicity, reproductive dysfunction and toxicity to the kidneys, blood and endocrine systems. Most lead exposures are preventable, and diagnosing lead poisoning is relatively simple compared with diagnosing health effects of exposures to other environmental toxins [30].

Accurate assessment of lead poisoning requires specific knowledge of the sources, high-risk groups and relevant laboratory tests. Lead has been associated with adverse reproductive outcomes in rats. Few studies have directly examined blood metal levels in relation to hormone levels and cycle length [29] (cadmium, lead and mercury) and menstrual cycle function assessed by prospectively collected data on cycle length and serum hormone levels (FSH, LH, E2 and progesterone) as measured on clinically relevant days of the menstrual cycle [31]. In our study, Blood lead levels of POF patients found significantly higher than control group (p< 0.05).

Etiology of most POI cases remains undetermined. Early recognition of predisposing factors of POI may help to make prevention about ovarian failure and would offer this patient population the opportunity to preserve fertility. Identifying people with elevated blood heavy metal levels will give chance of avoiding oncoming destructive health effects of heavy metals.

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