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Review

Evidence for Ovarian and Testicular Toxicities of Cadmium and Detoxification by Natural Substances

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Abstract: Cadmium (Cd) is an environmental toxicant, capable of reducing mitochondrial ATP production and promoting the formation of reactive oxygen species (ROS) with resultant oxidative stress conditions. The ovary and testis are the primary gonads in which female gametes (oocytes) and male gametes (spermatozoa), estrogen and testosterone are produced. These organs are particularly susceptible to Cd cytotoxicity due to their high metabolic activities and high energy demands. In this review, epidemiological and experimental studies examining Cd toxicities in gonads are highlighted together with studies using zinc (Zn), selenium (Se), and natural substances to reduce the effects of Cd on follicular genesis and spermatogenesis. Higher blood concentrations of Cd ($[Cd]_b$) were associated with longer time-to-pregnancy in a prospective cohort study. Cd excretion rate (E_{Cd}) as low as 0.8 μg/g creatinine was associated with reduced spermatozoa vitality, while Zn and Se may protect against spermatozoa quality decline accompanying Cd exposure. E_{Cd} > 0.68 μg/g creatinine were associated with an increased risk of premature ovarian failure by 2.5-fold, while $[Cd]_b \geq 0.34$ μg/L were associated with a 2.5-fold increase in the risk of infertility in women. Of concern, urinary excretion of Cd at 0.68 and 0.8 μg/g creatinine found to be associated with fecundity are respectively 13% and 15% of the conventional threshold limit for Cd-induced kidney tubular effects of 5.24 μg/g creatinine. These findings suggest that toxicity of Cd in primary reproductive organs occurs at relatively low body burden, thereby arguing for minimization of exposure and environmental pollution by Cd and its transfer to the food web.

Keywords: cadmium; ovary; testis; oxidative stress; fecundity; toxicity mitigation

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1. Introduction

Cadmium (Cd), a heavy metal in the IIB group of the periodic table, was first discovered as an impurity in zinc carbonate [1–3]. It is a rare element that occurs in the Earth's crust and the sea at 0.15 mg/kg and 1.1×10^{-4} mg/L, respectively [1–3]. In an elemental form Cd is unstable, and it forms a compound with sulfide as Cd sulfide (CdS), present in greenockite together with sphalerite, the zinc (Zn) ore which contains Zn sulfide (ZnS) [1–3]. Because greenockite and sphalerite are inseparable, Cd becomes a byproduct of mining, smelting, and refining zinc ore [1–3]. Cd has been used in many industrial processes, including as a plastic stabilizer, in the production of batteries, solar cells, pigments, alloys, plating, and coating [2,3]. The industrial application of Cd has resulted in the mobilization of Cd from geological sources to biologically accessible conditions, as does the use of phosphate fertilizers by the agricultural sector [4–6].

Like other metals, Cd is not biodegradable, and it can persist indefinitely in the environment which eases its food-chain transfer [1–3]. Because Cd is present in virtually all foodstuffs, diet is a major exposure source in the general non-smoking adult population worldwide [5,7–9]. Volcanic emissions, fossil fuel and biomass combustion, and cigarette smoke are additional environmental Cd sources [10–14]. The tobacco plant is a hyperaccumulator of Cd, and it is consistently reported that blood Cd levels ($[Cd]_b$) in cigarette smokers were two- to six-fold higher than non-smokers of similar age and gender [7]. Cd in cigarette smoke exists as oxide form (CdO), and a volatile metallic form with high transmission rates [14]. Thus, Cd can enter the body from the gut and lungs, and then accumulates in human tissues to induce toxicity in the tissues/organs it deposits [5,7,8,15].

The aim of this review is to provide an update of knowledge arising from recent epidemiological and experimental studies concerning ovarian and testicular toxicities of Cd. It emphasizes on how those studies attempted to demonstrate the utility of plant substances (phytochemicals), Zn and selenium (Se) to offset the toxic effects of Cd in ovaries and testes, where female gametes (oocytes) and male gametes (spermatozoa) are produced together with estrogen and testosterone. Gametogenesis (oogenesis, folliculogenesis and spermatogenesis) is known to be highly susceptible to persistent toxic chemicals, such as Cd, lead (Pb) and mercury (Hg) [16,17]. Chelating agents are prescribed as a conventional method for treatment of Pb intoxication, but many side effects are reported [18], while therapeutically effective chelation therapies for Cd are lacking. Several candidates for mitigation of the ovarian and testicular Cd toxicities have been suggested, including various forms of nanoparticles (carbon nanomaterials, magnetic nanoparticles, nano-imprinted polymers, nano-based metal–organic frameworks, silica nanoparticles), probiotics, antioxidant vitamins C and E, folate, and amino acids [19–21].

2. Environmental Cadmium Exposure and Human Reproduction

2.1. Dietary Intake Levels of Cadmium

The total diet study, known also as the "market basket survey", is a food safety monitoring program that has been used to estimate intake levels of various contaminants and identify their sources in the human diet. It provides a basis to define a maximum level (ML) or a maximally permissible concentration (MPC) of a given contaminant in a specific food group. Table 1 provides MPC for Cd in various food items according to the European Food Safety Agency (EFSA).

Table 1. Maximum permissible concentrations for cadmium in food.

No.	Foodstuffs	MPC * mg/kg Wet Weight
1.	Meat (excluding offal) of bovine animals, sheep, pig, and poultry.	0.05
2.	Horsemeat, excluding offal.	0.20
3.	Liver of bovine animals, sheep, pig, poultry, and horse.	0.50
4.	Kidney of bovine animals, sheep, pig, poultry, and horse.	1.0
5.	Muscle meat of fish, excluding species listed in #6 and #7.	0.050
6.	Bonito (*Sarda sarda*), common two-banded seabream (*Diplodus vulgaris*), eel (*Anguilla nguilla*), grey mullet (*Mugil labrosus labrosus*), horse mackerel or scad (*Trachurus* spp), louvar or luvar (*Luvarus imperialis*), mackerel (*Scomber* spp), sardine (*Sardina pilchardus*), sardinops (*Sardinops* spp), tuna (*Thunnus* spp, *Euthynnus* spp, *Katsuwonus pelamis*), and wedge sole (*Dicologoglossa cuneata*).	0.10
7.	Muscle meat of bullet tuna (*Auxis* spp).	0.20
8.	Muscle meat of anchovy (*Engraulis* spp) and swordfish (*Xiphias gladius*).	0.30

Table 1. *Cont.*

No.	Foodstuffs	MPC * mg/kg Wet Weight
9.	Crustaceans, excluding brown meat of crab and excluding head and thorax meat of lobster and similar large crustaceans (*Nephropidae* and *Palinuridae*).	0.50
10.	Bivalve mollusks.	1.0
11.	Cephalopods (without viscera).	1.0
12.	Cereals, excluding bran, germ, wheat, and rice.	0.10
13.	Bran, germ, wheat, and rice.	0.20
14.	Soybeans.	0.20
15.	Vegetables and fruit, excluding leaf vegetables, fresh herbs, fungi, stem vegetables, root vegetables, and potatoes.	0.050
16.	Stem vegetables, root vegetables and potatoes, excluding celeriac. For potatoes the maximum level applies to peeled potatoes.	0.10
17.	Leaf vegetables, fresh herbs, celeriac, and the following fungi: *Agaricus bisporus* (common mushroom), *Pleurotus ostreatus* (Oyster mushroom), *Lentinula edodes* (Shiitake mushroom).	0.20
18.	Fungi, excluding those listed in #17.	1.0
19.	Food supplements excl. food supplements listed in #20.	1.0
20.	Food supplements consisting exclusively or mainly of dried seaweed or of products derived from seaweed.	3.0

* According to Regulation (EC) No 1881/2006 latest amended by Regulation (EC) No 629/2008 [22].

Dietary intake levels of Cd, estimated from total diet studies, vary widely among populations. The Cd intake by average consumers in the U.S. [23], Spain [24], Belgium [25], Sweden [26], France [27], Korea [28], Germany [29] and China [30] were estimated as 4.63, 7.7, 9.8, 10.6, 11.2, 12.6, 14.6 and 32.7 μg/day, respectively. The median Cd intake levels for women who lived in two areas of Japan affected by Cd pollution were estimated as 47.8 and 55.7 μg/day [31]. The most significant dietary sources of Cd include foods that are frequently consumed in large quantities, such as rice, potatoes, wheat, leafy salad vegetables, and other cereal crops.

2.2. Effects of Cadmium on Human Reproduction

Although Cd was detectable in human ovaries [32], testes, epididymis, prostate glands, and seminal vesicles [33,34], limited population-based investigations have been undertaken to link Cd accumulations in these tissues to fecundity. In a recent population-based cohort study, higher blood concentrations of Cd ($[Cd]_b$) were associated with longer time-to-pregnancy (TTP), defined as the number of menstrual cycles or months of unprotected intercourse required to achieve pregnancy [34]. This prospective cohort study included 501 couples in Michigan and Texas who discontinued contraception to become pregnant. Among women, 11% smoked cigarettes while 15% and 14% of men smoked cigarettes and cigars, respectively. Compared with those who never smoked, $[Cd]_b$ levels were higher in smokers than those consumed smokeless tobacco products and never smoked. Adjusting for $[Cd]_b$ attenuated the association between cigarette smoking and TTP, particularly among women. This finding suggested that Cd may partially contribute to longer TTP in men and women who smoked [35]. Findings of other epidemiological studies showing the impacts of Cd exposure on human reproduction are highlighted in Sections 2.4 and 2.5.

2.3. Cadmium Exposure Estimates

Cd is a cumulative toxicant because no mechanisms have been evolved to eliminate it from the body. Owing to its miniscule elimination rate, the body burden of Cd is essentially determined by the absorption rate [5,8]. Numerous studies have shown that the intestinal absorption of Cd is mediated by transporters and receptors that the body uses to acquire iron (Fe), calcium (Ca), Zn, and manganese (Mn), all of which are influenced by age, physiological requirement, nutritional status, and dietary factors [5,8]. In theory, the

absorption rate of Cd will rise when the body is in short supply of the elements that share absorption and transport mechanisms with Cd (Fe, Ca, Zn, Mn). It will also rise in subjects whose diets are deficient in these elements.

Urinary concentration of Cd ($[Cd]_u$) and excretion rate of Cd (E_{Cd}) can be used as a measure of kidney burden, and an indicator of a cumulative lifetime exposure. These two parameters correlate closely with Cd contents of kidneys, and other determinants of kidney Cd accumulation rate, such as age, gender, smoking, and body status of Fe, Ca, Zn and Mn, described above [5,8]. $[Cd]_u$ and E_{Cd} have been measured in a bio-monitoring program such as the U.S. National Health and Nutrition Examination Survey (NHANES), becoming a rich data source for investigating potential adverse health effects of environmental exposures that can be generalized to the U.S. population. The geometric mean, the 50th, 75th, 90th, and 95th percentile values for E_{Cd} in the representative U.S. general population are 0.210, 0.208, 0.412, 0.678, 0.949 μg/g creatinine, respectively [36].

At any given time, blood concentration of Cd ($[Cd]_b$) reflects recent exposures and the contribution from tissues and organs, especially the liver and lungs. The geometric mean, the 50th, 75th, 90th, and 95th percentile values for $[Cd]_b$ in the representative U.S. general population are 0.304, 0.300, 0.500, 1.10, 1.60 μg/L, respectively [35]. Most Cd in whole blood is contained within the cytosol of red blood cells. The Cd that remains in the blood plasma (serum) is bound to the amino acid histidine and proteins, such as metallothionine (MT), pre-albumin, albumin, α_2-macroglobulin, and immunoglobulins G and A [37–39]. It is conceivable that a plasma/serum concentration of Cd ($[Cd]_s$) is more predictive of its toxicity than those in erythrocytes because it is readily exchangeable. Presently, $[Cd]_s$ is rarely used. Nonetheless, the utility of $[Cd]_s$ has been increasingly demonstrated in recent studies, including those examining effects of Cd exposure on semen quality (Section 2.5). Further, $[Cd]_s \geq 0.73$ μg/L were associated with a 2.5-fold increase in the risk of obstructive lung disease among participants in NHANES 2007–2010 [40], while $[Cd]_s$ in the highest quartile were associated with a 2.8-fold increase in the risk of wheeze and asthma in NHANES 2007–2012 participants, aged 20–79 years [41]. In a Japanese-population-based study (n = 1144, aged > 19 years, the median $[Cd]_s$ of 0.06 μg/L), $[Cd]_s$ in the highest quintile was associated with a 1.7-fold increase in risk of hypertension, compared with $[Cd]_s$ in the lowest quintile [42].

2.4. Epidemiological Investigations on Effects of Cadmium on Fecundity in Women

Table 2 summarizes data from six studies examining impacts of environmental Cd exposure on fecundity in women in the U.S. [43–46], China [47] and Korea [48].

Table 2. Epidemiological evidence for the effects of cadmium on fecundity in women.

Effects Observed	Study Design/Populations	Risk Estimates
Infertility [43].	NHANES 2013–2016 participants, aged 20–39 years. Data from 42 pregnant and 82 infertile women were analyzed. GM for $[Cd]_b$ was 0.26 μg/L.	OR for infertility increased by 1.84-fold per a 2-fold increment of $[Cd]_b$. OR for infertility increased by 1.15- and 2.47-fold, comparing $[Cd]_b$ 0.20–0.33 μg/L, 0.34–5.14 μg/L with $[Cd]_b$ 0.07–0.19 μg/L.
Endometriosis [44].	NHANES 1999–2002 participants (n = 1425) aged 20–49 years. GM for $[Cd]_b$ in women with endometriosis was 0.53 μg/L, 20.8% higher than those without endometriosis.	OR for endometriosis increased by 3.39-fold, comparing $[Cd]_b \geq 0.5$ μg/L) with $[Cd]_b < 0.3$ μg/L after adjusting for age, race/ethnicity, smoking status, use of birth control pills, and exposure to lead and mercury.

Table 2. *Cont.*

Effects Observed	Study Design/Populations	Risk Estimates
Polycystic ovary syndrome (PCOS) [45].	A prospective cohort study of 251 healthy women, aged 18–44 years (New York, NY, U.S.). Median $[Cd]_b$ was 0.30 μg/L.	The probability of having PCOS was increased by 18% per 0.1 μg/L increment of $[Cd]_b$, together with 2.2%, 2.9% and 7.7% increments of serum concentrations of testosterone, sex hormone-binding globulin and AMH, respectively. PCOS was based on serum AMH and testosterone levels.
Low ovarian reserve [46].	NHANES 1988–1994 participants (n = 1681) aged 35–49 years. Additional data from 65 postmenopausal women were analyzed.	RR for low ovarian reserve was increased by 1.4-, 1.6- and 1.8-fold, comparing $[Cd]_u$ 0.16–0.38, 0.39–0.77 and > 0.77 μg/L with $[Cd]_u$ < 0.16 μg/L, respectively. Low ovarian reserve was defined as $[FSH]_s \geq 10$ IU/L.
Ovarian insufficiency [47].	Chinese women in Zhejiang Province, 169 cases, 209 controls, aged 35–45 years. Median for E_{Cd} in cases was 0.58 μg/g creatinine, 25.6% higher than controls.	OR for ovarian insufficiency was increased by 2.5-fold, comparing E_{Cd} > 0.68 μg/g creatinine with E_{Cd} < 0.37 μg/g creatinine. E_{Cd} positively associated with $[FSH]_s$ and $[LH]_s$, while showing inverse associations with $[AMH]_s$ and $[estradiol]_s$. Ovarian insufficiency was defined as $[FSH]_s \geq 25$ IU/L.
Ovarian failure [48].	Korean women in Soul (n = 283), aged 30–45 years. GM for $[Cd]_b$ was 0.97 μg/L.	Ovarian reserve inversely associated with $[Cd]_b$ (adjusted $\beta = -0.34$, $p = 0.02$). An inverse association of ovarian reserve and $[Cd]_b$ was particularly strong in 30–35-yr age group (adjusted $\beta = -0.43$ ($p = 0.01$). Ovarian reserve was based $[AMH]_s$.

NHANES, National Health and Nutrition Examination Survey; n, sample size; GM, geometric mean; $[x]_u$, urinary concentration of x; E_x, excretion rate of x; $[x]_b$, blood concentration of x; $[x]_s$, serum concentration of x; OR, odds ratio; RR, risk ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Mullerian hormone; PCOS, polycystic ovary syndrome.

An increment of $[Cd]_b$ by two-fold was associated with 1.84-fold increase in risk of infertility in a study of women, aged 20–39 years, who participated in NHANES 2013–2016 [43]. The risk of infertility rose by 1.15- and 2.47-fold, comparing $[Cd]_b$ of 0.20–0.33, and 0.34–5.14 μg/L with $[Cd]_b \leq 0.19$ μg/L.

An association of Cd exposure with an increased risk of endometriosis was evident from a study of women, aged 20–49 years, enrolled in NHANES 1999–2002 [44]. Comparing $[Cd]_b \geq 0.5$ versus < 0.3 μg/L, OR for endometriosis was increased by 3.39-fold after adjustment for age, lead, mercury, race/ethnicity, smoking and use of birth control pills. An association of Cd exposure with an increased risk of polycystic ovary syndrome (PCOS) phenotype was seen in a prospective cohort study of healthy premenopausal women, aged 18–44 years [45]. Per 0.1 μg/L increment of $[Cd]_b$, the probability of a mild polycystic ovary syndrome phenotype was 18% higher, serum testosterone, sex hormone-binding globulin, and AMH were 2.2%, 2.9%, and 7.7% higher. Based on these data, Cd may act as an endocrine disruptor affecting the hypothalamic–pituitary–gonadal axis [45].

In a study of women, aged 35–49 years, who participated in NHANES 1988–1994, a dose–response relationship was seen between $[Cd]_u$ and ovarian reserve decline, defined by serum concentration of follicle-stimulating hormone ($[FSH]_s$) ≥ 10 IU/L [46]. The risk of ovarian reserve depletion was increased by 1.4-, 1.6- and 1.8-fold, comparing $[Cd]_u$ of 0.16–0.38, 0.39–0.77 and >0.77 μg/L with $[Cd]_u$ < 0.16 μg/L, respectively. An effect of Cd exposure and ovarian reserve has also been observed in Chinese and Korean studies [47,48]. In a Chinese study, OR for ovarian insufficiency was increased by 2.5-fold, comparing

E_{Cd} > 0.68 μg/g creatinine with E_{Cd} < 0.37 μg/g creatinine [47]. Median E_{Cd} in cases of 0.58 μg/g creatinine was 25.6% higher than controls, and E_{Cd} showed positive associations with serum concentrations of FSH and luteinizing hormone (LH) while showing inverse associations with serum concentrations of AMH and estradiol. An inverse association of $[Cd]_b$ and serum concentration of AMH was seen in a study of Korean women, aged 30–45 years. A particularly strong inverse association of $[AMH]_s$ with $[Cd]_b$ was in women aged 30–35 years (adjusted $\beta = -0.43$, $p = 0.01$) [48].

Of the six studies in women, five were reviewed using population-based design [43–46,48], and one center-based, case-control design study [47] was used. Accordingly, all participants were assumed to be environmentally exposed to Cd, and the diet was the most likely environmental Cd source. Regardless of the study designs, the environmental exposure to Cd reflected by $[Cd]_b$, $[Cd]_u$ and E_{Cd} reported for study women were comparable. They could be considered to be low to moderate. The body burden of Cd as $[Cd]_u$ in Chinese women (GM for $[Cd]_u$ of 0.42 μg/L in POI cases and 0.28 μg/L in controls) were comparable to the GM for $[Cd]_u$ of 0.30 μg/L recorded in the U.S. women study [47,48]. The average $[Cd]_b$ level in Korean women was three times higher than the average in U.S. women of the same age ($[Cd]_b$ 0.97 vs. 0.30 μg/L) [45,48].

2.5. Epidemiological Investigations on Effects of Cadmium on Fecundity in Men

Evidence for adverse effects of environmental exposure to Cd on male fecundity comes from studies in which semen (sperm) quality parameters were examined using the criteria prescribed by the World Health Organization [49]. The four main spermatozoa quality parameters were spermatozoa concentration, viability, morphology, and motility [49,50]. These parameters then were tested for their associations with Cd exposure levels, reflected by the levels of Cd in samples of urine, whole blood, blood plasma/serum and seminal plasma. Table 3 summarizes data from six research studies undertaken in Taiwan [51], Italy [52], China [53], Nigeria [54], Spain [55] and India [56].

Table 3. Epidemiological evidence for the effects of cadmium on semen quality.

Effects Observed	Study Design/Populations	Risk Estimates
Spermatozoa vitality [51].	Taiwan, *n* = 196, mean age 38, 62 (32%) had normal semen quality. Mean for $[Cd]_u$ was 0.7 μg/L and mean for E_{Cd} was 0.5 μg/g creatinine.	$E_{Cd} \geq 0.8$ μg/g creatinine were associated in an increased risk of spermatozoa viability decline. Percentages of sperm viability correlated inversely with $[Cd]_u$ ($r = -0.216$) and E_{Cd} ($r = -0.301$).
Spermatozoa counts, spermatozoa motility/Se as a protective factor [52].	Italy, *n* = 179, aged 18–46 years, 131 (73.2%) had two or more at abnormal sperm quality parameters. Seminal plasma Cd was more predictive of semen quality than blood Cd.	In men with abnormal semen quality, the median level for seminal plasma Cd was 2.2-fold higher (0.93 vs. 0.43 μg/L), while the median level for Se was 10.6-fold lower (1.17 vs. 12.36 μg/L), compared to controls. Sperm concentration, total sperm count and progressive motility were increased with increment of seminal plasma Se levels.

Table 3. *Cont.*

Effects Observed	Study Design/Populations	Risk Estimates
Spermatozoa motility, Zn as a protective factor [53].	China (Wuhan), n = 746, aged, 18–55 years, 482 (65%) had normal spermatozoa quality, 238, 200, 66, and 56 men were those with low total motility, low spermatozoa progressive motility, low concentration, and low total spermatozoa counts, respectively.	Seminal plasma Cd levels inversely associated with progressive sperm motility and total motility. Seminal plasma Zn levels positively associated with sperm concentrations. Compared with seminal plasma Zn quartile 1, sperm concentrations rose by 13%, 23%, and 25% in seminal plasma Zn quartiles 2, 3 and 4, respectively.
Spermatozoa concentration [54].	Nigeria, n = 130, aged 20–60 years, 30, 20 and 50 were azoospermic, oligozoospermic and normozoospermic.	Serum Cd concentrations inversely correlated with sperm concentrations. The means for serum Cd levels in azoospermic and oligospermic were 0.305 and 0.287 µg/L, respectively. These means for serum Cd levels were higher than normospermic group (0.219 µg/L).
Sperm motility [55].	Spain, n = 61, age 33.5 ± 3.8 years, 30 infertile cases and 31 controls, The respective GM values for $[Cd]_b$, serum Cd and seminal plasma Cd were 1.0, 0.8, 0.8 µg/L.	Seminal plasma Cd levels positively associated with percentages of immotile sperm after adjustment for age, BMI, and smoking (β = 4.9; 95% CI, 0.84, 9.1). An increment of seminal plasma Cd from 0.7 to 1.0 µg/L was associated with a rise of immotile sperms by 24.3%.
Sperm motility and concentration [56].	India (New Delhi), n = 119, aged 20–43 years, 73 infertile cases and 46 controls.	Seminal plasma Cd levels inversely correlated with sperm concentrations ($r = -0.33$) and sperm motility ($r = -0.33$). The mean for seminal plasma in cases was 0.591 µg/L, 31.2% higher than controls. The means for seminal plasma Cd were 23.9% and 30.8% higher in men with low sperm concentrations and impaired sperm motility, compared to controls.

Spermatozoa quality parameters were based on WHO criteria [36]. N, sample size; $[x]_u$, urinary concentration of x; E_x, excretion rate of x; $[x]_b$, blood concentration of x; $[x]_s$, serum concentration of x; $[x]_{sp}$, seminal plasma concentration of x; OR, odds ratio.

A Taiwanese study included men (mean age 38 years) who underwent an annual health examination at a main municipal hospital in the southern region of Taiwan [51]. Among 186 men recruited to the study, half (50%) were smokers and 62 (33%) had normal semen quality parameters (spermatozoa concentration, motility, viability, and morphology) by WHO criteria. Cd was detected in >98.5% urine samples from study subjects with mean (SD) values for $[Cd]_u$ and E_{Cd} of 0.7 (0.6) µg/L and 0.5 (0.3) µg/g creatinine, respectively. $[Cd]_u$ inversely correlated with sperm viability ($r = -0.216$, $p = 0.006$), as did E_{Cd} ($r = -0.301$, $p = 0.001$). $E_{Cd} \geq 0.8$ µg/g creatinine were associated with an enhanced risk of sperm viability decline, compared with $E_{Cd} \leq 0.4$ µg/g creatinine. The relationship seen between reduced sperm vitality and E_{Cd} was confirmed by a stepwise multiple regression analysis. Thus, data from the Taiwanese study linked long term Cd exposure, reflected by E_{Cd}, to decreased sperm viability.

In an Italian study, subjects were drawn from one industrial area and one agricultural area of eastern Sicily (South Italy) [52]. Among 179 men, 48 (26.8%) had normal sperm quality parameters, while 131 (73.2%) showed abnormality in more than one sperm quality parameters. Although both groups had the same median for blood Cd of 0.32 µg/L, the

median for seminal plasma Cd in men with abnormal semen quality parameters was 2.16-fold higher than those with normal semen quality parameters (0.93 vs. 0.43 μg/L). Thus, seminal plasma Cd appeared to be more predictive of an abnormal semen quality than blood Cd. The median for seminal plasma Se in men with abnormal semen quality parameters was 10.6-fold lower than those with normal sperm parameters (1.17 versus 12.36 μg/L). The median for sperm Se content in men with abnormal sperm parameters was 13.5% lower, compared to the control (0.193 versus 0.219 μg/g). A median for seminal plasma Cd levels in men with total sperm counts below WHO reference value was 2.17-fold higher than those with normal total sperm counts (1.43 versus 0.66 μg/L). Relative to median value, seminal plasma Cd levels at 75th percentile or higher were associated respectively with risks of having abnormal total sperm counts (OR 4.48, 95%CI 0.25–80) and abnormal sperm motility (OR 3.45, 95% CI 0.77–16). An interaction analysis suggested that Se may have minimized a decline in semen quality associated with Cd exposure [52].

A Chinese study included 746 men, aged 18–55 years, who underwent investigation for subfertility at the Wuhan Reproductive Medicine Center [53]. Among study subjects, 482 (65%) men had normal sperm quality parameters. The numbers of men showing low sperm total motility, low sperm progressive motility, low sperm concentrations, and low total sperm counts were 238, 200, 66 and 56, respectively. Inverse associations were seen between seminal plasma Cd levels and sperm motility (progressive and total motility). The inverse associations of seminal plasma Cd with progressive and total sperm motility persisted when other elements were included in a model. Likewise, a positive association of seminal plasma Zn with sperm concentrations was retained when other elements were included in a model. Compared with seminal plasma Zn quartile 1, sperm concentrations rose by 13%, 23%, and 25% in the seminal plasma Zn quartiles 2, 3, and 4, respectively.

In a Nigerian case-control study of men aged 20–60 years who underwent investigations for infertility, 30, 20, and 50 were azoospermic (no spermatozoa in semen), oligozoospermic (low sperm concentrations $< 20 \times 10^6$/mL) and normozoospermic (sperm concentration greater than $>20 \times 10^6$/mL), respectively [54]. The corresponding means for serum concentration of Cd ($[Cd]_s$) in these three groups were 0.305 ± 9.61, 0.287 ± 10.31 and 0.219 ± 14.43 μg/L, respectively ($p = 0.018$). The mean for serum Cd in azoospermic and oligospermic groups was higher than in the normospermic group. An inverse correlation was seen between serum Cd concentrations and spermatozoa concentrations.

In a Spanish study [55], 30 cases and 31 normospermic controls, mean age 33.5 years, were recruited from three infertility centers using semen quality criteria prescribed by the WHO [49]. Among 61 men, 31% were smokers and the GM values for blood Cd, serum Cd, and seminal plasma Cd were 1.0, 0.8, and 0.8 μg/L, respectively. After adjustment for age, BMI and smoking habits, seminal plasma Cd was positively associated with the percentage of immotile sperms (β = 4.9; 95% CI, 0.84, 9.1). An increase in seminal plasma Cd from 0.7 to 1.0 μg/L resulted in 24.3% increment of immotile sperms [55].

In an Indian study, 73 infertile cases, 46 controls aged 20–43 years were recruited from those who attended the Andrology Laboratory of Reproductive Biology Department, All India Institute of Medical Sciences, New Delhi [56]. Among 119 men, 59 (49.6%), and 71 (59.7%) men had low sperm concentrations and impaired sperm motility, respectively. Seminal plasma Cd concentrations inversely associated with sperm concentrations ($r = -0.33$) and sperm motility ($r = -0.33$). The adjusted mean for seminal plasma Cd was 31.2% higher in cases than the control (0.591 versus 0.403 μg/L). The adjusted means for seminal plasma Cd were respectively 23.9% and 30.8% higher in men with low sperm concentrations and impaired sperm motility than those with normal sperm concentrations and normal sperm motility.

3. Metal Binding Proteins in the Ovary and Testis

Metallothioneins (MTs), a group of low molecular weight (6–7 kDa) metal binding proteins can sequester both Cd and zinc (Zn) [57]. By virtue of the high molar cysteine content of 33%, MTs act as a scavenger of free radicals, notably hydroxyl and superoxide

radicals, thereby protecting cells from oxidative damage [57]. Hence, it is thought that cells lacking the ability to synthesize MT are susceptible to cadmium toxicity [58]. In cadmium-treated laying hens, MT protein and MT mRNA, Cd and Zn-MT were detected in the follicle walls of the ovaries, but not in the follicle yolks [59]. In rats treated with $CdCl_2$, vascular damage, testicular necrosis, degenerative changes in ovaries, and loss of reproductive potency were observed [60–62]. Rat and mouse testes are highly susceptible to the necrotizing and carcinogenic effects of Cd [61].

Unlike livers and kidneys, however, effects of Cd in ovaries and testes were unrelated with changes in MT protein or MT mRNA levels [60–63]. The high sensitivity to Cd toxicity in ovaries may thus be attributable to a lack of MT expression [64]. This phenomenon was seen in a study using Syrian hamsters [64]. The Syrian hamster ovaries underwent a hemorrhagic necrosis when exposed to Cd, as did the testes. An analysis of amnio acid sequences of cytosolic ovarian protein, isolated by reverse-phase HPLC, showed that the ovarian protein contained much less cysteine than MT. Furthermore, the ovarian metal binding protein contained a significant amount of aromatic amino acids (phenylalanine) and had higher glutamate molar content than MT, but lacked leucine, and arginine. Thus, Syrian hamster ovaries contained a specific metal binding protein distinct from MT [64]. Of note, the expression of ovarian specific metal-binding protein was not induced by Zn treatment, although the ovaries from Zn-treated hamsters showed resistance to necrosis, caused by Cd. Further research is required to unravel the mechanism underlying the resistance to Cd-induced necrosis after Zn treatment.

4. The Cellular Toxic Mechanisms of Cadmium

Owing to the multiplicity of adverse effects, the exact mechanisms underlying cellular toxicity of Cd remain elusive. Experimental studies attempting to elucidate how Cd affects cells are abundant. Consequently, several mechanisms have been postulated, such as altered gene expression, apoptosis, oxidative stress, aberrant cell signaling, and disruption of endocrine system [65,66]. However, it is noteworthy that Cd must first enter cells to cause toxicity and that members of Zn transporters of the Zrt- and Irt-related protein (ZIP) family, such as ZIP8 and ZIP14, have been shown to mediate Cd uptake by cells [67–69]. Indeed, ZIP8 has been shown to be involved in Cd-induced testicular injury [70–72].

Numerous studies have shown that Cd disrupted cellular redox homeostasis by promoting the generation of reactive oxygen species (ROS), i.e., superoxide ion, hydrogen peroxide and hydroxyl radicals, while suppressing cellular antioxidant systems [73–75]. Examples of antioxidant enzymes affected by Cd are catalase, manganese superoxide dismutase (Mn-SOD), zinc and copper superoxide dismutase (Zn/Cu-SOD or SOD1) [73]. In mitochondria, Cd reduced cell respiration and oxidative phosphorylation, even in low concentrations [65]. Other reported toxic effects of Cd are depletion of reduced glutathione (GSH), inactivation of proteins with sulfhydryl groups and dysregulation of ROS production [75].

Due to high energy demands and autophagy reliance, gonads are highly susceptible to mitochondrial toxicants such as Cd. An effect of Cd on mitochondrial membrane potential, leading less ATP synthesis and enhanced ROS formation was evident from a study using the human granulosa-like tumor (KGN) cells [76], known to express FSH receptor and retain progesterone synthesis similar to those of normal human ovarian granulosa cells [77]. Likewise, a study using the rat Leydig tumor cell line, R2C, has linked effects of Cd on mitochondrial membrane potential and cAMP production to a reduction in progesterone secretion [78]. A follow-up study has identified the suppression of mitochondrial expression of dihydrolipoamide dehydrogenase (LDH) enzyme by Cd to underlie a fall of progesterone synthesis in R2C cells [79]. Knockdown of the mitochondrial LDH gene expression reduced progesterone synthesis by 40% as did Cd treatment [79].

In rats, a single i.p. Cd at 0.5 or 1.0 mg/kg was sufficient to adversely affect the differentiation of Leydig cells, leading to an irreversible loss of their regenerative capacity, and a fall of serum testosterone and LH 41, 55, and 76 days after Cd treatment [80]. A

marked fall in serum testosterone was observed in another study using C57BL/6J mice treated with i.p. Cd at 1.0 mg per kg of body weight for 1 week [81]. The decrease in serum testosterone was attributed to an elevation of heme oxygenase-1 expression induced by Cd, causing a release of iron from heme moiety, lipid peroxidation and death of Leydig cells [81]. Cd-induced germ cell death has been observed and attributed to autophagy in Sertoli cells in rats given a single i.p. Cd at 2 mg/kg which produced serum Cd concentrations of 4–10 μg/L, and testicular Cd contents of 0.2–0.3 μg/g wet weight [82].

5. Experimental Trials to Mitigate Ovarian Toxicity

Table 4 summarizes studies in which various natural substances, chemicals and a nutritionally essential metal Zn were tested for their propensities to reduce toxic effects of Cd accumulation in ovaries.

Table 4. Experimental ameliorating ovarian cadmium toxicities.

Cadmium Dose/Form/Species	Toxic Signs	Substance	Beneficial Effects	References
50 mg/L as $CdCl_2$ p.o. Wistar rats	Extended estrous cycle; decreased number of primary and antral follicles; larger number of atretic follicles.	Melatonin	Improved estrous cycle duration; improvement in count of primary, secondary, antral and atretic follicles.	Kechiche et al., 2020 [83]
100 mg/kg b.w. $CdCl_2$ p.o. Wistar rats	Alteration of the cytoarchitecture of the ovaries.	*Hibiscus sabdariffa*	Restoration of cytoarchitecture; follicle proliferation.	Oyewopo et al., 2020 [84]
2 mg/kg $CdCl_2$ p.o. Wistar rats	Severe tissue necrosis; follicular cell degeneration, atresia, and no formation of new follicles.	*Xylopia aethiopica*	Significant improvement of the ovarian histological structure and increment of follicle numbers.	Godam et al., 2020 [85]
5 mg/kg b.w. $CdCl_2$ p.o. Sprague Dawley rats	Increased number of antral and atretic follicles; morphological abnormalities; decrease in number of follicles.	Tualang honey	Reduced morphological abnormalities in the ovary; restoration of the gonadotropin hormones; reduction in lipid peroxidation levels; increased levels of antioxidant enzymes.	Ruslee et al., 2020 [86]
5 mg/kg b.w./day $CdCl_2$ p.o. albino Wistar rats	Decrease in viable follicular cells as a result of apoptosis; decreased levels of FSH and LH.	Quercetin	Beneficial effects on the ovaries in cadmium induced toxicity; decrease in apoptosis.	Nna et al., 2017 [87]
3 mg/kg of feed mixture; 118 days $CdCl_2$ p.o. Japanese quails	Lower relative volume of primary follicles; decrease number of growing follicles; increased relative volume of atretic primary and growing follicles.	Selenium (Na_2SeO_3) Zinc ($ZnSO_4$)	Se and Zn improved the relative volume of primary and growing follicles.	Nad' et al., 2007 [88]
2.5, 5 and 10 mg/kg b.w. CdCl s.c. CFY rats	Reduced steroidogenesis in cultured granulosa cells; effects on steroid biosynthesis in vitro.	$ZnCl_2$	Potentiated FSH-stimulated progesterone production.	Paksy et al., 1996 [89]

p.o.—per os administration; s.c.—subcutaneous administration.

In a recent experimental trial using rats, the propensities of melatonin to offset toxicity of Cd in ovaries have been observed [83]. The autophagy and apoptosis in ovaries resulted from Cd-induced changes in the phosphorylation of mTOR was minimal when melatonin

was simultaneously administered with Cd [83]. Adverse effects of Cd on cytoarchitecture of the ovaries, such as the deterioration of ovarian follicles and poor vascularization, was normalized in rats treated with Cd plus *Hibiscus sabdariffa* [84]. In addition to restoration of cytoarchitecture, the proliferation of follicles was observed [84].

A study of the effects of *Xylopia aethiopica* on ovarian histology reported severe tissue necrosis, follicular cell degeneration, atresia, and absence of new follicles in Wistar rats treated only with $CdCl_2$ [85]. Simultaneous treatment with *Xylopia aethiopica* extracts increased the number of primary and secondary follicles [85]. Authors attributed the observed ameliorative effects of *X. aethiopica* to antioxidant properties. In another study using rats, the number of antral and atretic follicles were increased in the Cd treated only group [86]. In contrast, the number of antral and atretic follicles in the ovaries were reduced in rats treated with Cd and Tualang honey, thereby suggesting protective effects of Tualang honey [86].

Likewise, the propensities of quercetin to offset ovarian toxicity of Cd have been noted [86]. In the Cd plus quercetin treated group, the structure of ovaries, the number of follicles, Graafian follicles, and the presence of follicles in various stages of development were comparable to controls [87]. Effects of Se and Zn on Cd-induced changes in the structure of ovaries have been investigated in Japanese quails [88]. The number of follicles undergoing atresia in the group treated only with Cd was significantly increased, evident from higher numbers of atretic primary and growing follicles, compared with groups treated with Cd plus Se and Zn. In an early study, the propensities of Zn to offset Cd-induced sterility were investigated, and Cd was found to suppress progesterone accumulation stimulated by the follicle-stimulating hormone and cAMP [89]. Co-treatment of Cd with Zn protected against Cd-induced sterility in vivo, but it failed to counteract an effect of Cd on progesterone biosynthesis [89].

6. Experimental Trials to Mitigate Testicular Toxicity

Notable effects of Cd on testicular tissue architecture include degeneration of the seminiferous tubules with absence of germ cells and vacuolization of the seminiferous epithelium [16,90,91]. Table 5 summarizes studies in which various natural substances, chemicals, and nutritionally essential metals were tested for their propensities to reduce toxic effects of Cd accumulation in testes.

Table 5. Experimental ameliorating testicular cadmium toxicities.

Cadmium Dose/Form/Species	Toxic Signs	Substance	Beneficial Effects	References
140 mg/kg $CdCl_2$ p.o. chicken	Deformed seminiferous tubules; mild lesions.	*Ganoderma* Triterpenoids	Enhanced activity of antioxidant enzymes; reduced MDA content and inflammatory cytokines; reduced damage to testicular morphology.	Wang et al., 2018 [92]
1 mg/kg $CdCl_2$ i.p. Kunming mice	Pathological lesion in testis; reduced supporting cells and greatly decreased number of spermatozoa in the lumen.	Betulinic acid	Reduced residual levels of cadmium in organs–promotion of cadmium excretion; inhibition of apoptosis.	Fan et al., 2018 [93]
1 mg/kg b.w./day i.p. Wistar rats	Decrease in spermatozoa count, morphology, motility; degenerative changes in the seminiferous tubule – loss of spermatogenesis; severe necrosis of seminiferous tubules; absence of spermatogenic cells.	$ZnCl_2$, $MgCl_2$	Spermatozoa observed in seminiferous tubules; lower severity of necrosis; Mg administration significantly reduced Cd effects on spermatozoa quality (at high doses).	Babaknejad et al., 2018 [94]

Table 5. *Cont.*

Cadmium Dose/Form/Species	Toxic Signs	Substance	Beneficial Effects	References
30 mg/L; 90 days p.o. Wistar rats	Reduced seminiferous epithelium; decreased tubular lumen; increased vascular surface area and vascular volume.	Diazinon	Combined administration produced fewer pathological alterations in testes than single cadmium administration.	Adamkovicova et al., 2014 [95]

s.c.—subcutaneous administration; p.o.—per os administration; i.p.—intraperitoneal administration.

A protective effect of *Ganoderma* triterpenoids on testicular damage by Cd was investigated in chickens [92]. In histological examination, deformation of the seminiferous tubules in the testes was observed together with germ cells shedding into the lumen in the Cd-treated group. The activities of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) in the testes of the Cd group were decreased. In the group co-treated with *Ganoderma* triterpenoids, mild lesions were seen [92]. A study in Kunming mice suggested that betulinic acid may lessen pathological lesions in testes, namely abnormal morphology, reduced supporting cells, decreased number of spermatozoa in the lumen, caused by Cd [93]. Another study in rats suggested that Zn and magnesium (Mg) may decrease testicular weight loss and the necrosis of seminiferous tubules that were induced by Cd [94]. Effects of diazinon on testicular Cd toxicity have been investigated in rats under sub-chronic exposure conditions that resulted in moderate to severe testicular degeneration and distortion due to lumen contraction [94]. These changes were less pronounced in rats given both Cd and diazinon as were the disorganization and degeneration of seminiferous epithelium [95].

7. Conclusions

Low environmental exposure to Cd does produce detrimental effects on the functions of female and male gonads, including sex hormone production and gametogenesis. Premature ovarian failure observed in studies of women in the U.S., China and Korea has been linked to deranged serum concentrations of testosterone, estradiol, FSH, LH, and AMH associated with environmental Cd exposure. These data may represent an effect of Cd on the hypothalamic–pituitary–gonadal axis. A fall of sperm concentration, total sperm count, and spermatozoa motility have been observed in studies of Chinese and Italian men, while protective effects of Zn and Se have been noted. The toxicities of Cd in gonads have been detectable at low body burden, reflected by E_{Cd} below 1 µg/g creatinine. Thus, a greater effort needs to be made to reduce dietary intake of Cd. Long-term management of Cd in the environment and agricultural produce is required to minimize the food-chain transfer of Cd, notably from use of phosphate fertilizers. Avoidance of further soil Cd contamination needs much more awareness of Cd levels in phosphate fertilizers, mining waste and wastewater. The persistence of Cd in the environment requires a long-term management approach to minimization of human exposure through environmental management and maintenance of the lowest possible Cd level, wherever possible.

In numerous experimental studies, reported effects of Cd in ovaries include decreased follicular growth, follicular atresia, and prolonged estrus cycle, while disorganization of germinal epithelium in seminiferous tubules and abnormal spermatogenesis are notable Cd effects in testes. Some of the ovarian Cd toxicities could be ameliorated by *Hibiscus sabdariffa*, *Costus afer* leaves, *Ganoderma* triterpenoids, Betulinic acid, Zn, Mg, *Xylopia aethiopica*, Tualang honey, melatonin, quercetin, and selenium. *Costus afer* leaves, *Ganoderma* triterpenoids, betulinic acid, Zn and Mg showed the propensities to reduce Cd toxicities in testes. In the absence of therapeutically effective chelating agents for lowering body burden of Cd, these substances may be of use in the mitigation of Cd toxicity. Further research is required to demonstrate suitable dose regime and efficacy.

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