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Chapter

Effects of Lead on Reproductive Health

Osmel La Llave León and José M. Salas Pacheco

Abstract

It has been documented that lead can cause a wide range of adverse reproductive outcomes. In men, lead can reduce the libido and affect spermatogenesis reducing the quality of sperm. Other effects in exposed men include disturbance of prostatic function and damage in serum testosterone. In pregnant women, lead can cross the placenta and impair the development of the fetus. Therefore, exposed women are at risk of suffering spontaneous abortion, premature delivery, gestational diabetes mellitus, pregnancy hypertension, preeclampsia, premature rupture of membranes, intrauterine growth restriction, low weight birth, and other pregnancy complications. In both men and women, lead has been associated with infertility. Harmful effects of this heavy metal have been observed even at low levels of exposure. Thus, exposure to lead remains a public health problem, especially for reproductive health. Some strategies should be considered to prevent harmful effects of lead on both male and female reproductive systems.

Keywords: lead exposure, blood lead levels, reproductive outcomes, pregnant complications, sperm quality, infertility, reproductive health

1. Introduction

Lead is one of the most dangerous toxic metals. This metal has no known beneficial function in the human body. In contrast, lead can impair every system of the human body and specially the renal, hematopoietic, neurological, and reproductive systems. Exposure to lead has been associated with a broad range of physiological, biochemical, and behavioral and harmful effects. There is evidence of several reproductive damages in humans exposed to lead. In women, lead exposure has been associated with spontaneous abortion [1], low birth weight [2], preterm delivery [3], fetal growth restriction [4], premature rupture of membranes [5], pregnancy hypertension [6], preeclampsia [7], and gestational diabetes [8]. Maternal blood lead has also been associated with a decrease in length of gestation [9].

With respect to men, exposure to inorganic lead has been linked to a decrease in some parameters of semen quality. Lead exposure has been considered to adversely affect spermatogenesis [10] and reduced fertility [10]. High lead concentrations in seminal plasma can reduce the sperm count [10]. Sperm motility and sperm morphology also can be affected by lead [11].

The present chapter focuses on the harmful effects of lead on reproductive health of both men and women, due to the importance to established preventive measures to protect the health of parents and children exposed to this toxic metal.

2. Lead exposure and male reproductive health

Exposure to lead has been associated to several reproductive dysfunctions in men, such as decreased libido, impairment of spermatogenesis, and chromosomal damage, among others. However, studies about the relationship between lead exposure and male reproductive damage have shown inconsistent results. Most of the studies have analyzed the relationship between blood lead and semen quality due to the correlation observed between semen lead and blood lead [12]. Some studies have reported reduction in sperm count, morphology, and motility in men exposed to lead [13].

The effects of lead on sperm quality have been frequently studied in occupationally exposed individuals. National Institute for Occupational Safety and Health (OSHA) recommends that blood lead levels (BLL) above 40 μg/dL require health intervention. Nevertheless, studies in men without occupational exposure also showed evidence of the effects of lead on fertility. In a prospective, double-blind study carried out to evaluate the impact of seminal plasma lead levels on fertility, seminal plasma lead below this threshold value was associated with adverse effects on in vitro fertilization rates. In this survey, semen donors who participated in an artificial insemination program were included. Sperm lead concentrations were also negatively correlated with mannose receptors and mannose-induced acrosome reactions, the two biomarkers of sperm function. [14]. These results show that increased lead concentrations in semen can harm male fertility.

Although most studies on the relationship between lead and infertility have been carried out in occupationally exposed workers, alterations in semen concentration of lead have been also observed in men without occupational exposure, probably due to other sources of exposure such as environment and foods. In a prospective and randomized clinical study carried out in men from infertile couples without occupational exposure to lead, a negative correlation between semen lead concentration and sperm count was observed in semen samples collected after 3–5 days of abstinence [10]. These results provide evidence that lead from environment and diet can also affect semen quality and, therefore, male fertility.

Several studies have evaluated the effect of lead exposure on the endocrine system. In lead smelting workers without clinical symptoms of lead poisoning, a decrease in serum testosterone (T) and an increase in steroid-binding globulin (SGG) levels were observed [15–18]. It is considered that lead impairs the majority of the endocrine glands. The analysis of the effect of long-term exposure to lead on thyroid function in exposed workers showed a negative association with T4 and FT4, and the depressed thyroid function was especially observed when the exposure was the most intensive [18]. In a group of workers occupationally exposed to lead from three battery factories, concentrations of FSH and LH were higher in comparison with a control group of non-exposed men, which constitutes an indicator that lead exposure alters testicular function [19]. From the biochemical point of view, it is considered that lead first causes testicular damage, and long-term exposure alters the hypothalamic-pituitary axis [17, 18, 20].

However, the results on this topic cannot be considered conclusive. In a study of the relationship between lead exposure and sex hormone levels in 133 men who had worked, at least for 6 months, in a battery manufacturing plant, BLL was measured, and endocrine system function was assessed by measuring testosterone, free testosterone, follicle stimulated hormone (FSH), and luteinizing hormone (LH). Workers were classified into two groups based on OSHA BLL standard: with BLL lower than 40 μg/dl and those with BLL equal or higher than 40 μg/dL. Statistical analysis showed no significant association between blood lead concentrations (BLC) and the sex hormone values. The authors concluded that lead exposure is not related to changes in male hormone levels [21]. In contrast, the evaluation of sperm count,

sperm morphology, and hormonal levels (LH and FSH) of individuals attended in an infertility clinic in Iran showed negative significant correlations with BLL, while no correlation between BLC and sperm morphology was found [22].

Despite some contradictory results, there is a growing concern about the harmful effects of lead on male fertility, semen quality, and hormonal levels [15, 22]. Experiments in animal models have demonstrated that lead contributes to decreased male reproductive function [23]. In humans, lead exposure has been also associated with male endocrine dysfunction [24]. It is considered that oxidative stress plays an important role on male infertility. Lower total antioxidant capacity (TAC) and vitamin E concentrations were observed in seminal plasma of infertile men in comparison with fertile subjects [25]. In addition, there were significant differences between compared groups in accumulation of malondialdehyde. Moreover, concentration of malondialdehyde negatively correlated with sperm motility and morphology. On the basis of these results, it is suggested that seminal antioxidants and blood antioxidants can be used as biomarkers of sperm quality.

The effect of lead on reproductive health may vary due to the length of exposure. Taking into account the above-mentioned points, in a cross-sectional study of male workers, the effects of current and long-term occupational lead exposures on several biomarkers of male reproductive health were evaluated [11]. Semen and blood samples from male employees of a lead smelter were obtained, and concentrations of testosterone, follicle stimulated hormone, luteinizing hormone, and blood lead were determined. A decreasing trend in total sperm count was observed in relation to the increase in BLL. In addition, total motile sperm count, sperm concentration, and total sperm count showed an inverse relationship with long-term lead exposure. Nevertheless, lead exposure was not associated to sperm motility, sperm morphology, or serum concentrations of reproductive hormones.

The effects of lead exposure on male reproductive function have also been studied in animals. Experiments in mouse have shown that lead can interfere with the binding of androgens [26], suppress follicle stimulating hormone production [27], affect the function of Sertoli cell, and increase the lactate production, which constitute an essential substrate for spermatogenesis [28]. Lead exposure has been also associated with decreases in the activity of testicular oxidizing enzymes [29] and in the synthesis of testicular RNA in rats [28]. A study conducted in rats showed a positive correlation between blood lead and levels of lead in epididymal sperm and demonstrated that lead can cause generation of reactive oxygen species in sperm, which led to oxidative stress and, therefore, impairment of sperm function [30].

Epidemiological data indicate that exposure to lead can cause prostate diseases in adult males. In a study, blood lead in patients suffering from prostate cancer (PCA), patients with benign prostate hyperplasia (BPH), and a control group of men living in similar socioeconomic conditions was examined [31]. Results indicated significant higher concentrations of lead in blood in PCA and BPH males in comparison with controls. In addition, patients with PCA and BPH had significantly lower blood levels of zinc and copper than the comparative group. It is well known that Zn has an essential role in the regulation of prostate epithelium homeostasis and in ejaculation [32]. Zinc is a cofactor for many enzymes and an essential metal for the integrity of cellular membrane [33]. Lead can displace zinc ions at the proteins, provoking the inhibition of the enzymes. The displacement of zinc by lead in seminal fluid could determine the effects of prostate function, leading to decreased fertility [32].

Some authors consider that the main effect of lead on the male reproductive system is the alteration of the reproductive hormonal axis and the hormonal control of spermatogenesis, instead of the direct effect on the seminiferous tubules of the testes [23, 34]. Moreover, there is evidence that the blood-testis barrier acts as a protection for the testis cells against the harmful effects of lead [35, 36]. On the other

Effects of lead on male reproductive system
➢ Decrease in sperm count ➢ Decrease in sperm motility ➢ Abnormal sperm morphology ➢ Decreased volume of ejaculation ➢ Decreased serum testosterone ➢ Increase in serum follicular staining hormone (FSH) ➢ Increase in serum luteinizing hormone (LH) ➢ Impairment of sperm DNA

Figure 1.
Some effects of lead on male reproductive system.

hand, some researchers pay more attention to the impairment of sperm parameters, such as volume of ejaculation, sperm density, abnormal morphology, sperm count, and motility, by the toxic effect of lead [10, 14, 22, 37].

Although the mechanisms by which lead affects male reproductive health are still unclear, there is no doubt that this toxic metal can jeopardize fertility in men due to alterations in semen quality, in the function of reproductive hormones, or both (see **Figure 1**). Despite conflicting reported results, there is growing evidence that lead exposure, even at low levels, can impair male reproductive health. Future research should deepen the analysis concerning these issues.

3. Lead exposure and female reproductive health

It is well known that lead has harmful effects on female reproductive system. Women at reproductive age are at risk of suffering some health disorders due to the toxic effects of this metal. Occupational exposure to lead is more frequent in men compared to women. However, there are some reports on the harmful effects of lead suffered by women who work in places where lead or some lead compounds are used. In a study conducted to determine the effects of occupational exposure on bone and lead blood levels, women who were former workers at a smelter were compared with a cohort of women with no-known occupational exposure. Higher levels of lead in blood and tibia were found in the exposed group. In addition, the difference in bone lead levels between compared groups was significantly higher than the difference in BLCs [38]. In accord with these findings, a study carried out in Mexico showed that women who work with lead have greater probability to have BLCs above the CDC recommended value of 5 μg/dL compared to non-exposed women [39].

It is necessary to consider that women can be exposed to lead not only at work but also through the clothes, shoes, and work instruments that are taken home by the cohabitants who work in places where lead is used. Higher BLCs in pregnant women who live with someone who is exposed to lead at work in comparison with those who live in houses where nobody works in places that lead is used have been observed [40]. In addition, lead exposure may occur when women use some cosmetics, such as surma or kolh, and other beauty products [41–43].

Women can also be exposed to lead by pica habit, an eating disorder that consists of the consumption of non-food items without nutritional value. Among the most harmful types of pica is the consumption of soil, paint chips, and pottery. Pregnant women consuming these items put both themselves and the fetus at risk of lead poisoning [44, 45]. In Mexican, women who were recognized that they used to eat soil had significantly higher BLL compared to those who did not have this habit [40]. In one study in New York, pica behavior among lead-poisoned pregnant women (BLL ≥ 20 μg/dL) was 9%. The most common practice among them was

eating soil (64.6%). The probability of having BLLs ≥40 μg/dL among women who reported pica was three times higher in comparison with those women who did not report this habit. In addition, pica-reporting women had a mean peak of BLL during pregnancy significantly higher compared to those who did not report pica (29.5 μg/dL vs. 23.8 μg/dL) [45].

In addition to the effects of lead on women's fertility, a wide range of published reports refers to the damage caused by this heavy metal during pregnancy (see **Figure 2**). Prenatal exposure to lead can cause several obstetric complications and adverse pregnancy outcomes [46]. Lead absorbed into the body, mainly by ingestion or inhalation, enters the bloodstream and accumulates in soft organs (mostly in brain, liver, and kidney) and bones [47, 48]. It is considered that lead in bone represents approximately 95% of the total body burden in adults [47]. During pregnancy, the demand of calcium rises, and lead stored in bone can replace the calcium and recirculate in the bloodstream, becoming an endogenous source of exposure [16, 48–50]. Lead from the blood can cross the placenta and impair the development of the fetus [51, 52]. Therefore, lead-exposed women are at risk of suffering various pregnancy complications, such as spontaneous abortion [1, 53], preterm delivery [54, 55], GDM [8, 56], pregnancy hypertension [57–59], preeclampsia [60–64], premature rupture of membranes [65, 66], intrauterine growth restriction [67], and low weight birth [68, 69], among others.

Although some researchers have failed to demonstrate the relationship between lead and abortion [70, 71], a study conducted in Mexico showed evidence that, even low-to-moderate lead exposure, below 30 μg/dL of blood lead can increase the risk of spontaneous abortion [1]. In this case, the range of BLLs in pregnant women was 1.4–29 μg/dL. Those lead concentrations can be considered common in general population in many countries, and lower to those observed in occupationally exposed women. It is considered that the mechanism by which lead induces abortion is related to the direct transmission of the metal to the developing fetus due to the demineralization of bones during pregnancy [72, 73].

Several studies have confirmed that pregnant women exposed to lead have more probability of having a preterm delivery compared with non-exposed women. Nevertheless, results are still inconsistent. In a prospective cohort study carried out in China, maternal urinary lead was measured and adjusted by creatinine, and newborns were classified as preterm birth and early term birth. The mean urinary lead levels were significantly higher in preterm births. In addition, among all newborns, an increase in maternal urinary lead was associated with a decrease in gestational age [3].

Effects of lead on female reproductive system
➢ Impairing menstruations ➢ Reduction of libido ➢ Premature rupture of membranes ➢ Intrauterine grow restriction ➢ Abortion ➢ Premature delivery ➢ Stillbirths ➢ Pregnancy hypertension ➢ Preeclampsia ➢ Neonatal death ➢ Gestational diabetes ➢ Low birth weight

Figure 2.
Harmful effects of lead on female reproductive health.

Lead can displace calcium because they both have similar chemical characteristics and follow analogous metabolic pathways [74]. It has been recognized that when lead crosses from the bloodstream to the placenta, the growth of the fetus can be impaired due to the interference of lead with calcium metabolism [68, 69]. The evaluation of prenatal exposure to lead has shown inverse association between maternal urine lead levels and preterm low birth weight [68]. Other studies analyzed the relationship between the levels of lead in tibia and patella and birth weight, considering that bone lead is a better biomarker to estimate the effect of lead on the fetus compared to blood lead [75, 76].

In a study conducted to evaluate the relationship between lead exposure and birth weight in Mexican women, lead levels were measured in maternal venous blood, umbilical cord, and tibia and patella. The weight of newborns was determined within the first 12 hours of delivery. Although all biomarkers of lead exposure were negatively associated with a decreased size of newborns, this association resulted statistically significant only for tibia lead levels [75]. Similar results were observed in the analysis of the relationship between maternal lead burden and early postnatal growth in a cohort of breastfed newborns [75]. In this study, maternal BLL measured at 1 month postpartum and maternal bone lead levels were significantly associated with infant BLL. Moreover, infant BLL and maternal patella lead level were inversely associated with weight gain. The weight gain from birth to the first month of life was 142 g lower in infants with BLL $\geq$ 10 compared to those with lower BLCs.

There is growing evidence that lead is a risk factor for gestational diabetes mellitus. Experiments with rats have demonstrated that lead exposure can induce glucose intolerance and hyperglycemia [8]. But epidemiological studies showed contradictory results. In women at 22–28 weeks of gestation, slightly mean BLCs were observed compared to those without GDM, but this difference was not statistically significant. The geometric mean BLCs were 6.13 ng/g in women with GDM and 6.05 ng/g in women without GDM. Based on this result, authors suggested that lead at these low levels of exposure is not associated with the risk of suffering GDM [77]. In contrast, in a French mother-child prospective cohort study, blood lead was associated with IGT, supporting the evidence that maternal exposure to lead is a risk factor for GDM [56]. Further studies have to be performed to confirm the deleterious effect of lead on metabolic processes and, particularly, on the development of GDM.

A large number of investigations provide evidence that exposure to lead is associated with hypertension in adults [78–81]. For this reason, the question of whether lead is associated with gestational hypertension (GH) and preeclampsia (PE) has gained a great importance in recent years.

In a cohort of pregnant women in Los Angeles, California, blood and bone lead were assessed in the 3rd trimester and post-delivery, and the prevalence of hypertension was measured [82]. The relationship of both biomarkers with GH was analyzed. After adjusting by covariables, no significant association between BLLs in 3rd trimester and hypertension was observed. Nevertheless, calcaneus bone lead was significantly associated with the risk of hypertension.

In a cross-sectional study with Maltese Caucasian women at third trimester of gestation, significantly higher BLCs in hypertensive women compared to normotensive women were observed [83]. Moreover, BLL showed a positive relationship with systolic and diastolic blood pressure.

The relationship between BLL at mid-pregnancy and blood pressure was assessed in a study carried out in pregnant women of two French municipalities [83]. In this study, hypertensive women had significantly higher BLL than normotensive women. Additionally, lowest frequency of hypertension was observed among women in the lowest quartile of BLL. These findings are in accord with

those observed in Nigeria, in which the impact of lead on pregnancy outcomes was investigated [84]. Significantly higher frequency of hypertension was observed in women with BLL ≥ 10 μg/dL compared to those who had lower concentrations of lead in blood.

The findings on the association of lead exposure with GH led to investigate if this toxic metal could be considered a risk factor for preeclampsia, a pregnancy disorder characterized by high blood pressure and proteinuria detected after 20 weeks of gestation [85]. In a cross-sectional study that included women between 29 and 43 weeks of gestation, significantly higher concentrations of lead in red blood cells of pregnant women diagnosed with preeclampsia were found compared to those without hypertension. Furthermore, women with severe preeclampsia had also higher blood cell lead concentrations than mild preeclamptic women [61]. In contrast, in a case-control study conducted in women without occupational exposure, BLCs measured within 24 hours of delivery did not differ between women with preeclampsia and normotensive group, but a significant difference between the groups was observed with respect to umbilical cord lead (UCB) concentration [64]. In addition, the ratio of umbilical cord lead to whole blood lead was significantly associated with preeclampsia.

Despite the contradictory results of some studies, the majority of those supported the hypothesis that lead can cause preeclampsia. Some possible mechanisms have been suggested to explain the roll of lead in the development of this pregnancy disorder. It is considered that lead increases the circulating levels of endothelin, a vasoactive substance that causes constriction of the blood vessels, leading to the increase of blood pressure [63]. Lead also interferes in the increase of reactive oxygen species reducing the serum levels of nitric oxide (NO) and other vasodilator substances [86–89]. From the molecular point of view, lead causes inhibition of membrane adenosine triphosphatases (ATPases), which produces vasoconstriction due to the increase of intracellular calcium ions [63, 90].

4. Effects of gender on lead toxicity

The influence of sex in the effect of lead on health is a controversial subject. Although sex differences regarding exposure, absorption, and metabolism of lead have been reported by certain researchers [91, 92], the results are not conclusive. In a prospective cohort, the effects of gender differences in the relationship between lead exposure and neurodevelopmental toxicity were analyzed [91]. Lead levels were determined in maternal blood in early and late pregnancy, in cord blood at birth, and in children's blood at 2, 3, and 5 years old. As a result, significant association between lead concentrations at late pregnancy and the risk of behavioral problems was observed in males, while blood lead measured in 2- and 5-year-old children was associated with an increased risk of behavioral problems in females. According to previous data, early in life, the susceptibility to neurotoxic effect of lead is higher in boys than in girls. On the other hand, experimental data suggest that susceptibility to immunotoxic effects of lead is higher in females [92]. More research is needed to elucidate these inconsistencies.

The biological effects of lead exposure in human also appear to be different according to the gender. In a study carried out in Japan, the authors aimed to determine the effects of gender on porphyrin metabolic disorders induced by lead exposure [93]. Blood lead, plasma delta-aminolevulinic acid (ALA), urinary ALA, and urinary coproporphyrin (CP) were determined in exposed workers. Although no significant differences in blood lead concentrations between male and female workers were observed, women had higher plasma ALA concentrations, as well as

higher excretion of urine ALA and CP in comparison with men. The mechanism that could explain this difference is still unclear.

With respect to the reproductive system, health damages in female have been observed even at very low levels of exposure. In a study carried out in Taiwan, the relationship between low-level lead exposure and risk of infertility was evaluated [94]. The average lead concentration in infertile women (3.5 μg/dL) was significantly higher than in a control group (2.78 μg/dL). Furthermore, women with BLL >2.5 μg/dL had a threefold higher risk of infertility than those with BLL ≤ 2.5 μg/dL. In contrast, the harmful effects of lead in male reproductive system have been detected at higher levels of exposure than those in female. The importance of finding explanation of gender effects for lead and other environmental toxic substances was discussed by the Society for Women's Health Research in a roundtable at the National Institute of Environmental Health Sciences in October 2002 [95].

Despite the above-mentioned results, gender differences in susceptibility to lead poisoning have been considered in few investigations. Some studies have included gender as a confounding factor in the relationship between lead exposure and health impairment [96]. However, in other investigations, differences between male and female in regard to the harmful effects of lead have not been found.

According to the results of the investigations, the following differences between men and women regarding lead exposure can be highlighted:

- Generally, in non-exposed individuals, blood lead levels are higher in males than in females.
- Damages to female reproductive health can occur at lower levels of exposure than in men.
- The risk of suffering behavioral problems in relation to prenatal lead exposure at early childhood is higher in females.
- The susceptibility to neurotoxic effects of lead appears to be higher in boys than in girls.
- The susceptibility to immunotoxic effects of lead is higher in females.
- From the biological point of view, porphyrin metabolic disorders induced by lead exposure affect females more than males.
- The impairment in the synthesis and function of hormones has been observed in both genders. But, little is known about the differences between male and female regarding the mechanisms by which lead affects the reproductive system.

In summary, gender difference should be considered an important factor for a better evaluation of the harmful effects of lead on health. Further research is needed to better understand the role of sex as a modifier of the effects of lead exposure.

5. Lead exposure and children's reproductive system

Lead is considered to be able to affect the development of children's reproductive system. There is evidence that both paternal and maternal lead exposure can cause a detrimental impact on the structure and function of gametes, which might cause adverse effects on newborn's health [97]. Embryos and fetus are extremely sensitive

to environmental toxicants. Exposure to lead during pregnancy is known to be able to impair fetal development, since lead can cross the placental barrier and reach the fetus [51, 52].

Lead is known to affect testosterone levels in adults, leading to reproductive dysfunction. Low levels of testosterone can reduce semen quality in men and increase genital malformations [98]. In contrast, high levels of testosterone in women are associated with higher frequency of polycystic ovary syndrome (POS) [99] and puberty disorders [100]. In spite of this, there are few studies that have focused on the relationship between lead exposure and androgen hormone levels in children. One of the few longitudinal studies on this issue was carried out in Russia [101]. This study evaluated the impact of organochlorine chemicals and lead in growth and pubertal timing in 516 boys. Children were enrolled in the study at the age of 5–7 years and were followed up until the age of 18–19 years. Lead exposure was negatively associated with growth during puberty. In addition, it was suggested that lead may delay the timing of male puberty.

In a study carried out to evaluate the relationship between blood metal concentrations and testosterone levels in the USA, children and adolescents' concentrations of lead, cadmium, mercury, and selenium in blood, as well as serum testosterone levels, were determined [102]. Although no significant association between blood lead and total testosterone (TT) was observed, the concentrations of TT were significantly higher for girls in the fourth quartile compared to those in the first quartile. On the other hand, in a prospective study conducted in Mexico City, maternal patella lead and early childhood blood lead were inversely associated with breast growth in girls [103]. Furthermore, an increase in girl's maternal patella lead was associated with later age of menarche. In addition, blood lead during childhood negatively associated with pubic hair growth in girls. No associations were observed in boys.

6. Preventive strategies to avoid harmful effects of lead on reproductive health

The fact that lead exposure is related to a wide range of adverse effects on reproductive health is accepted by most researchers nowadays. The main source of exposure remains occupational. But there is no doubt that, in recent years, the environmental exposure to lead has decreased, especially in developed countries like the United State, Canada, and others [104]. A main role in this reduction is attributed to the elimination of leaded gasoline [105]. Nevertheless, the risk of lead poisoning still remains, mainly in developing countries, due to some sources of exposure, such as lead paint, cosmetics, traditional medicines, electronic waste, and glazed ceramic vessels, among others [106].

It is very difficult to dispense with lead due to its uses in a wide range of industrial lines, such as smelting, manufacturing and recycling of car batteries, and lead crystal glassware. However, in recent years, there has been an increase in the diffusion of the damage that lead can cause and the measures that must be taken to protect people's health. The identification of risk factors for having high BLLs has contributed to reduce the prevalence and severity of lead poisoning. In a way, the results of research have helped people to become aware of the toxicity of this metal and the danger it poses to their health.

Health interventions in last decades have led to a decrease in lead exposure. In spite of this, it is necessary to increase protection measures, especially for women and children. To date, there is no exposure lead level that can be considered safe. Although the CDC established 5 μg/dL as the reference value for BLLs in children, epidemiological research has demonstrated that even at lower lead concentrations

adverse health effects can occur. With respect to females, adverse reproductive outcomes have been observed also at BLLs below 5 μg/dL, decrease in delta-aminolevulinic acid dehydratase (ALAD) activity has been detected in pregnant women at mean blood lead ≥2.2 μg/dL [107], and damages in female reproductive system have been reported at BLLs above 2.5 μg/dL [95]. Some prevention strategies should be considered for protection of the toxic effects of lead. Preventive measures should include at least the following:

- Developing public awareness campaigns to identify sources of health exposure
- Evaluation of risk factors for all pregnant women in their prenatal care
- Education of childbearing age women to avoid sources of lead exposure
- Screening of lead exposure for all pregnant women by means of diagnosis tests, such as blood lead, ALAD activity, and urine ALA
- Keeping children and pregnant women with BLL ≥ 5 μg/dL out of exposure sources
- Requiring employers to take measures to reduce lead levels in workplaces
- Requiring exposed workers to use protective means
- To carry out a review of regulations to ensure greater protection for the exposed population
- Increasing environmental monitoring (lead in air, soil, water, etc.) to detect any deviation from established standards
- Searching for new biomarkers, with high sensitivity and specificity, to assess the exposure and effects of lead in the body

7. Conclusions

There is enough evidence that lead exposure can harm reproductive health of both men and women. The harmful effects of lead have been mostly observed in occupationally exposed people. Nevertheless, in recent decades, research has demonstrated that these damages can occur at levels of lead formerly considered harmless. Most observed effects on male reproductive system are related to the direct impact of lead on semen quality, such as volume of ejaculation, sperm density, abnormal morphology, sperm count, and motility. In addition, lead can alter the concentrations of some male reproductive hormones, such as follicle stimulating hormones, testosterone, and luteinizing hormone.

In women, prenatal exposure to lead, even at very low levels of exposure, has shown to be harmful for both the mother and the fetus. Thus, any level of lead exposure could be associated with adverse reproductive outcomes. Lead has been associated with a wide range of adverse outcomes, including spontaneous abortion, intrauterine growth restriction, premature delivery, stillbirths, pregnancy hypertension, preeclampsia, and low birth weight, among others.

Several recent studies have suggested hypothesis related to the mechanisms by which lead affects male and female reproductive health. However, more research is

needed to clarify these mechanisms. In conclusion, lead exposure remains a health problem for both male and female reproductive health. It is important to implement protective measures to avoid the harmful effects of this toxic metal on reproductive health of both men and women.

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Conflict of interest

The authors declare no conflicts of interest.

Author details

Osmel La Llave León* and José M. Salas Pacheco
Institute of Scientific Research at Juarez University of Durango State, Durango, Mexico

*Address all correspondence to: ollave56@yahoo.es; olallavel@ujed.mx

References

[1] Borja-Aburto VH, Hertz-Picciotto I, Rojas-Lopez M, Farias P, Rios C, Blanco J. Blood lead levels measured prospectively and risk of spontaneous abortion. American Journal of Epidemiology. 1999;**150**:590-597

[2] Irgens A, Krüger K, Skorve AH, Irgens LM. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. American Journal of Industrial Medicine. 1998;**34**:431-437. DOI: 10.1002/(SICI)1097-0274(199811)34:5<431::AID-AJIM3>3.0.CO;2-T

[3] Cheng L, Zhang B, Huo W, Cao Z, Liu W, Liao J, et al. Fetal exposure to lead during pregnancy and the risk of preterm and early-term deliveries. International Journal of Hygiene and Environmental Health. 2017;**220**:984-989. DOI: 10.1016/j.ijheh.2017.05.006

[4] Rahman A, Kumarathasan P, Gomes J. Infant and mother related outcomes from exposure to metals with endocrine disrupting properties during pregnancy. Science of the Total Environment. 2016;**569-570**:1022-1031. DOI: 10.1016/j.scitotenv.2016.06.134

[5] Huang S, Xia W, Sheng X, Qiu L, Zhang B, Chen T, et al. Maternal lead exposure and premature rupture of membranes: A birth cohort study in China. BMJ Open. 2018;**8**:1-7. DOI: 10.1136/bmjopen-2018-021565

[6] Sowers M, Jannausch M, Scholl T, Li W, Kemp FW, Bogden JD. Blood lead concentrations and pregnancy outcomes. Archives of Environmental Health. 2002;**57**:489-495

[7] Bede-Ojimadu O, Amadi CN, Orisakwe OE. Blood lead levels in women of child-bearing age in sub-Saharan Africa: A systematic review. Frontiers in Public Health. 2018;**6**:1-18. DOI: 10.3389/fpubh.2018.00367

[8] Tyrrell JB, Hafida S, Stemmer P, Adhami A, Leff T. Lead (Pb) exposure promotes diabetes in obese rodents. Journal of Trace Elements in Medicine and Biology. 2017;**39**:221-226. DOI: 10.1016/j.jtemb.2016.10.007

[9] Cantonwine D, Hu H, Sánchez BN, Lamadrid-Figueroa H, Smith D, Ettinger AS, et al. Critical windows of fetal lead exposure. Journal of Occupational and Environmental Medicine. 2010;**52**:1106-1111. DOI: 10.1097/jom.0b013e3181f86fee

[10] Wu HM, Lin-Tan DT, Wang ML, Huang HY, Lee CL, Wang HS, et al. Lead level in seminal plasma may affect semen quality for men without occupational exposure to lead. Reproductive Biology and Endocrinology. 2012;**10**:1. DOI: 10.1186/1477-7827-10-91

[11] Alexander BH, Checkoway H, Van Netten C, Muller CH, Ewers TG, Kaufman JD, et al. Semen quality of men employed at a lead smelter. Occupational and Environmental Medicine. 1996;**53**:411-416. DOI: 10.1136/oem.53.6.411

[12] Debnath B, Ibrahim M, Fatima P. Study of blood lead and semen lead concentration in male infertility. Pulse. 2011;**4**:10-13. DOI: 10.3329/pulse.v4i1.6956

[13] Hosni H, Selim O, Abbas M, Fathy A. Semen quality and reproductive endocrinal function related to blood lead levels in infertile painters. Andrologia. 2013;**45**:120-127. DOI: 10.1111/j.1439-0272.2012.01322.x

[14] Benoff S, Centola GM, Millan C, Napolitano B, Marmar JL, Hurley IR. Increased seminal plasma lead levels adversely affect the fertility potential of sperm in IVF. Human Reproduction. 2003;**18**:374-383. DOI: 10.1093/humrep/deg020

[15] Erfurth EM, Gerhardsson L, Nilsson A, Rylander L, Schütz A, Skerfving S, et al. Effects of lead on the endocrine system in lead smelter workers. Archives of Environmental Health. 2001;**56**:449-455. DOI: 10.1080/00039890109604481

[16] Gulson BLL, Jameson CWW, Mahaffey KRR, Mizon KJJ, Korsch MJJ, Vimpani G. Pregnancy increases mobilization of lead from maternal skeleton. The Journal of Laboratory and Clinical Medicine. 1997;**130**:51-62. DOI: 10.1016/S0022-2143(97)90058-5

[17] Rodamilans M, Osaba MJM, To-Figueras J, Fillat FR, Marques JM, Pérez P, et al. Lead toxicity on endocrine testicular function in an occupationally exposed population. Human & Experimental Toxicology. 1988;**7**:125-128. DOI: 10.1177/096032718800700203

[18] Tuppurainen M, Wägar G, Kurppa K, Sakari W, Fröseth B, Alho J, et al. Thyroid function as assessed by routine laboratory tests of workers with long-term lead exposure. Scandinavian Journal of Work, Environment & Health. 1988;**14**:175-180. DOI: 10.5271/sjweh.1934

[19] Nigg JT, Elmore AL, Natarajan N, Friderici KH, Nikolas MA. Variation in an iron metabolism gene moderates the association between blood lead levels and attention-deficit/hyperactivity disorder in children. Psychological Science. 2016;**27**:257-269. DOI: 10.1177/0956797615618365

[20] Doumouchtsis KK, Doumouchtsis SK, Doumouchtsis EK, Perrea DN. The effect of lead intoxication on endocrine functions. Journal of Endocrinological Investigation. 2009;**32**:175-183. DOI: 10.1007/BF03345710

[21] Haghighi KS, Aminian O, Chavoshi F, Bahaedini LS, Soltani S, Najarkolaei FR. Relationship between blood lead level and male reproductive hormones in male lead exposed workers of a battery factory: A cross-sectional study. International Journal of Reproductive Biomedicine. 2013;**11**:673-676

[22] Al-Omary HL, Alawa ZM, Jaafar I. Environmental lead exposure and male infertility. IOSR Journal of Dental and Medical Sciences. 2016;**15**:49-54. DOI: 10.9790/0853-1509044954

[23] Sokol RZ. Hormonal effects of lead acetate in the male rat: Mechanism of action1. Biology of Reproduction. 1987;**37**:1135-1138. DOI: 10.1095/biolreprod37.5.1135

[24] Ng TP, Goh HH, Ng YL, Ong HY, Ong CN, Chia KS, et al. Male endocrine functions in workers with moderate exposure to lead. British Journal of Industrial Medicine. 1991;**48**:485-491. DOI: 10.1136/oem.48.7.485

[25] Benedetti S, Tagliamonte MC, Catalani S, Primiterra M, Canestrari F, Stefani S De, et al. Differences in blood and semen oxidative status in fertile and infertile men, and their relationship with sperm quality. Reproductive Biomedicine Online 2012;**25**:300-306. DOI: 10.1016/j.rbmo.2012.05.011

[26] Goyer RA, Clarkson T. Toxic effects of metals. In: Klaassen C, editor. Essentials of Toxicology. 6th ed. New York: McGraw-Hill; 2001. p. 811-867

[27] Wiebe JP, Salhanick AI, Myers KI. Life Sciences. Vol. 32. USA: Pergamon Press; 2005. pp. 1997-2005

[28] Batarseh LI, Welsh MJ, Brabec MJ. Effect of lead acetate on sertoli cell lactate production and protein synthesis in vitro. Cell Biology and Toxicology. 1986;**2**:283-292. DOI: 10.1007/BF00122696

[29] Winder C. Reproductive and chromosomal effects of occupational exposure to lead in the male.

Reproductive Toxicology. 1989;**3**:221-233. DOI: 10.1016/0890-6238(89)90016-6

[30] Hsu PC, Liu MY, Hsu CC, Chen LY, Guo YL. Lead exposure causes generation of reactive oxygen species and functional impairment in rat sperm. Toxicology. 1997;**122**:133-143. DOI: 10.1016/S0300-483X(97)00090-5

[31] Siddiqui MK, Srivastava S, Mehrotra PK. Environmental exposure to lead as a risk for prostate cancer. Biomedical and Environmental Sciences. 2002;**15**:298-305

[32] Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. Nature Reviews. Urology. 2016;**13**:379-386. DOI: 10.1038/nrurol.2016.89

[33] Kelada SN, Shelton E, Kaufmann RB, Khoury MJ. δ-Aminolevulinic acid dehydratase genotype and lead toxicity: A HuGE review. American Journal of Epidemiology. 2001;**154**:1-13. DOI: 10.1126/science.3.53.32

[34] Vigeh M, Saito H, Sawada S. Lead exposure in female workers who are pregnant or of childbearing age. Industrial Health. 2011;**49**:255-261. DOI: 10.2486/indhealth.MS1192

[35] Xu B, Chia SE, Tsakok M, Ong CN. Trace elements in blood and seminal plasma and their relationship to sperm quality. Reproductive Toxicology. 1993;**7**:613-618

[36] El-Zohairy EA, Youssef AF, Abul-Nasr SM, Fahmy IM, Salem D, Kahil AK, et al. Reproductive hazards of lead exposure among urban Egyptian men. Reproductive Toxicology. 1996;**10**:145-151. DOI: 10.1016/0890-6238(95)02057-8

[37] Robins TG, Bornman MS, Ehrlich RI, Cantrell AC, Pienaar E, Vallabh J, et al. Semen quality and fertility of men employed in a South African lead acid battery plant. American Journal of Industrial Medicine. 1997;**32**:369-376. DOI: 10.1002/(SICI)1097-0274(199710)32:4<369::AID-AJIM8>3.0.CO;2-P

[38] Popovic M, McNeill FE, Chettle DR, Webber CE, Lee CV, Kaye WE. Impact of occupational exposure on lead levels in women. Environmental Health Perspectives. 2005;**113**:478-484. DOI: 10.1289/ehp.7386

[39] La-Llave-León O, Salas Pacheco JM, Estrada Martínez S, Esquivel Rodríguez E, Castellanos Juárez FX, Sandoval Carrillo A, et al. The relationship between blood lead levels and occupational exposure in a pregnant population. BMC Public Health. 2016;**16**:1231. DOI: 10.1186/s12889-016-3902-3

[40] La-Llave-Leon O, Estrada-Martinez S, Salas-Pacheco JM, Pena-Elosegui R, Duarte-Sustaita J, Rangel JLC, et al. Blood Lead levels and risk factors in pregnant women from Durango, Mexico. Archives of Environmental & Occupational Health. 2011;**66**:107-113. DOI: 10.1080/19338244.2010.511311

[41] Kaličanin B, Velimirović D. A study of the possible harmful effects of cosmetic beauty products on human health. Biological Trace Element Research. 2016;**170**:476-484. DOI: 10.1007/s12011-015-0477-2

[42] Nourmoradi H, Foroghi M, Farhadkhani M, Dastjerdi MV. Assessment of lead and cadmium levels in frequently used cosmetic products in Iran. Journal of Environmental and Public Health. 2013;**2013**:2-7. DOI: 10.1155/2013/962727

[43] Al-Saleh I, Al-Enazi S, Shinwari N. Assessment of lead in cosmetic products. Regulatory Toxicology and Pharmacology.

2009;**54**:105-113. DOI: 10.1016/j.yrtph.2009.02.005

[44] Phipps A, Fels H, Burns MS, Gerstenberger SL. Lead poisoning due to geophagia: The consumption of miniature pottery. Open Journal of Pediatrics. 2012;**02**:60-66. DOI: 10.4236/ojped.2012.21010

[45] Thihalolipavan S, Candalla BM, Ehrlich J. Examining pica in NYC pregnant women with elevated blood lead levels. Maternal and Child Health Journal. 2013;**17**:49-55. DOI: 10.1007/s10995-012-0947-5

[46] Bellinger DC. Teratogen update: Lead and pregnancy. Birth Defects Research Part A – Clinical and Molecular Teratology. 2005;**73**:409-420. DOI: 10.1002/bdra.20127

[47] Barry PS, Mossman DB. Lead concentrations in human tissues. British Journal of Industrial Medicine. 1970;**27**:339-351. DOI: 10.1136/oem.27.4.339

[48] Rădulescu A, Lundgren S. A pharmacokinetic model of lead absorption and calcium competitive dynamics. Scientific Reports. 2019;**9**:1-38. DOI: 10.1038/s41598-019-50654-7

[49] Gulson BL, Mizon KJ, Korsch MJ, Palmer JM, Donnelly JB. Mobilization of lead from human bone tissue during pregnancy and lactation - a summary of long-term research. Science of the Total Environment. 2003;**303**:79-104. DOI: 10.1016/S0048-9697(02)00355-8

[50] Gulson B, Taylor A, Eisman J. Bone remodeling during pregnancy and post-partum assessed by metal lead levels and isotopic concentrations. Bone. 2016;**89**:40-51. DOI: 10.1016/j.bone.2016.05.005

[51] Ying WY, Xu SK, Li H, Yan MH. The effects of lead exposure on placental NF-κB expression and the consequences for gestation. Reproductive Toxicology. 2009;**27**:190-195. DOI: 10.1016/j.reprotox.2008.12.006

[52] Gundacker C, Hengstschläger M. The role of the placenta in fetal exposure to heavy metals. Wiener Medizinische Wochenschrift. 2012;**162**:201-206. DOI: 10.1007/s10354-012-0074-3

[53] Hertz-Picciotto I. The evidence that lead increases the risk for spontaneous abortion. American Journal of Industrial Medicine. 2000;**38**:300-309. DOI: 10.1002/1097-0274(200009)38:3<300::AID-AJIM9>3.0.CO;2-C

[54] Vigeh M, Yokoyama K, Seyedaghamiri Z, Shinohara A, Matsukawa T, Chiba M, et al. Blood lead at currently acceptable levels may cause preterm labour. Occupational and Environmental Medicine. 2011;**68**:231-234. DOI: 10.1136/oem.2009.050419

[55] Taylor CM, Golding J, Emond AM. Adverse effects of maternal lead levels on birth outcomes in the ALSPAC study: A prospective birth cohort study. BJOG: An International Journal of Obstetrics and Gynaecology. 2015;**122**:322-328. DOI: 10.1111/1471-0528.12756

[56] Soomro MH, Baiz N, Huel G, Yazbeck C, Botton J, Heude B, et al. Exposure to heavy metals during pregnancy related to gestational diabetes mellitus in diabetes-free mothers. Science of the Total Environment. 2019;**656**:870-876. DOI: 10.1016/j.scitotenv.2018.11.422

[57] Wells EM, Navas-Acien A, Herbstman JB, Apelberg BJ, Silbergeld EK, Caldwell KL, et al. Low-level lead exposure and elevations in blood pressure during pregnancy. Environmental Health Perspectives. 2011;**119**:664-669. DOI: 10.1289/ehp.1002666

[58] Vigeh M, Yokoyama K, Mazaheri M, Beheshti S, Ghazizadeh S, Sakai T, et al. Relationship between increased

blood lead and pregnancy hypertension in women without occupational lead exposure in Tehran, Iran. Archives of Environmental Health. 2004;**59**:70-75. DOI: 10.3200/AEOH.59.2.70-75

[59] Yoon JH, Ahn YS. The association between blood lead level and clinical mental disorders in fifty thousand lead-exposed male workers. Journal of Affective Disorders. 2016;**190**:41-46. DOI: 10.1016/j.jad.2015.09.030

[60] Bayat F, Akbari SAA, Dabirioskoei A, Nasiri M, Mellati A. The relationship between blood Lead level and preeclampsia. Electronic Physician. 2016;**8**:3450-3455. DOI: 10.19082/3450

[61] Dawson EB, Evans DR, Kelly R, Van Hook JW. Blood cell lead, calcium, and magnesium levels associated with pregnancy-induced hypertension and preeclampsia. Biological Trace Element Research. 2000;**74**:107-116. DOI: 10.1385/BTER:74:2:107

[62] Disha SS, Goyal M, Kumar PK, Ghosh R, Sharma P. Association of raised blood lead levels in pregnant women with preeclampsia: A study at tertiary centre. Taiwanese Journal of Obstetrics & Gynecology. 2019;**58**: 60-63. DOI: 10.1016/j.tjog.2018.11.011

[63] Ikechukwu IC, Ojareva OIA, Ibhagbemien AJ, Okhoaretor OF, Oluwatomi OB, Akhalufo OS, et al. Blood lead, calcium, and phosphorus in women with preeclampsia in Edo State, Nigeria. Archives of Environmental and Occupational Health. 2012;**67**:163-169. DOI: 10.1080/19338244.2011.619212

[64] Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Sakai T, Morita Y, et al. Lead and other trace metals in preeclampsia: A case-control study in Tehran, Iran. Environmental Research. 2006;**100**:268-275. DOI: 10.1016/j.envres.2005.05.005

[65] Vigeh M, Yokoyama K, Shinohara A, Afshinrokh M, Yunesian M. Early pregnancy blood lead levels and the risk of premature rupture of the membranes. Reproductive Toxicology. 2010;**30**:477-480. DOI: 10.1016/j.reprotox.2010.05.007

[66] Huang S, Xia W, Sheng X, Qiu L, Zhang B, Chen T, et al. Maternal lead exposure and premature rupture of membranes: A birth cohort study in China. BMJ Open. 2018;**8**:e021565. DOI: 10.1136/bmjopen-2018-021565

[67] Srivastava S, Mehrotra PK, Srivastava SP, Tandon I, Siddiqui MKJ. Blood lead and zinc in pregnant women and their offspring in intrauterine growth retardation cases. Journal of Analytical Toxicology. 2001;**25**:461-465. DOI: 10.1093/jat/25.6.461

[68] Zhu M, Fitzgerald EF, Gelberg KH, Lin S, Druschel CM. Maternal low-level lead exposure and fetal growth. Environmental Health Perspectives. 2010;**118**:1471-1475. DOI: 10.1289/ehp.0901561

[69] Zhang B, Xia W, Li Y, Bassig BA, Zhou A, Wang Y, et al. Prenatal exposure to lead in relation to risk of preterm low birth weight: A matched case-control study in China. Reproductive Toxicology. 2015;**57**:190-195. DOI: 10.1016/j.reprotox.2015.06.051

[70] Murphy MJ, Graziano JH, Popovac D, Kline JK, Mehmeti A, Factor-Litvak P, et al. Past pregnancy outcomes among women living in the vicinity of a lead smelter in Kosovo, Yugoslavia. American Journal of Public Health. 1990;**80**:33-35. DOI: 10.2105/AJPH.80.1.33

[71] Tabacova S, Balabaeva L. Environmental pollutants in relation to complications of pregnancy. Environmental Health Perspectives. 1993;**101**:27-31. DOI: 10.2307/3431372

[72] Hertz-Picciotto I, Schramm M, Watt-Morse M, Chantala K, Anderson J, Osterloh J. Patterns and determinants of blood lead during pregnancy. American Journal of Epidemiology. 2000;**152**:829-837. DOI: 10.1093/aje/152.9.829

[73] Silbergeld EK, Schwartz J, Mahaffey K. Lead and osteoporosis: Mobilization of lead from bone in postmenopausal women. Environmental Research. 1988;**47**:79-94. DOI: 10.1016/S0013-9351(88)80023-9

[74] Potula V, Kaye W. Is lead exposure a risk factor for bone loss? Journal of Women's Health. 2005;**14**:461-464. DOI: 10.1089/jwh.2005.14.461

[75] Sanín LH, González-Cossío T, Romieu I, Peterson KE, Ruíz S, Palazuelos E, et al. Effect of maternal lead burden on infant weight and weight gain at one month of age among breastfed infants. Pediatrics. 2001;**107**:1016-1023. DOI: 10.1542/peds.107.5.1016

[76] González-Cossío T, Peterson KE, Sanín LH, Fishbein E, Palazuelos E, Aro A, et al. Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics. 1997;**100**:856-862. DOI: 10.1542/peds.100.5.856

[77] Oguri T, Ebara T, Nakayama SF, Sugiura-Ogasawara M, Kamijima M, Saito H, et al. Association between maternal blood cadmium and lead concentrations and gestational diabetes mellitus in the Japan Environment and Children's Study. International Archives of Occupational and Environmental Health. 2019;**92**:209-217. DOI: 10.1007/s00420-018-1367-7

[78] Vaziri ND, Gonick HC. Cardiovascular effects of lead exposure. The Indian Journal of Medical Research. 2008;**128**:426-435

[79] Schwartz J. The relationship between blood lead and blood pressure in the NHANES II survey. Environmental Health Perspectives. 1988;**78**:15-22. DOI: 10.1289/ehp.887815

[80] Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. Lead exposure and cardiovascular disease - a systematic review. Environmental Health Perspectives. 2007;**115**:472-482. DOI: 10.1289/ehp.9785

[81] Han L, Wang X, Han R, Xu M, Zhao Y, Gao Q, et al. Association between blood lead level and blood pressure: An occupational population-based study in Jiangsu province, China. PLoS One. 2018;**13**:1-10. DOI: 10.1371/journal.pone.0200289

[82] Rothenberg SJ, Kondrasho V, Manalo M, Jiang J, Cuellar R, Garcia M, et al. Increases in hypertension and blood pressure during pregnancy with increased bone lead levels. American Journal of Epidemiology. 2002;**156**:1079-1087. DOI: 10.1093/aje/kwf163

[83] Magri J, Sammut M, Savona-Ventura C. Lead and other metals in gestational hypertension. International Journal of Gynecology & Obstetrics. 2003;**83**:29-36. DOI: 10.1016/S0020-7292(03)00212-1

[84] Ugwuja E, Ejikeme B, Obuna J. Impacts of elevated prenatal blood lead on trace element status and pregnancy outcomes in occupationally non-exposed women. International Journal of Occupational Environmental Medicine. 2011;**2**:143-156

[85] Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Practice & Research: Clinical Obstetrics & Gynaecology. 2011;**25**:391-403. DOI: 10.1016/j.bpobgyn.2011.01.006

[86] Vaziri ND, Khan M. Interplay of reactive oxygen species and nitric oxide in the pathogenesis of experimental lead-induced hypertension. Clinical

and Experimental Pharmacology & Physiology. 2007;**34**:920-925. DOI: 10.1111/j.1440-1681.2007.04644.x

[87] Vaziri ND. Mechanisms of lead-induced hypertension and cardiovascular disease. American Journal of Physiology. Heart and Circulatory Physiology. 2008;**295**:H454-H465. DOI: 10.1152/ajpheart.00158.2008

[88] Gonick HC, Ding Y, Bondy SC, Ni Z, Vaziri ND. Lead-induced hypertension: Interplay of nitric oxide and reactive oxygen species. Hypertension. 1997;**30**:1487-1492. DOI: 10.1161/01.HYP.30.6.1487

[89] Carmignani M, Volpe AR, Boscolo P, Qiao N, Di Gioacchino M, Grilli A, et al. Catcholamine and nitric oxide systems as targets of chronic lead exposure in inducing selective functional impairment. Life Sciences. 2000;**68**:401-415. DOI: 10.1016/S0024-3205(00)00954-1

[90] Moreau T, Hannaert P, Orssaud G, Huel G, Garay RP, Claude JR, et al. Influence of membrane sodium transport upon the relation between blood lead and blood pressure in a general male population. Environmental Health Perspectives. 1988;**78**:47-51. DOI: 10.1289/ehp.887847

[91] Joo H, Choi JH, Burm E, Park H, Hong YC, Kim Y, et al. Gender difference in the effects of lead exposure at different time windows on neurobehavioral development in 5-year-old children. Science of the Total Environment. 2018;**615**:1086-1092. DOI: 10.1016/j.scitotenv.2017.10.007

[92] Vahter M, Åkesson A, Lidén C, Ceccatelli S, Berglund M. Gender differences in the disposition and toxicity of metals. Environmental Research. 2007;**104**:85-95. DOI: 10.1016/j.envres.2006.08.003

[93] Oishi H, Nomiyama H, Nomiyama K, Tomokuni K. Comparison between males and females with respect to the porphyrin metabolic disorders found in workers occupationally exposed to lead. International Archives of Occupational and Environmental Health. 1996;**68**:298-304. DOI: 10.1007/BF00409414

[94] Chang SH, Cheng BH, Lee SL, Chuang HY, Yang CY, Sung FC, et al. Low blood lead concentration in association with infertility in women. Environmental Research. 2006;**101**:380-386. DOI: 10.1016/j.envres.2005.10.004

[95] Keitt SK, Fagan TF, Marts SA. Understanding sex, differences in environmental health: A thought leaders' roundtable. Environmental Health Perspectives. 2004;**112**:604-609. DOI: 10.1289/ehp.6714

[96] Llop S, Lopez-Espinosa MJ, Rebagliato M, Ballester F. Gender differences in the neurotoxicity of metals in children. Toxicology. 2013;**311**:3-12. DOI: 10.1016/j.tox.2013.04.015

[97] Kumar S. Occupational, environmental and lifestyle factors associated with spontaneous abortion. Reproductive Sciences. 2011;**18**:915-930. DOI: 10.1177/1933719111413298

[98] Main KM, Skakkebæk NE, Virtanen HE, Toppari J. Genital anomalies in boys and the environment. Best Practice & Research. Clinical Endocrinology & Metabolism. 2010;**24**:279-289. DOI: 10.1016/j.beem.2009.10.003

[99] Escobar-Morreale HF. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. Nature Reviews. Endocrinology. 2018;**14**:270-284. DOI: 10.1038/nrendo.2018.24

[100] Cole TJ, Ahmed ML, Preece MA, Hindmarsh P, Dunger DB. The relationship between insulin-like growth Factor 1, sex steroids and timing of the pubertal growth spurt. Clinical

Endocrinology. 2015;**82**:862-869. DOI: 10.1111/cen.12682

[101] Sergeyev O, Burns JS, Williams PL, Korrick SA, Lee MM, Revich B, et al. The association of peripubertal serum concentrations of organochlorine chemicals and blood lead with growth and pubertal development in a longitudinal cohort of boys: A review of published results from the Russian Children's Study. Reviews on Environmental Health. 2017;**32**:83-92. DOI: 10.1515/reveh-2016-0052

[102] Yao Q, Zhou G, Xu M, Dai J, Qian Z, Cai Z, et al. Blood metal levels and serum testosterone concentrations in male and female children and adolescents: NHANES 2011-2012. PLoS One. 2019;**14**:1-14. DOI: 10.1371/journal.pone.0224892

[103] Liu Y, Téllez-Rojo MM, Sánchez BN, Zhang Z, Afeiche MC, Mercado-García A, et al. Early lead exposure and pubertal development in a Mexico City population. Environment International. 2019;**125**:445-451. DOI: 10.1016/j.envint.2019.02.021

[104] Wani AL, Ara A, Usmani JA. Lead toxicity: A review. Interdisciplinary Toxicology. 2015;**8**:55-64. DOI: 10.1515/intox-2015-0009

[105] Markowitz M. Lead poisoning: A disease for the next millennium. Current Problems in Pediatrics. 2000;**30**:62-70. DOI: 10.1067/mps.2000.104053

[106] Obeng-Gyasi E. Sources of lead exposure in various countries. Reviews on Environmental Health. 2019;**34**: 25-34. DOI: 10.1515/reveh-2018-0037

[107] La-Llave-León O, Méndez-Hernández EM, Castellanos-Juárez FX, Esquivel-Rodríguez E, Vázquez-Alaniz F, Sandoval-Carrillo A, et al. Association between blood lead levels and delta-aminolevulinic acid dehydratase in pregnant women. International Journal of Environmental Research and Public Health. 2017;**14**:1-10. DOI: 10.3390/ijerph14040432