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TOXIC EFFECTS OF CADMIUM ON THE FEMALE REPRODUCTIVE ORGANS A REVIEW

Maretta, M., Marettová, E.
Department of Morphological Disciplines,
University of Veterinary Medicine and Pharmacy in Košice
Komenského 73, 041 81 Košice
Slovakia

elena.marettova@uvlf.sk

ABSTRACT

Cadmium (Cd) is a common environmental pollutant present in soil and associated with many modern industrial processes. Cadmium may adversely influence the health of experimental animals and humans and exert significant effects on the reproductive tract morphology and physiology. During embryonic development, cadmium suppresses the normal growth and development of the ovaries, and in adults it disrupts the morphology and function of the ovaries and uterus. The exposure to cadmium has adverse effects on the oocyte meiotic maturation affecting the structure of ovarian tissue. The distribution of follicles and corpus luteum in the ovarian tissues has been shown to be disrupted, affecting the normal growth and development of the follicles. In the ovarian cortex, the number of follicles at different stages of maturation decreased, and the number of atretic follicles increased. In the medulla, oedema and ovarian haemorrhage and necrosis appears at higher doses. Granulosa cells exposed to cadmium exhibited morphological alterations. Oocyte development was inhibited and the amount of oocyte apoptosis was higher. Cadmium exposure also caused changes in the structure of the ovarian blood vessels with reduction in the vascular area. Cadmium effects included increased uterine weight, hyperplasia and hypertrophy of the endometrial lining. Exposure to cadmium had specific effects on gonadal steroidogenesis by suppressing steroid biosynthesis of the ovarian granulosa cells and luteal cells. Progesterone, follicle stimulating hormone, and luteinizing hormone decreased significantly after $CdCl_2$ administration. Cadmium can suppress the female's ovulation process and cause temporary infertility.

Key words: cadmium; female; mammals; reproductive organs

INTRODUCTION

Cadmium toxicity is associated with several clinical complications, hepatic dysfunction and bone diseases. Cadmium can also cause various forms of diseases: osteomalacia and osteoporosis, hypertension, arteriosclerosis, and anaemia [25, 85, 92]. Chronic exposure leads to: obstructive airway diseases, emphysema, end-stage renal failures, diabetic and renal complications, deregulated blood pressure, bone disorders, and immune-suppression

[24, 26, 30]. Cadmium accumulates over time in blood, kidney, and liver as well as, in the reproductive organs, including the placenta, testis, and ovaries [20, 21, 29, 57].

At the cellular level, Cd stimulates: cell proliferation, inhibit apoptosis, inhibit DNA repair, and promote cancer in a number of tissues [63, 76]. Several authors have outlined the genotoxic effects of Cd on animal cells and tissues [15, 87]. Cadmium acts as a mitogen by promoting cancer cell proliferation and is associated with increased risk of carcinogenesis in multiple organs, most notably: kidney, prostate, liver, pancreas, lung, stomach, and testis [9, 23, 44, 86, 87]. Cadmium is known as an endocrine disruptor compound, interfering with the synthesis and regulation of some hormones in both females and males [75]. Exposure of rodents to the metal resulted in a down-regulation of pituitary hormones; including: gonadotropins, prolactin, ACTH, growth hormone, and thyroid-stimulating hormone [33, 65].

Cadmium exposure is associated with reproductive toxicity, resulting in both animal and human male and female. The detrimental effects of Cd on morphology, physiological and biochemical dysfunctions of male reproductive organs have been documented [4, 25, 41, 45, 70]. Experimental animal studies have shown *in vivo* that Cd was also able to temporarily induce sterility in female reproductive systems [80]. Long-term exposure to low doses of Cd had adverse effects on the health of the next generation. Some harmful effects showed gender differences in offspring [100]. In this article, we review the findings of the effect of Cd on the female reproductive organs of mammals in relation to hormonal disturbances obtained in experimental animals.

Mechanism of toxicity

At the cellular level, cadmium affects: cell proliferation, differentiation, apoptosis and other cellular activities. Current evidence suggests that the exposure to Cd induces genomic instability through complex and multifactorial mechanisms. Cadmium may cause the DNA single chain breaks, and harmed the DNA repaired system, inducing apoptosis in many kinds of cells [94].

Cadmium has the potential to affect reproduction and development in many different ways, and at every stage of the reproductive system. Gestational Cd treatment induces ovarian toxicity and reproductive dysfunction through increased oxidative stress [6, 14, 38, 56, 68]. Furthermore, the deregulation of cell growth, the resistance to apoptosis, as well as epigenetic alterations have been demonstrated in diverse experimental systems. This had been reported to cause apoptosis, necrosis and cell proliferation [7, 18]. Epigenetic changes in DNA expression [90], stimulates the synthesis of Cd binding proteins metallothioneins and heat proteins [32], inhibit or upregulate transport pathways [78, 81, 89].

Cadmium-induced oxidative stress has been associated with production of reactive oxygen species comprising mainly superoxide radical anion, hydrogen peroxide and hydroxyl radicals which lead to lipid peroxidation, membrane protein and DNA damage [72, 73]. Recent studies have described lipid peroxidation to be an early and sensitive consequence of cadmium exposure, and free radical scavengers and antioxidants have been reported to attenuate cadmium-induced toxicity. Toxicity could result from Cd interacting with cellular components even without entering the cell, but by interaction with receptors on their surface [8].

The overall effect of Cd on any cell or tissue is likely due to the synergy of several mechanisms. A large proportion of the cellular reactions affected by ionic Cd2+ are mediated by cellular signalling cascades [77, 79]. The combination of the multiple mechanisms can give rise to a high degree of genomic instability in cadmium-adapted cells, relevant not only for tumour initiation but also for later steps in tumour development [19]. Other mechanisms of Cd toxicity have been suggested, including ionic and molecular mimicry, interference with cell adhesion and signalling, genotoxicity and cell cycle disturbance [80].

Distribution of Cd in female reproductive organs

In female reproductive organs, Cd was found mainly in the ovaries and uterus [52]. In the ovary, the presence of Cd has been identified in follicular fluid and oocytes [95] which may accumulate in ovaries, eventually affecting the quality of developing oocyte and embryo [22]. The incorporation of Cd into the chromatin of the developing gamete has been demonstrated [80]. In the mouse, Cd was deposited in the ovary after 8 days of its injection [91]. Cadmium chloride in a dose of 0.25 $mg.kg^{-1}$ per week resulted in almost the same Cd content in ovaries, adrenals, and the pituitary gland [53, 82]. Several studies have demonstrated increased accumulation of Cd in the ovary with an increase in age [102], thus leading to failure of progres-

sion of the oocyte development from primary to secondary stage, and failure to ovulate [80, 97, 102]. A significant increase in Cd concentration was also found in the uterine tissue. After 30 days of administration, the mean Cd concentration increased in uterine tissues depended on the dose. Cadmium displays the ability to accumulate in human endometrium, and the lining of the uterus [66]. There was a significant correlation between the Cd concentration in the blood and in the uterine tissues just after 30 days of Cd administration, as well as, 3 months after the exposure termination [48].

Effects of cadmium on the structure of the ovary

The deleterious effects of Cd reflected in the structure of the ovary and its toxicity was seen in all zones of the ovary. In the ovary cortex, a decreased number of follicles in different stages of maturation have been noticed. In the interfollicular zone areas of disorganization, oedema and necrosis has been identified, whereas in the medulla, congestion, hyperaemia and large sanguineous vasodilatation tending to haemorrhage was observed [42]. The distribution of follicles and corpus luteum became highly confused in ovarian tissues in the Cd group. The average size of the corpus luteum seemed to be larger [42]. The histopathology of the ovaries revealed a significant decrease in follicle number of follicles [52]. These changes resulted in the increased constituent ratio of the original follicles and a decreased diameter of all levels of follicular oocytes [99].

Cadmium affected the maturation of follicles, and increased the number of atretic follicles. In mouse foetal gonads, Cd increased female germ cell apoptosis [3]. Cadmium, at concentrations as low as 1 μM, significantly decreased the germ cell density in human foetal ovaries. The developing or mature follicles are sensitive to cadmium treatment. Cadmium is able to block the growth of follicles; and developing follicles transform into atretic follicles [80], and increases the apoptotic follicular cells [52]. The follicle growth and differentiation were significantly disturbed by ≥1.2 $\mu g.ml^{-1}$. The exposure to $CdCl_2$ with concentrations of 1.6 $\mu g.ml^{-1}$ on day 2, had caused a significantly reduced survival rate and rate of antral follicles, and increased abnormal follicle rate [81].

A decrease in the granulosa cell numbers and changes in their morphology with Cd exposure was found [5, 27, 50, 55, 71]. Cadmium has a catalytic role on mouse ovarian granulosa cell apoptosis [16, 40]. Apoptosis of the granulosa cells surrounded the oocyte as well as, the apoptosis due to the oocyte may cause follicular atresia [46, 83, 93]. Cadmium caused a significant reduction in gonadotropin binding, which altered the steroidogenic enzyme activity of granulosa cells. These changes exhibited a positive correlation with membrane changes of the granulosa cells [49]. The oocyte nucleus damage and the morphological changes of granulosa cells, and the cells of the internal and external theca layers of the ovarian follicle caused by Cd were found in the ovary of the $CdCl_2$ group [91]. Cd causes damage to the folliculogenesis which results in the decline in the number and quality of ovulated oocytes and the failure in the fertilization [62].

The exposure to Cd of cultured human ovarian granulosa cells caused morphological alterations in a time- and dose-dependent manner [80]. *In vitro* study revealed that the suppression of steroid forming was due to the direct influence to the granulosa cells and luteal cells function [54]. In ovarian granulosa cells isolated from 21-day-old female Sprague Dawley rats cultured *in vitro* for 36 h and exposed to $CdCl_2$ (0, 5, 10, and 20 μM) was found that mRNA and protein levels of all factors were upregulated in each cadmium-dose group [40]. Cadmium decreased: antioxidants like superoxide dismutase, catalase, glutathione peroxidase and glutathione, and raised the concentrations of malondialdehyde and hydrogen peroxide in the uterus and ovaries of rats [52].

Cadmium and oocyte development

Oocyte development and associated events were seen to be disrupted by Cd administration in several species, although variations have been observed. Cadmium had affected the development of mice ovaries, it induced the oocytes into the status of apoptosis, resulting in the death of a large number of oocytes [36]. The amount of oocyte apoptosis in mouse treatment groups was remarkably higher. Cd induced apoptosis in meiotic cells as it also decreased the number of mouse oocytes after meiotic initiation [3].

Cadmium caused a reduction in the maturation of oocytes. Cadmium chloride was toxic to the bovine oocyte maturation process *in vitro* in a concentration-dependent manner [43]. This was related to the failure of the progression of oocyte development from primary to secondary stage [80] and had direct detrimental effects on the bovine oocyte maturation and developmental ability [1]. The high concentrations of Cd completely suppressed the oocyte

maturation rate and also, suppressed an integral component of expanded cumulus cells in porcine oocytes [84]. When oocytes were exposed to different concentrations of Cd (0.4, 2, 10 or 50 μM) for 44 h during *in vitro* maturation Cd exposure, prominently resulted in the failure of cumulus cell expansion and arrested meiotic progression [102]. It was found that maturation rate of the bovine oocyte was significantly affected at 2 and 20 M $CdCl_2$ and also reduced the percentage of oocytes reaching metaphase II stage. Both Cd concentrations also decreased numbers of oocytes resting in MII, reduced numbers of fertilized ovine oocytes in culture, and increased the rate of oocyte degeneration in both groups [34]. At the lowest dose tested Cd *in vitro* affects the physiological function of ovine gametes, but at higher dose tested can compromise cell viability [34]. A significant decline in viability of buffalo oocytes was observed at 1.0 $mg.ml^{-1}$ Cd [1]. The concentration of cadmium causing 100 % oocyte death (1-day culture) was 18 $\mu g.ml^{-1}$ [51]. The germinal vesicle breakdown of oocyte was disturbed dose-dependently after the culture follicles were exposed to ≥1.6 $\mu g.ml^{-1}$ $CdCl_2$ [88, 89].

Cadmium exposure decreased the number of ovulated oocytes and impaired oocyte meiotic maturation rate both *in vivo* and *in vitro*. In female mice, Cd impaired meiotic maturation of oocytes by affecting the cytoskeletal organization, mitochondrial function, and histone modifications. Cadmium disrupted meiotic spindle morphology and actin filament, which are responsible for successful chromosome segregation and the polar body extrusion during oocyte maturation and fertilization [17, 103]. Cadmium exposure impeded the mouse oocyte meiotic progression by disrupting the normal spindle assembly, chromosome alignment and actin cap formation [11]. Cadmium exposure perturbed the assembly of spindle structure by weakening the microtubule stability, accompanied by the misaligned chromosomes at the equatorial plate. Failure of meiotic progression results from the dysfunctional dynamics of cytoskeleton and nuclear maturation in Cd-exposed oocytes [102]. Exposure to Cd-induced oxidative stress with increased reactive oxygen species leads to abnormal mitochondrial distribution, insufficient energy supply and DNA damage, ultimately leads to oocyte deterioration [11]. Its exposure led to faulty nuclear maturation of oocytes through damage to the cytoskeleton assembly, resulting in: aberrant spindle organization, chromosome alignment, and actin polymerization [11, 103]. The subchronic cadmium poisoning may destroy or suppresses the oocyte fission process, as well as reduce the activity of ATP enzyme in the ovary.

The exposure of Cd changed the ultrastructure of cells in the ovary tissues. Remarkable changes have been observed on the fine structure of oocytes. Under the electron microscope, chromatin margination, karopyknosis, swelling of mature cisternae of Golgi apparatus, mitochondrial cristae disappearance, and swelling of the rough endoplasmic reticulum can be observed in the $CdCl_2$ group mice [91]. At the same time, the numbers of DNA damage of mouse oocytes in treatment groups were higher. The ultrastructure of oocyte in periods of apoptosis showed the phenomena such as mitochondrion vacuole, and karyotheca invagination [36]. Cd exposure caused the impaired cytoplasmic maturation by showing the disrupted dynamics of mitochondrial integrity and cortical granules, and thereby resulting in the compromised sperm binding ability and fertilization capacity of porcine oocytes [102].

Effect of Cd on ovulation and the oestrous cycle

Cadmium can suppress the female ovulation process and cause temporary infertility [36]. A minimum dose of 5 $mg.kg^{-1}$ of $CdCl_2$ was needed to inhibit ovulation. Ovulation was suppressed when the dose of 10.0 $mg.kg^{-1}$of $CdCl_2$ was administered on the day before ovulation. Cadmium is able to decrease preovulatory luteinizing hormone levels in the blood and inhibit ovulation in rats [55]. When $CdCl_2$ was given closer to the time of the luteinizing hormone surge on the day of proestrus, a more pronounced effect on ovulation was recorded. An administration of Cd to female rats during oestrus and diestrus resulted in increased serum progesterone levels [10].

The circulation sex hormone disturbances in Cd-exposed rats caused irregular oestrous cycle, persisting for 3 months after exposure termination [48]. The ovarian Cd concentration increased with age, and has been associated with failure of progression of oocyte development from primary to secondary stage, and failure to ovulate. The incidence of the failure of ovulation was associated with the decreased progesterone levels in serum and inflammation, haemorrhages and necrosis in the ovary. The mechanism by which ovulation could be rendered ineffective is by the failure of pick-up of the oocyte by the tubal cilia due to suboptimal expansion of the oocyte-cumulus complex and mis-expression of cell adhesion molecules [80].

Effects on steroidogenesis

Many experiments have revealed that the Cd administration profoundly alters ovarian steroidogenesis [55, 59, 98]. Several well-characterized estrogenic responses were induced in rodents after intraperitoneal injection of low doses of Cd [28]. Exposure to even low concentrations of Cd is sufficient to significantly affect the steroidogenic pathway [20]. Cadmium at nanomolar concentrations displayed xenoestrogenic activities by affecting lactotroph proliferation and hormone release from anterior pituitary cells [65].

Depending on the identity of the steroidogenic tissue involved and the dosage used enhance or inhibit the biosynthesis of progesterone, a hormone that is inexorably linked to both normal ovarian cyclicity and the maintenance of pregnancy. *In vitro* and *in vivo* studies showed that Cd can both increase and inhibit the secretion of the major classes of steroid hormones: oestradiol (E2) and progesterone (P). Oral Cd exposure induced changes in the plasma levels of steroid hormones: decrease in E2 and increase in P after the highest dose of Cd in female rats [48]. On the other hand, extremely low doses have been reported to stimulate luteal progesterone biosynthesis in the ovaries [20]. The exposure of cultured rat ovarian granulosa cells to Cd causes a decrease in progesterone production [96]. *In vitro*, there were significant differences in P and E between different concentrations of Cd and also between different stages of the oestrous cycle. When Cd was administered i. p. for 5 days per week for 6 weeks at doses of 1.0, 0.5, 0.25 and 0 mg.kg^{-1}, this suggested that Cd may inhibit progesterone and release oestradiol in the ovaries [98].

Acute Cd effects on steroidogenesis are most severe in rats evaluated in proestrus or in early pregnancy, while in late pregnancy steroidogenesis is relatively unaffected [58]. It was found that after Cd exposure, the most affected were productions of progesterone and testosterone in proestrus rats and less in pregnant dams, whereas oestradiol was not affected at all. Cadmium appears to interfere with the ovarian steroidogenic pathway in rats at more than one site [58] and was able to reduce the level of progesterone, by disrupting the function of two steroidogenic enzymes, cytochrome P450 and 3β-hydroxysteroid dehydrogenase, which are essential for the synthesis of progesterone [20]. Once the corpus luteum is formed, the effect of $CdCl_2$ is reduced. Several *in vitro* studies suggested that these effects are mediated via oestrogen receptors [2]. At lower concentrations, Cd competes with oestradiol for binding to oestrogen receptors and activates the receptors, leading to changes in gene expression [74].

Cadmium displays the ability to mimic oestrogens. Cd exposure induces a limited spectrum of estrogenic responses *in vivo* and that, in certain targets, effects of Cd might not be mediated via classical oestrogen receptors signalling through oestrogen responsive element-regulated gene [2]. It seems that Cd inhibit ovarian steroidogenesis by downregulating StAR gene expression along with inhibiting activities of steroidogenic enzymes and antioxidant system [60].

Toxic effects of Cd on the vascular system of the ovary

An important route of Cd exposure is the circulatory system whereas blood vessels are considered to be the main stream organs of Cd toxicity [61]. Light microscopy revealed that small arteries in developing follicles and the interstitial stroma were particularly susceptible to damage. In rats, haemorrhagic necrosis and endothelial damage in the vessels has been found [12]. Exposure to $CdCl_2$ resulted in the coagulation of blood around the ovarian follicles of the female Golden hamster, which follicles within 24 h showed signs of degeneration [67]. In Syrian hamsters the small arteries of the developing follicles and interstitial stroma seemed selectively susceptible to $CdCl_2$ toxicity while the corpora lutea, mesothelium, primordial oocytes, and the rete ovarii appeared resistant [64]. In the ovarian medulla, hyperaemia and large sanguineous vasodilatation tending to haemorrhage have been found [42].

Cd toxicity on uterus

Cadmium effects included, increased uterine weight, hyperplasia, and hypertrophy of the endometrial lining [101]. The high levels of steroid hormones led to the proliferation of the endometrium. In the ovariectomized rats treated with cadmium by the dose of 0.1–2.5 mg.kg^{-1}, uterine weight was increased and a dose-effect manner was found [69]. The increase in wet weight was accompanied by proliferation of the endometrium and induction of progesterone receptor and complement component C3 [28, 39]. Both 3-day and 4-week oral Cd administration resulted in a dose-dependent stimulation of C3 expression in the uterus, significant at and above 0.5 mg.kg^{-1} b.w. [22].

Differences in Cd tissue levels and hormonal potency for the two routes of administration was found. A single

i.p. injection of Cd increased dose-dependently uterine wet weight. Uterine wet weight increased 1.7 times when ovariectomized rats were administered a single intraperitoneal injection of 5 μg $CdCl_2$ kg^{-1} b.w. [28] and 1.2 and 1.4 times after a single intraperitoneal injection of 500 or 2,000 μg $CdCl_2.kg^{-1}$ b.w. [22]. The thickness of the endometrium and weight of the uterus were also increased in F1 female offspring. A marked increase in the endometrial thickness during oestrus after 30-day exposure to Cd was found [48]. Histological evaluation of uterine tissues showed that the height of the luminal epithelium was significantly increased [2, 22]. The increase of uterine weight and by the increase of the thickness of luminal epithelium cell and endometrium was accompanied by the decrease of nuclear/cytoplasm of luminal epithelium cell and endometrium [96].

Cadmium caused morphologic alterations and dysfunction in blood vessels. The effects of Cd are a multisystem phenomenon involving inflammation, hypertrophy, apoptosis and angiogenesis [31]. Exposure to Cd increase the thickness of the basal lamina in the blood vessels in a dose-related manner in the uterus of female rats subcutaneously injected with 0.36 and 0.18 $CdCl_2.kg^{-1}$ for 8 to 60 weeks. Uterine and cervical stromal haemorrhages were seen in immature hamsters at doses of ≥30 μmol $CdCl_2.kg^{-1}$ [12].

In the vasculature of the uterus, Cd interacts with the vessels, leading to an inflammatory response, that finally causes the formation of high endothelial venules, blood vessel dilatation and oedematisation [13, 47]. A dose- and time-related increase of the thickness of the media in arteries with signs of perivascular inflammatory reaction could be observed [37]. Cadmium might affect endometrial angiogenesis and as a consequence cause endometrial dysfunction with an increased risk for fertility problem. Long-term exposure was reported to give rise to changes in the blood vessels of the myometrium of the uterus in female rats and may cause small vessel wall thickening in the rat uterus [35]. After Cd exposure, the endometrial endothelial cells of blood vessels have a key role in the regulation of endometrial angiogenesis.

CONCLUSIONS

Female reproductive organs are sensitive to Cd treatment. Cadmium has been shown to exert significant effects on ovarian and reproductive tract morphology. It has the potential to affect reproduction in many different ways, and at every stage of the reproductive process. Experiments in animals showed dose- and age-dependent Cd-toxicity in the ovaries, uterus, and cervix. Oral exposure of rats to Cd induced damage of the ovaries. Cadmium caused the reduction in the ovary size and inhibited folliculogenesis which resulted in the diminution of the numbers of primordial, growing, and tertiary follicles. After Cd exposure, oocyte development is inhibited, and ovarian haemorrhage and necrosis supervene at higher Cd doses. The cadmium may suppress ovarian granulosa cells. Exposure was linked to a decline in the number of corpora lutea, as well as a reduction in their vascular area. Cadmium exposure has the adverse effects on the oocyte meiotic maturation and can suppress the female animal's ovulation process and cause temporary infertility. Morphometric changes in the epithelium of uterus have been presented. An increase of stroma was a sign of uterus oedamatisation caused by damage in the wall of the blood vessels. The effects of Cd, are a multisystem phenomenon involving: inflammation, hypertrophy, apoptosis, angiogenesis and important processes involved in vascular remodelling systems. Cadmium has been proposed to be an endocrine disruptor by inducing estrogenic responses and luteal cells steroid biosynthesis and had the ability to alter the levels of circulating hormones and sexual cycle phases.

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