

Effects of Environmental Exposure to Lead and Cadmium on Male Fertility

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ABSTRACT

KEYWORDS

Lead,
Cadmium,
FSH,
LH.

Chronic exposure to heavy metals represents a medical challenge especially in developing countries. The aim of the present study was to measure the levels of (lead and cadmium) in infertile male and correlate these levels with male fertility. After free informed consent, the present study included 70 infertile couples (without female infertility factor) attending the infertility clinics (Dermatology and Venereology Department; Al-Azhar Faculty of Medicine; New Damietta); who were well-known to be exposed to lead and/or cadmium confirmed by measuring blood lead and cadmium levels, and another 30 healthy fertile males without evidence of environmental exposure were included as controls. All patients underwent history taking, clinical and andrological examination and laboratory investigations (complete blood count, blood glucose level, renal and liver function tests and hormonal profile (serum FSH, LH, estrogen and testosterone) with measurement of lead and cadmium levels using graphite furnace atomic absorption spectrophotometry. Finally, a sample of semen was obtained for semen analysis. It was concluded that there was high concentrations of lead and cadmium linked to male infertility as revealed by changes in hormonal profile and seminal parameters.

Introduction

Worldwide, about 1 in 7 couples have problems in conceiving. About 80% or higher of couples with regular intercourse with no use of any methods of contraception would attain a pregnancy by one year and about 92% could get a pregnancy by 2 years (Sandhu and Tu, 2017).

Infertility affects males and females equally; although many people believe that infertility is a female problem. In industrial

countries, 15% of couples at their reproductive years have difficulty conceiving naturally (Jurewicz et al. 2013).

A male factor was included in about half of such couples and the cause still unidentified in 25% of male factor infertility cases. As medical history cannot be elucidated in all male factor infertility subjects, these observations may be associated with an effect of occupational and environmental factors (De Fleurian et al., 2009).

Although many factors, e.g., diseases, lifestyle, stress and obesity, are accountable for decreasing semen excellence, environmental toxins are also suggested to play a pivotal role in worsening male reproduction health. Environmental toxicants as lead (Pb), cadmium (Cd) or phthalate esters (di (2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and diethyl phthalate (DEP)) extensively found in

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diverse environmental strata are associated with reduction of sperm count and motility (Sengupta, 2013). Human exposure to metals usually happens by oral intake of contaminated foodstuffs, drinking polluted water, exposure to cigarette smoke and via eating food packed and preserved in recycled plastic materials. Highly acidic food has a greater detrimental effect on human health because plasticizers leak more easily to such foods (Bernard, 2008). Studies evaluating the toxic link with semen quality and sex steroid hormones in humans provide conflicting results, these findings either have no association (Mendiola et al., 2011) or have significant association (ShuGuang et al., 2011).

These chemical substances exert its function by an endocrine-disrupting action with disruption of hormone regulations, through the hypothalamic-pituitary-testicular axis or direct inhibition of androgen formation in Leydig cells (Jurewicz et al. 2013). The aim of the present study was to estimate the level of (lead and cadmium) in infertile males.

Patients and methods

This study was designed as an analytical observational case-controlled study. The study was conducted on (100) subject divided into two groups.

Group (1): Case group: Seventy patients were males in infertile couples (without female infertility factor) attending the infertility clinics (Dermatology and Venereology Department; Al-Azhar Faculty of Medicine; New Damietta); who were well-known to be exposed to lead and/or cadmium confirmed by measuring blood lead and cadmium levels.

Group (2): Control group: thirty fertile males, without evidence of environmental exposure were included as a control group. Levels of lead and cadmium were measured to confirm absence of exposure.

Inclusion criteria were as the following:

1) Male patients aged 18 to 45 years; and 2) Absence of current medication known to impair semen parameters.

On the other hand, *exclusion criteria* included: 1) Patients with history of varicocele, cryptorchidism or endocrine hypogonadism (abnormal hormonal concentrations), 2) Patients with chemo- and/or radiotherapy, and 3) Patients with anomalies in the karyotype or Y chromosome microdeletions, 3) Male patients with chronic diseases such as diabetes mellitus, hypertension, bilharziasis, syphilis and tuberculosis.

The following questionnaire was filled with the patient himself or by the researcher. The items of the questionnaire were divided into 4 parts: Part (1) collected general information of the participant included: age, place of birth and age of marriage. The second part is about risk factors known to impair semen quality, including history of genital pathology. Part (3) asked about lifestyle: current [for a duration of at least 3 months] consumption of tobacco, alcohol, or drugs. Part (4) assessed the subjects' professional exposure using: 1] the social and economic class; 2] current and past occupations and occupational exposure considering the exact professional activity. An occupation exposure was marked as positive if there was current exposure [>1 h/wk and since 3 months or more] or past exposure [not current; was continued for 1 or more years in the past and >1 h/wk].

Full clinical and andrological examination were done for all participants. A 10 ml of venous blood were obtained for investigation of complete blood count (C.B.C), blood glucose level, renal and liver function tests and hormonal profile (FSH, LH, serum estrogen and testosterone) and measurement of cadmium and lead.

Finally, a sample of semen was obtained for semen assessment. All participants were instructed to abstain from sexual intercourse for at least 3 successive days before giving the semen sample. The semen samples were collected in sterile plastic containers and permitted to liquefy for 30 min. Thereafter, samples were analyzed by direct microscopy.

Statistical Analysis

The statistical package for social science (SPSS), version 22 (IBM® SPSS® Inc, USA) was studied to perform statistical analysis. Quantitative data was expressed as mean and standard deviation; while qualitative were expressed as frequency and percent distribution. For comparison between two groups, the independent samples student (t) test and Chi square (χ^2) test were used for quantitative and qualitative data respectively. P value < 0.05 was considered significant.

Results

The present study includes 70 infertile males, and another 30 healthy controls. Patient age ranged from 24 to 38 years, the mean age was 33.75 ± 2.84 years. The age at marriage ranged from 20 to 30 years, the mean age at marriage was 24.01 ± 1.56 years; and there was no significant difference between study and control groups regarding age and age at marriage.

Weight of studied populations in the present study ranged from 62 to 85 Kg, the

mean value was 72.95 ± 5.57 Kg; the height ranged from 162 to 179 cm, the mean value was 170.95 ± 3.92 cm; BMI ranged from 20.96 to 29.07 Kg/m^2 , the mean value was $24.93 \pm 1.34 \text{ Kg/m}^2$; there was no significant difference between study and control groups regarding weight, height or BMI.

Smoking habit was positive in 41% of studied populations, and there was statistically significant increase of smokers in study when compared to control group (52.9% versus 13.3% respectively) (Table 1). Regarding CBC findings, there was statistically significant decrease of hemoglobin, RBCs and hematocrit in the study when compared to the control group (9.95 ± 0.60 , 3.19 ± 0.32 and 31.44 ± 2.87 versus 12.48 ± 0.54 , 4.16 ± 0.34 and 40.89 ± 3.53 successively).

On the other side, there was no significant difference between study and control groups as regard to white blood cells and platelet count. In the present study, serum creatinine ranged from 0.30 to 2.30, the mean value was 1.02 ± 0.40 mg/dl; blood urea ranged from 10 to 47, the mean value was 29.28 ± 10.56 mg/dl and there was significant increase of serum creatinine and blood urea in the study group when compared to control group (1.20 ± 0.32 , 35.85 ± 3.51 versus 0.60 ± 0.21 and 13.93 ± 1.77 respectively).

There was no significant difference between study and control groups as regard to serum albumin, ALT or AST. Results of the present study revealed that, there was no significant difference between study and control groups as regard to fasting and postprandial blood sugar.

Table (1): Distribution of the studied populations as regard to personal characteristics.

Variables	Study group n:70 mean ± SD	Control group n:30 mean ± SD	test	p value
Age (year) mean ± SD	34.04±2.72	33.06±3.06	1.58	0.11
Age at marriage (year) mean ± SD	23.90±1.48	24.26±1.74	1.07	0.28
Weight (Kg) mean ± SD	73.10±5.15	72.60±6.52	0.40	0.68
Height (cm) mean ± SD	170.67±3.19	171.60±5.26	1.08	0.28
BMI (Kg/m ²) mean ± SD	25.07±1.36	24.61±1.26	1.60	0.11
Smoking n (%)	37(52.9%)	4(13.3%)	13.56	<0.001*

BMI: body mass index, SD: standard deviation, Kg: kilogram, cm: centimeter, n: number, * significant.

There was statistically significant increase of FSH and LH in study when compared to control group (6.08±0.42 IU/L, 8.04±0.90 IU/L versus 4.48±0.38 IU/L and 6.83±0.77 respectively). On the other hand, there was statistically significant decrease of estradiol and testosterone in study when compared to control group (51.87±6.70 pg/ml, 351.02±34.47 ng/ml versus 82.23±4.99 pg/ml and 380.02± 57.53 ng/ml respectively) (Table 2).

Semen analysis revealed that there was statistically significant decrease of ejaculate

volume, sperm count, sperm concentrations, live sperms, rapid and progressive motility in study when compared to control group (Table 3).

Regarding levels of lead, it ranged from 12 to 30.1µg/dl and there was statistically significant increase in study when compared to control group (37.26±7.64 versus 17.32±3.45 µg/dl respectively). In addition, cadmium levels ranged from 1 to 9 µg/dl, and there was statistically significant increase in study when compared to control group (5.36±1.45 vs 1.87±0.83 µg/dl respectively) (Table 4).

Table (2): Laboratory investigations in the studied populations.

Variables	Study group n:70 mean ± SD	Control group n:30 mean ± SD	test	p value
Creatinine (mg/dl)	1.20±0.32	0.60±0.21	9.08	<0.001*
Blood urea (mg/dl)	35.85±3.51	13.93±1.77	32.23	<0.001*
Albumin (g/dl)	4.23±0.33	4.36±0.27	1.80	0.07
ALT (IU/dl)	24.28±1.88	24.00±1.89	0.69	0.49
AST(IU/dl)	35.05±9.48	35.13±8.48	0.04	0.97
Fasting blood sugar (mg/dl)	107.52±4.58	106.13±5.38	1.32	0.18
Postprandial blood sugar (mg/dl)	167.28±10.83	169.86±13.94	0.99	0.32
FSH (IU/L)	6.08±0.42	4.48±0.38	17.74	<0.001*
LH (IU/L)	8.04±0.90	6.83±0.77	6.34	<0.001*
Estradiol (pg/ml)	51.87±6.70	82.23±4.99	22.26	<0.001*
Testosterone (ng/ml)	351.02±34.47	447.66±41.35	12.08	<0.001*

ALT: Alanine transaminase, AST: Aspartate transaminase, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, n: number, * significant, SD: standard deviation.

Table (3): Semen analysis of studied populations.

Variables	Study group n:70		Control group n:30		t	p
	Mean	SD	Mean	SD		
Ejaculate volume (ml)	3.74	0.66	4.43	0.67	4.71	<0.001*
Semen pH	8.13	0.04	8.13	0.05	0.40	0.68
Sperm count x10 ⁶	201.90	12.82	268.40	24.03	17.99	<0.001*
Sperm concentration%	55.31	8.84	61.72	9.79	3.21	0.002
Abnormal forms%	46.65	2.35	46.56	2.327	0.17	0.86
Live sperms%	55.45	2.371	66.13	3.37	18.06	<0.001*
Rapid motility	49.12	1.91	51.10	2.33	4.41	<0.001*
Progressive motility	38.04	2.03	42.60	4.108	7.42	<0.001*

SD: Standard deviation, n: number, * significant.

Table (4): Lead and cadmium levels of studied populations.

		Mean	SD	Minimum	Maximum	t	p
Lead (µg/dL)	Study	37.26	7.64	22.00	55.00	13.67	<0.001*
	Control	17.32	3.45	12.00	30.10		
Cadium (µg/L)	Study	5.36	1.45	2.00	9.00	12.24	<0.001*
	Control	1.87	0.83	1.00	4.20		

SD: Standard deviation, * significant.

In the present work, each of cadmium and lead were inversely correlated with ejaculate volume, sperm count, sperm concentration, live sperms, rapid mobility,

estradiol and testosterone, while both metals were proportionally correlated with FSH and LH (Table 5).

Table (5): Correlation of lead and cadmium with semen analysis and reproductive hormonal profile.

	Cadmium ($\mu\text{g/L}$)	Lead ($\mu\text{g/dL}$)
Ejaculate volume	-0.293*	-0.270*
Sperm count	-0.703*	-0.708*
Sperm concentration	-0.301*	-0.322*
Live sperms	-0.648*	-0.758*
Rapid motility	-0.373*	-0.339*
Progressive motility	-0.408*	-0.538*
Follicle-stimulating hormone	0.621*	0.707*
Luteinizing hormone	0.405*	0.534*
Estradiol	-0.750*	-0.772*
Testosterone	-0.579*	-0.599*

* significant at p 0.01.

Discussion

Male infertility can result from anatomical or genetic abnormalities, systemic or neurological diseases, infections, trauma, iatrogenic injury, gonadotoxins and development of sperm antibodies. When a husband and his wife fail to attain pregnancy beyond 1 year of regular sexual activity, an evaluation of both partners is crucial. For male, this assessment includes history, clinical examination, endocrine evaluation and analysis of semen. Several lifestyle factors and environmental issues can have a negative effect on male reproductive health, and the general physician has an essential role in patients' education about modifiable risk factors (National Institute for Health and Care Excellence, 2013).

A male factor is proposed to be responsible for about 50% of infertile cases, with single main responsibility in 30% of cases and a co-factor to a female factor in 20% of cases (Winters and Walsh, 2014).

In the present study, there was no

significant difference between study and control groups as regard to age and age at marriage. This age reflected the relatively higher age of patients that coincides with some reduction in testosterone. It was reported that, levels of testosterone decreased with advancement of age in most males, even in males who are healthy and this decrease may start around the age of thirty. The reduction of about 1% per year of testosterone after the age of 30 years has been called the andropause (Pasqualotto et al., 2004). However, age-specific reduction in testosterone itself cannot explain infertility in the present study, as it was technically accurate described for the decline in testosterone might be "symptomatic hypogonadism in aging males." Hypogonadism is not characterized by any definite level of serum androgens because the testosterone levels that lead to dysfunction varies broadly among individuals (Bhasin et al., 2006).

In addition, the non-significant difference between cases and controls, contradicts the effect of age-associated reduction in testosterone as a causative factor for infertility. There was no significant difference between study and

controls regarding weight, height or BMI. These results are comparable to previous study which reported that, infertility is more prevalent among men with elevated BMIs. Excess weight is not only linked to high risk of chronic disease, but also increases the risk of reproductive problems. Obesity has negative impact on male fertility (Loret, 2009). Jensen et al. (2004) evaluated over 1558 young males who have paramilitary physical and reported that overweight and obese men had decreased sperm concentration when compared to normal weight age matched controls. Also, the action of obesity on sperm characters has been investigated in different trials that linked increased incidence of azoospermia and oligozoospermia to overweight and obesity (Sermondade et al., 2013).

In the present study, regarding smoking habit, it was positive in 41% of studied populations, and there was statistically significant increase of smokers in study when compared to control group. Tobacco smoke is harmful to different reproductive functions. Benzo[a]pyrene (B[a]P) is reported to be a potent carcinogen, which is one of main constituents in cigarette smoke. Its reactive metabolite adducts with DNA, which can result in mutations. This can result in both male and female infertility. In addition, male smokers had reduced sperm counts, impaired motility of sperms, more abnormal forms and decreased testosterone values; they can possibly contribute to congenital abnormalities and asthma in their sons (Zenzes et al., 1999). Furthermore, the exposure of sperms from non-smokers to the seminal plasma of smokers leads to a marked decrease in sperm motility, acrosome reaction and increased MDA (Arabi and Moshtaghi, 2005).

Evidence of different studies proposes that cigarette smoking may have a harmful action on male fertility by reduction of sperm creation, motility and increasing abnormal forms. Smokers are 60% more prone to be infertile than non-smokers. Smokers also have high levels of serum estradiol and low levels of LH, FSH and prolactin than non-smokers, all these findings can negatively affect spermatogenesis (Olayemi, 2010).

There was significant increase of serum creatinine and blood urea in the study group when compared to control group. These results are comparable to previous literature, where a convincing relation between abnormal renal function and blood lead levels (BLLs) <10 µg/dL was reported (Fadrowski et al., 2010; Spector et al., 2011). Most of the studies revealed significant changes in kidney functions notably low glomerular filtration rate (GFR) around BLLs 2µg/dL to 3 µg/dL (Fadrowski et al., 2010; Spector et al., 2011; Basgen and Sobin, 2014).

Some studies reveal association between exposure to lead and renal function; others found no significant difference in renal function in lead workers compared with control subjects (Weaver et al., 2003; Schrader and Marlow, 2014). The contradicting data reported by clinical trials may reflect differences in the methodology of obtaining eGFR (Chung et al., 2014). However, experimental and animal studies show clear evidence of renal injury after low-dose lead exposure. Chronic lead exposure primarily leads to proximal tubular insult with mitochondrial functional damage (Wang et al., 2010).

Semen analysis remains the single most important and useful investigation with a sensitivity of 89.6%, that it is capable to identify 9 out of 10 males with a genuine problem of male infertility (Butt and Akram, 2013).

Infertility in males is diagnosed when sperm characters are below the WHO normal values (Plachot et al., 2002). The most important of these are decreased sperm concentration (oligospermia), poor sperm motility (asthenospermia) and abnormal morphology (teratospermia). Less important factors include the volume of semen and other markers of epididymal, prostatic and seminal vesicle function (Harris et al., 2011).

The most important and critical cause of infertility is decreased sperm concentration, 90% of male infertility problems are due to decreased count and there is a proportional correlation between the abnormal semen data and sperm count (Sabra and Al-Harbi, 2014).

The problems with count, motility and abnormal forms of semen arise from disarray in control mechanism, including pre-testicular, testicular and post-testicular factors (Wamoto et al., 2007). Hjollund et al. (2000) documented that, Pb, Cd, and Hg, could negatively affect the male reproduction, by disruption of hypothalamic - pituitary - gonadal axis or by direct negative effect on spermatogenesis, leading to impairment of semen quality. A tendency towards reduction of quality has been reported in males exposed to heavy metals. There is significant agreement that high or even moderate values of lead led to fertility problems in males. Fatima et al. (2010) showed that >40 µg/dL of lead in blood leads to a reduction in sperm count. In addition, they reported lower motility (<50%) with levels >35 µg/dL in whole blood.

Telisman et al. (2007) also showed that high lead concentration in blood (36.7 µg/dL) significantly lowers sperm density and motility. High levels of lead seem to be evidently linked to sperm damage.

Available data also indicate that, lead could exert a harmful effect on semen quality, even at blood lead concentrations <15 µg/dL. In a study included 123 males who had never been exposed to metals, the median blood lead concentrations was 57 µg/dL (range: 2.5–14.9). After adjusting for confounding variables (e.g. age, smoking, alcohol, blood cadmium, serum copper, zinc and selenium), an increase in blood lead was markedly associated with reducing percentages of morphologically healthy and subnormal sperm and with increasing percentages of slow sperm and overly wide sperm (Jurasovic et al., 2004).

In another study, the seminal plasma lead values of males not exposed to lead in their occupation or environment were found to negatively correlate with fertilization ability of sperm acrosome reaction and the fertilization rate when using the IVF procedure, and also with seminal plasma zinc levels (Benoff et al., 2003).

Taken together, the previous trials propose that lead may significantly reduce quality of semen, even at low-levels that is common for general people all over the world. Several trials including lead labors have proved that paternal blood levels of lead of about 30–40 µg/dL are a most likely threshold for high rate of spontaneous abortions, decreased rate of live births and prolonged time to pregnancy (Shiau et al., 2004), although inconsistent findings or a minor incompatibility were also reported (Snijder et al., 2012).

In addition, results are comparable to previous literature reported that, at high concentrations, cadmium could also affect semen quality. According to Akinloye et al. (2006) men with high cadmium levels in seminal plasma (65 µg/dL) had less sperm count and 36% of motile sperms. Furthermore, cadmium has been detected in markedly high values in blood of ex-smoker males and involved as one of the etiologies of asthenoteratozoospermia (Omu et al., 1995).

In a more recent study, the relationship between Cd levels and spermatograms or the hypothalamic-pituitary-gonadal (HPG) – axis and the correlation of blood and seminal plasma Cd concentrations with semen characters and hormonal levels were investigated in 60 infertile Nigerian males. The blood and seminal plasma levels of cadmium were higher in azoospermic men in comparison to oligozoospermic and control males while a significant inverse correlation was shown between serum Cd and all examined semen characters except volume of semen. A proportional correlation between seminal plasma Cd and FSH was also observed. The data establish the role of Cd in male infertility (Akinloye et al., 2006). Furthermore, results of the present study are comparable to results of the study done by Jurasovic et al. (2004) who reported that, an inverse correlation has been reported between blood cadmium, sperm motility, volume of semen, sperm count and concentration. In other studies, marked relationships were found between high serum values of estradiol, FSH and testosterone that have been found with respect to blood cadmium (Jurasovic et al., 2004).

Another study of males not exposed to Cd also revealed a crucial relationship between high serum testosterone and blood Cd levels (Telisman et al., 2000).

The aftercoming acute effects have been reported in experimental animals injected with soluble salts of Cd: reduced testosterone; a low testicular weight and size and similar low weight and size of epididymis, vas deferens, prostate and seminal vesicles; reduced sperm production and motility; and suppressed libido and reproductive capacity (Chen et al., 2012).

On the other hand, results of the present work are in contradiction to those reported by Sengupta (2013) who reported that, there were no significant correlations between semen quality and cadmium levels in semen, seminal plasma, or blood. This can be explained by different sample size and ethnicity. A study on the effect of combined exposure to lead and cadmium on the testes of rats showed that animals orally exposed to the combination exhibited significantly more pronounced pathological testicular changes, with a reduction in sperm counts, compared with animals exposed to either of the metals alone (Pandya et al., 2012).

In short, results of the present work revealed that, higher levels of lead and cadmium were significantly associated with male infertility as revealed by changes in hormonal profile and seminal parameters.

Conclusion

Higher levels of lead and cadmium were associated with male infertility as revealed by changes in hormonal profile and seminal parameters. Environmental exposure to Pb and Cd may adversely affects fertility in men.

Smoking habits and anemia are significant factors in male infertility. Kidney functions and reproductive hormonal profile are deleteriously affected in males exposed to Pb and Cd in regular manner.

Each of cadmium and lead were inversely correlated with semen parameters as, ejaculate volume, sperm count, sperm concentration, live sperms and rapid mobility. Semen analysis is the single most useful and fundamental investigation of male infertility.

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تأثير التعرض البيئي لكل من الرصاص والكاديوم علي الخصوبة لدي الذكور

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لايزال التعرض المزمن للمعادن الثقيلة يمثل حالة طبية صعبة خاصة في الدول النامية. الهدف من هذه الدراسة هو تقدير مستوى (الرصاص والكاديوم) في الذكور غير القادرين على الإنجاب والعلاقة بين مستوى الرصاص والكاديوم بالدم والخصوبة عند الرجال. بعد الحصول على الموافقة الحرة المستنيرة من الحالات المساهمة في هذه الدراسة، تم ضم ٧٠ من الأزواج المصابين بالعقم (بدون وجود عامل للعقم عند زوجاتهم) في عيادات العقم (قسم الأمراض الجلدية والتناسلية والعقم، كلية طب الأزهر، دمياط الجديدة) ومن المعروف أنهم يتعرضون للرصاص و / أو للكاديوم والمؤكد عن طريق قياس مستويات الرصاص والكاديوم في الدم وعدد ٣٠ حالة أخرى من الذكور الاصحاء (لا يعانون من العقم) الذين لا يحملون أي دليل على التعرض البيئي للرصاص و / أو الكاديوم كحالات قياس. خضع جميعهم لعملية أخذ التاريخ المرضي والفحص السريري وفحص أمراض الذكورة والتحليل المختبرية (تم الحصول على ١٠ مل من الدم الوريدي كعينات لفحص صورة دم كاملة ومستوى جلوكوز الدم ووظائف الكبد والكلية ومستوى الهرمون المحفز للتبويض وهرمون التلاوات، وهرمون الاستروجين والتستوستيرون) مع قياس مستويات الرصاص والكاديوم باستخدام طيف الامتصاص الذري بأفران الجرافيت ، وأخيرا تم الحصول على عينة من السائل المنوي للفحص، وقد اثبت البحث وجود علاقة بين ارتفاع مستويات الرصاص والكاديوم والعقم عند الرجال والذي تم تأكيده بالتغيرات التي حدثت بمستوى الهرمونات بالدم وتحليل السائل المنوي.