REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2015, Vol 22, No 2, 259–264
www.aaem.pl

Impact of heavy metals on the female reproductive system

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Rzymski P, Tomczyk K, Rzymski P, Poniedziałek B, Opala T, Wilczak M. Impact of heavy metals on the female reproductive system. Ann Agric environ Med. 2015; 22(2): 259–264. doi: 10.5604/12321966.1152077

Abstract

Introduction. It has been recognized that environmental pollution can affect the quality of health of the human population. Heavy metals are among the group of highly emitted contaminants and their adverse effect of living organisms has been widely studied in recent decades. Lifestyle and quality of the ambient environment are among these factors which can mainly contribute to the heavy metals exposure in humans.

Objective. A review of literature linking heavy metals and the female reproductive system and description of the possible associations with emission and exposure of heavy metals and impairments of female reproductive system according to current knowledge.

Results. The potential health disorders caused by chronic or acute heavy metals toxicity include immunodeficiency, osteoporosis, neurodegeneration and organ failures. Potential linkages of heavy metals concentration found in different human organs and blood with oestrogen-dependent diseases such as breast cancer, endometrial cancer, endometriosis and spontaneous abortions, as well as pre-term deliveries, stillbirths and hypotrophy, have also been reported.

Conclusions. Environmental deterioration can lead to the elevated risk of human exposure to heavy metals, and consequently, health implications including disturbances in reproduction. It is therefore important to continue the investigations on metal-induced mechanisms of fertility impairment on the genetic, epigenetic and biochemical level.

Key words

heavy metals, female reproductive system, cadmium, lead, mercury

INTRODUCTION

A recent WHO report confirms that the quality of the environment plays a significant role in human health status. It was estimated that one-quarter of the global disease burden and more than one-third of the burden among children is due to modifiable environmental factors [1]. It is believed that healthier environments can help in the prevention of a wide range of disorders and decrease the morbidity rate among humans. On the other hand, the relentless growth of the human population forces a higher demand for food, consumption, and industrial products, and consequently, leads *inter alia* to increasing environmental contamination. The group of heavy metals represents pollutants which concern serious health problems connected with high a global annual emission rate. These elements are not only resistant to decomposition in natural conditions, but may also bioaccumulate and biomagnify in the food chains [2, 3].

However, 'heavy metals' is imprecise term, it is widely used in scientific literature and commonly defined as a group of elements with a specific density of more than 5 g/cm^3 [4]. It is also generally accepted that some of these metals are essential for living organisms in small quantities, but toxic in higher concentrations or in other speciation forms, e.g. copper (Cu), chromium (Cr), manganese (Mn) and zinc (Zn), while other are not considered to have any specific metabolic role and are generally classified as obligatory toxic, e.g. cadmium (Cd), mercury (Hg) and lead (Pb). Arsenic (As), although chemically classified as a metalloid, is also often included in the heavy metals group. These elements are natural constituents of the earth's crust and it is beyond any doubt that indiscriminate human activities have drastically altered their geochemical cycles and biochemical balance. The main global sources of anthropogenic contamination by heavy metals include different branches of industry, the power industry, transport, municipal waste management, waste dumping sites, fertilizers and waste used to fertilize soil [5]. Emission of heavy metals into the environment occurs through a wide range of processes and pathways, including to the air (e.g. combustion, extraction and processing), to surface water (through direct deposition, runoff and releases from storage and transport), and to the soil (and hence into crops and other organisms through the food chain) [6]. Despite directives and regulations mandating reductions and limits of their release, the atmospheric emission is still the main source of heavy metals distribution in the environment in Poland as well as other European countries (Fig. 1). This, in turn, contributes to a greater exposure of humans, occuring mainly via inhalation of contaminated air (or tobacco smoke) or consumption of contaminated food and water.

OBJECTIVE

The presented study aims to summarize available epidemiological and experimental data obtained from human

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Received: 24 June 2013; accepted: 02 October 2013

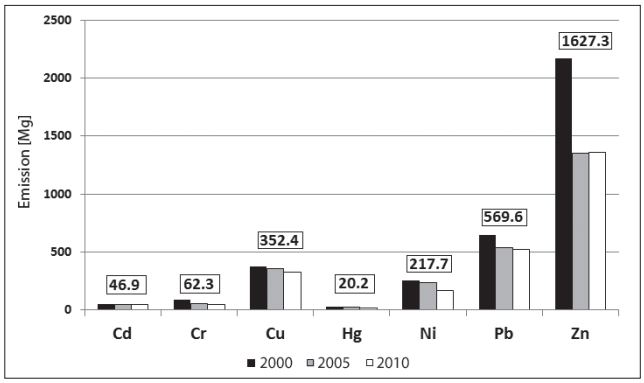

Figure 1. Atmospheric emission of heavy metals distribution in the environment in Poland. The numbers in rectangles correspond to the mean level emitted between 2000–2010

studies and animal experimental research which concerned the effect of heavy metals on the female reproductive system. Special emphasis is given to one of the most toxic and health threatening agents – Cd, Pb and Hg. The contribution of tobacco smoke (important source of Cd and Pb) in the disturbance of the human reproduction success is also discussed.

Epigenetic mechanisms in heavy metal toxicity. Epigenetics is the study of modification of the genes leading to the control and regulation of their expression without the involvement of any structural modification.The processes, which can be altered in the epigenetic modification, include DNA methylation, histone modification, RNA regulation, DNA repair, transcription, RNA stability, alternative RNA splicing, protein degradation, gene copy number, and transposon activation [7, 8]. Pollutants such as heavy metals, as well as pharmaceuticals, hormones, nutrition, and behaviour, can modify the expression of genes. Furthermore, some chemically-induced changes in gene regulation can be associated with serious and complex human diseases. These include, *inter alia*, cancer, diabetes, obesity, respiratory diseases, allergies, Parkinson and Alzheimer diseases. It is also suggested that epigenetics can be involved in the pathogenesis of preeclampsia, intrauterine growth restriction and infertility [7, 8].

The current flurry of research on epigenetics and the increasing documentation of the effects of various environmental factors on DNA methylation have expanded the scope of research on the etiology of health disorders. It appears that heavy metals can be involved in alterations of gene expression and lead to associated epigenetic changes. For example, Arita et al. have demonstrated in the Chinese hamster G12 cell line that nickel(Ni)-induced changes of DNA methylation led to the inactivation of gene expression. This mechanism was also found to lead to Ni-induced tumors in the wild type of C57BL/6 mice [9]. Other reported Ni-induced epigenetic modifications included: the loss of acetylation in H2A, H2BH3 and H4 histones, increases in H3K9 histone dimethylation, and increases in the ubiquitylation of H2A and H2B at a global level [9]. Several studies have reported that As exposure can induce hyper- or hypo-methylation of the DNA and alter the global histone methylation levels in human lung carcinoma A549 cells [9, 10, 11]. Furthermore, Florea et al. revealed that trivalent forms of As can induce apoptosis in several cellular systems with the involvement of membrane-bound cell death receptors, activation of caspases, changes of the intracellular glutathione level and release of calcium ions [12]. Deregulation of calcium ions levels in the nuclei might lead to toxicity in the cells and is a well-known mechanism of apoptosis. [12]. Other As-incuded epigenetic mechanisms have also been demonstrated, such as intracellular glutathione-reactive oxidation, up-regulation of proteins (e.g. heat-shock antioxidative stress proteins, alphaB-crystallin and ferritin light chain) and enzymes (e.g. aldose reductase, heme oxygenase-1), as well as down–regulatation of glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase and inactivation of extracellular signal regulated kinases ERK-1 and ERK2 [12]. It is thus well documented that As can induce genomic damage and alter cell cycle. DNA methylation was also found in case of Cr and Cd exposure [9, 10, 11]. Chronic exposures to trivalent forms of Cr (potentially biologically-essential in trace quantities) were associated through the epigenetic changes in the sperm (significant increase in the number of undermethylated copies of the 45S ribosomal RNA gene) that alter parental imprinting, with an increased risk of ovarian cysts, uterine abnormalities and reproductive gland tumours (in male offspring only), as well as pheochromocytomas, thyroid follicular and Harderian gland tumours, lung tumours (in female offspring only), and renal non-neoplastic lesions (in male offspring only) [13].

According to the study of Benbrahhim-Tallaa et al., Cd-induced DNA hypermethylation at the global and gene specific levels (an overexpression of methyltransferase-3-beta [DNMT3b] DNA without changes in DNMT1 expression) induced malignant transformation of human prostate epithelial cells [14]. Interesting investigations were also conducted by Larson et al. which suggested that environmental exposures to trivalent As and bivalent Cd can alter cell-cell and cell-matrix interactions in the normal urothelial cells through a reduction in the expression of SPARC (extracellular matrix-associated proteins that have counteradhesive properties) – the mechanism participating in the multi-step process of bladder carcinogenesis [11]. In terms of neoplasia, Zalejska-Fiolka et al. in their study showed increased activity of superoxide dismutase in the serum of people protractedly exposed to Pb. It seems to be a possible adoptive mechanism against the increased amount of reactive oxygen species (also caused by Pb) which, as is known, are involved in carcinogenesis [15].

The given examples are contributing to the growing evidence that environmental heavy metal exposure involves changes in epigenetic marks, which may lead to a possible link between inheritable changes in gene expression and disease susceptibility and development.

Effects of cadmium, lead and mercury on the female reproduction system. The main health hazards of contamination by heavy metals have been associated with exposure to Cd, Pb and Hg – currently the most widely-distributed pollutants in the environment which, at the same time, demonstrate a high level of toxicity against living organisms. Recent decades have seen extensive toxicological studies reporting their adverse effect on humans as neurotoxicity, immunodeficiency, osteoporosis, kidneys and other organ failures, as well as potential implications in impaired fertility [16, 17]. There is enough epidemiological data concerning acute metal poisonings in which the real

health concern mainly relates to chronic exposures to low concentrations which can potentially affect a large part of the human population [18].

Infertility has been already recognized by the World Health Organization as a considerable public health issue worldwide and has became a serious medical challenge [19]. It is believed that approximately 15% – 30% of couples are diagnosed with unexplained infertility [20]. It is beyond any doubt that lifestyle and quality of the ambient environment can play a fundamental role in human reproductive success [21]. Below it is demonstrated that exposures to heavy metals such as Cd, Pb or Hg may be highly involved in impaired human fertility.

Cadmium (Cd). The emission of Cd and its compounds widely used in different industrial branches have increased dramatically during the 20th century. Currently, cigarette smoking is considered as a major source of Cd exposure. It is also suggested that the adverse health effects of Cd may occur at lower levels than previously anticipated. The primary targets of Cd in the human body include the kidneys and bones [2]. The reproductive system also appears to be susceptible to Cd action in the human body. As demonstrated, Cd can accumulate in human endometrial tissue and its levels are increased in female with smoking history [22].

Cd is considered as a metalloestrogen. It was demonstrated that it can join the oestrogen receptors alpha and beta and stimulate it [23], and simultaneously, Cd can also up-regulate the progesterone receptors. It was thus linked as a potential causative agent of oestrogen-dependent diseases, such as breast and endometrial cancer, endometriosis and spontaneous abortions [22, 24]. For example, Nasiadek et al. demonstrated that low levels of Cd in the blood (0.33–3,5 mcg/l) of women with uterine myomas correlated with the metal content in the uterus, and significantly decreased estradiol (E2) concentration in serum [25]. An interesting study was conducted by Akesson et al. in which long-term dietary Cd intake was investigated (10 years of an average 15 mug/day of cadmium intake). Higher endometrial cancer risk was shown to be associated with higher intake of Cd [26]. Endometriosis was also demonstrated to be potentially associated with Cd exposures. For example, Jackson et al. found that the blood level of Cd in women with endometriosis was significantly higher than in the group of healthy individuals [27]. Experiments by Hofer et al. revealed that Cd can be involved in hypertrophy and hyperplasia of the endometrium. Ovariectomized rats treated with Cd via the oral route (0.05–4 mg kg^{-1} bw for 3 days), drinking water (0.4–9 mg kg^{-1} bw for 4 weeks) and intraperitoneal injection (0.00005–2mg kg^{-1} bw), developed a significant increase in the relative weight of the uterus. Even in the case of a single injection, the dose-dependent increase in uterine wet weight and thickness of the uterine epithelium [28]. In another study by Liu et al., increased uterine wet weight, as well as endometrial thickness and endometrial stromal thickness, were observed in a group of rats that during 3 days of exposure to 0.8 mg kg^{-1} Cd in intraperitoneal injections. Moreover, at low doses of Cd (0.00005–0.05 mg kg^{-1} bw) given in those injections, the C3-complement component mRNA expression in the uterus was down-regulated but strongly stimulated by the highest-treated dose of 2 mg kg^{-1} bw [29]. Furthermore, Cd can be responsible for increase in the amount of angiogenic molecules VEGF-A (vascular endothelial growth factor) and PLGF (placentation growth factor) due to the changes in the mRNA expression in human endometrial endothelial cells [30]. It was also found that this phenomenon is altered by the presence of endometrial stromal cells and that Cd can have an indirect adverse impact on cadherin dependent cell-cell junctions.

Expression of VEGF-A and PLGF mRNA affects the angiogenesis processes (formation of new blood vessels) in endometrial cells which play significant role in the embryogenesis, implantation and placentation. These disorders lead to endometrial dysfunctions, implantation failure, premature delivery, subfertility, spontaneous abortions and preeclampsia [30].

Lead (Pb). Pb is another heavy metal highly emitted worldwide. The general population is exposed to Pb from the air and food in roughly equal proportions. During the last century, Pb emissions into the ambient air caused considerable pollution, mainly due to emissions from petrol. Children are particularly susceptible to Pb exposure due to a high gastrointestinal uptake and the permeable blood–brain barrier [2]. Although Pb in petrol has dramatically decreased over the last decades it is still widely used in industrial branches.

The concentration of Pb in the human body depends on several factors in which place of residence, lifestyle and age play crucial roles. Increased levels of Pb in human serum were found in individuals inhabiting industrialized areas, who smoked and abused alcohol. Increased levels of Pb in human endometrium were demonstrated in smoking female [22]. It was also found that its level increases with age, which may be associated with the release of Pb previously accumulated in bones. Some studies demonstrated that Pb can be highly toxic even at low doses, although there is no clear evidence that at such levels it can affect the reproduction system. This, however, cannot be ruled out and requires further, complex investigations.

Some studies have postulated that Pb can directly lead to a higher risk of spontaneous abortion through its potential teratogenic action [24,31]. Indirect reasons behind this conclusion are the well-studied adverse effect of Pb on the quality of human sperm or inducement of hormonal disorders and placental vascular disorders due to arterial hypertension [32]. It was also found that pregnancy-related metabolic changes can increase Pb mobilization from bone stores and lead to exposure of the foetus to endogenous metal content. Interestingly, calcium has been reported to play a protective role against this process, and it is therefore suggested that its intake during the second half of pregnancy might reduce Pb mobilization.

The Szkup-Jabłońska et al. study revealed that higher blood Pb levels (19.71 mcg/l Pb as a mean level) in the developing organism of a child is associated with future behavioural consequences as attention disorders, hyperactivity and impulsive behaviour [33].

Mercury (Hg). Human activities, particularly mining and coal burning, have contributed to the mobilization of Hg and raised its levels in air, soils, fresh and marine waters. The majority of Hg emission have occurred since 1800, its increase being related to the Industrial Revolution [2]. Despite an efforts to minimize its use and release to the environment, it is still emitted in high concentrations in many countries, including Poland (Fig. 1). Due to Hg bioaccumulation and

biomagnifications in the food chain the main source of Hg exposure includes consumption of contaminated food, with fish and aquatic invertebrates in particular being a major source of methyl Hg exposure. The group of special concern also include individuals working or having contact with dental amalgam (an alloy of mercury with various other metals used for dental fillings). Rowland et al. conducted a questionnaire survey in which dental assistants working with amalgam demonstrated a lower fertility ratio [34].

Despite the well-known neurotoxicity of Hg compounds, still little is known about the potential effect of this metal on reproduction in humans. However, there are several reports on the adverse effect on fertility in animals in which chronic Hg exposure led to oestrous cycle disruption, impaired embryo implantation and impendent follicular development. All existing chemical forms of Hg administered to animals have induced reproductive disturbances, such as stillbirth or spontaneous abortions, congenital malformations, infertility and inhibition of ovulation [35]. In humans, so far, there are only six epidemiological data findings (mostly from Europe) demonstrating menstrual cycle abnormalities, including changes in bleeding patterns and cycle length among women occupationally exposed to Hg [36]. Compounds of Hg appear also to affect the pregnancy outcome – it was found that the metal levels in maternal blood and infant hair was inversely associated with birth weight [37]. However, there is no evidence of anthropometrics, such as at birth [38].

These observations clearly suggest that Hg may have a significant impact on human reproduction, especially for some occupational groups or populations with prevalence of aquatic food in the diet (especially in Asia). There is a need to understand the mechanisms behind the Hg-induced impairment of fertility, and the complete ecotoxicological risk assessment requires further and complex investigations while the aquatic food – strict quality advisories.

Cigarettes smoking as the source of heavy metals and its implications in reproduction. It was demonstrated that smoking can be a significant source of heavy metals especially Cd and Pb. This is due to the tendency of tobacco plants to accumulate metals available in soils and translocation from the roots to the above-ground parts, including leaves which are harvested for cigarettes production [39]. Tobacco smoking is prevalent among males but is also widespread among women. Globally, 1 billion men and 250 million women smoke every day. In 2011, over 30% of Poles smoked cigarettes regularly [40]. It was estimated that 100,000 children in Poland are born annually by mothers who smoked during pregnancy. It is forecasted that between 2000 – 2025, the number of cigarette-smoking women will increase by 8% [41].

There is evidence that cigarette smoking leads to an overload of human body with heavy metals. Significant number of studies demonstrated that among smokers elevated levels of Cd and Pb in blood are usually found; some even indicated a considerable correlation between metal concentration and number of cigarettes smoked daily [42]. Increased levels of Cd and Pb are also being found in endometrium of cigarrete smoking female [22].

Jensen et al. found that fecundability was lower in women exposed *in utero* to cigarette smoke compared to those who were unexposed. Furthermore, decreased fecundability was also found in women who discontinued smoking *in utero*. They summarise that male exposure to cigarette smoke *in utero* was also associated with a decreased fecundability odds ratio, whereas present smoking did not significantly reduce fecundability [43]. Not only direct smoking but also the passive smoke has been demonstrated to impair fertility. For example, Wdowiak et al. found that women who were exposed to cigarette smoke developed poor quality embryos [44]. On the other hand, Dechanet et al. found that cigarette smoking among women can lead to implantation failure and higher risk of miscarriage [45]. Another problem is the preterm delivery, stillbirth and the smaller weight of the newborn, as well as the future health problems of those children (bronchopulmonary dysplasia, upper and lower respiratory infections, asthma) [46]. A recent systematic data review found an association between maternal smoking and reduced cognitive abilities later in the life of child [47]. Klejewski et al. also found that tobacco smoking, both active and passive, affects pregnant women and can lead to preterm delivery, stillbirth and a lower weight of the newborn. These, in turn, can be followed by health issues during early childhood [48]. On the other hand, it was a surprising fact that non-smokers more often had a miscarriage in their medical history than other groups [48].

Several investigations have highlighted the potential impact of tobacco smoking on the occurrence of some gynaecological disorders. Jabłonowska et al. examined tobacco smoking, HPV (human papillomavirus) infections, and changes in the cervix, and their results revealed a direct relationship between cigarette smoking, HPV infection and significant increase of high grade squamous intraepithelial lesion (HSIL) in histological images [49]. Cerqueira E. et al., examining the cytogenetic effects of cigarette smoking on exfoliated cells from the uterine cervix in women with normal smears, and women with inflammatory atypia, squamous intraepithelial lesion (SIL) (cervical intraepithelial neoplasia, CIN 1–3) and cervical cancer, confirmed these results [50]. On the other hand, according to Yuping Zhou et al., exposure to cigarette smoke may provide a protective effect in case of endometrial disease among smokers. They revealed that *in vivo*, mice exposed to cigarette smoke similarly showed increased expression of HOXA10 (homeobox A10) and PGR (progesterone receptor) in the endometrium. HOXA10 and PGR drive endometrial differentiation, and both are suppressed in endometrial tumours and in endometriosis. The authors suggest that smoking has direct effects on the uterus endometrium, rather than being secondary to ovarian alterations [51].

Another aspect is the impact of smoking on semen. Studies have produced different results. The relationship between smoking and semen analysis parameters (morphology, motility and concentration) have been confirmed, but the mechanism is still not completely understood [52, 53, 54]. Mitra et al. revealed that lower sperm motility ($P < 0.001$) and increased sperm morphological defects ($P < 0.0001$) were associated with smoking habits[53]. In the study by Taszarek et al. in Egypt and Hassan et al. in Turkey, morphology and concentration were not statistically different between smokers and non-smokers, although motility was significantly lower in smokers [54, 55]. Davar et al. obtained opposite results. Their study revealed an inverse correlation between pack/years and morphology, motility and concentration, but P-Values from that study were not significant [52]. In addition, their results (similar to the Hassan et al. study) did not show any relationship between the number of cigarettes smoked and sperm parameters [52]. The results are therefore conflicting.

Substantial harmful effects of cigarette smoke on fertility have become apparent but are not generally appreciated. Cigarette smoking has a negative impact on the ability to become pregnant and carry a pregnancy to term. It is important to include these issues in future social campaigns and to gain public health attention. Obviously, it is known that tobacco smoke is not only a source of heavy metals, but also over 4,000 other harmful chemical compounds (polycyclic aromatic hydrocarbons, acenapthelene, phenanthrene, pyrene and chrysene], nitrosamines, alkaloids, aromatic amines, etc.) which altogether can have a synergistic effect on the human body, including the reproductive system.

CONCLUSIONS

Increasing urbanization and industrialization can lead to the elevated risk of human exposure to heavy metals, and consequently, health implications including disturbances in reproduction. It is therefore important to continue the investigations on metal-induced mechanisms of fertility impairment on the genetic, epigenetic and biochemical level. Simultaneously, parallel epidemiological data are necessary to assess the real risk of exposure for each population, and the participation of heavy metals in unexplained fertility problems. Analytical data on the accumulation of metals in gynaecological organs and tissues can also provide interesting information, particularly if correlated with the quality of the environment, lifestyle and diet.

In the authors' opinion, understanding the linkages existing between the contamination of the environment and decrease in health quality are necessary to develop effective methods of fertility protection. This can be gained not only by implementation of law regulations and directives concerning the emission limits, but also through social and educational campaigns developed and maintained in order to decrease harmful habits and lifestyles in the human population.

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