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Mini-Review

Adverse effects of metal pollutants on reproductive health

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ABSTRACT

Consumption of essential metals is needed for function of certain protein to maintain normal cell integrity. Incorporation and excretion of these metals are governed by the cells, but changes in environmental levels of metals can cause stress. There are areas in which the ambient environment contains non-essential metals that function as toxicants, which alter metal homeostasis thus causing oxidative stress and epigenetic alterations. Ambient air and water, as well as food items in poorly protected areas contain toxic metals, such as arsenic, cadmium, and chromium. Often the exposure to these common metal pollutants is associated with inflammatory diseases and carcinogenesis. However, epidemiology studies and animal experiments demonstrate these metals affect fertility spermatogenesis, sperm concentration, sperm motility, oocyte integrity via epigenetic changes, and contribute to gestational complications. In this review, we present a comprehensive summary of studies demonstrating the detrimental effects of exposure to these metals commonly found in ambient environment on the reproductive health of both males and females.

KEYWORDS: toxic metals, pollution, fertility, reproductive health.

INTRODUCTION

As the global population grows, use and production of hazardous materials to advance manufacturing and food production adds to the global crisis of air pollution. There is growing evidence from multiple sources across the world that air pollution introduces exposure of various metals in both ambient and household environments that result in various maladies, such as cancer and other inflammatory diseases [1, 2]. Additionally, studies have also examined the role of contaminated environments in female and male fertility [2], as well as reproductive outcome [2, 3]. Damage to fertility and reproductive outcome may be induced by the materials in the air. Ambient and household environments contain fine particulates ($PM_{2.5}$ and PM_{10}) that comprise of metals, both essential and nonessential.

Essential metals participate in normal function of various proteins in the daily maintenance of cellular homeostasis. Essential metal ions such as iron, calcium, magnesium, copper, and zinc are required to carry oxygen, mediate cadherin function, and participate in the function of transcription factors. As such, metals and the balance of those metals within cells contribute to successful reproductive health. For example, iron (Fe) is essential for both female and male fertility. While free Fe is toxic and may induce oxidative stress, most of the body's Fe is bond to proteins, such as hemoglobin, myoglobin, ferritin and transferrin [4, 5]. In humans, Fe deficiency is associated with ovulatory infertility [6], as well as shorter gestation and low birth weights [7]. Examination of rat and human ovarian tissue demonstrate that the distribution of Fe bound to transferrin is important for optimal granulosa cell function and thus proper ovarian follicle maturation and ovum development [8]. In mammalian males, certain concentrations of Fe bound to transferrin

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correlates to normal spermatogenesis [9, 10]. Moreover, transferrin is found to be secreted by Sertoli cells that is then incorporated into maturing germ cells *via* transferrin receptors [11]. Additionally, Fe is stored by the protein ferritin within Leydig and Sertoli cells [5]. Sertoli cells, which compartmentalize maturing germ cells, provide iron to the meiotic spermatocytes and differentiating spermatids [11]. In mice, the loss of ferritin results in lower spermatozoa and fewer neonates per litter, which suggests deficiency in sperm motility or viability [12].

Similarly exposure to toxic or nonessential metals may result in disruption of cellular homeostasis by inducing oxidative stress, altering function of metal-dependent proteins, and/or causing epigenetic changes. Disruption of the metal homeostasis of essential metals contributes to a variety of pathologies. This review will explore a few of the most common metals found in ambient environment associated with disruption to female and male reproductive health and fertility, as well as explore possible mechanisms for these alterations.

Metal pollutants and female fertility

Diet and environment play important roles in female health and reproductive health. Female fertility includes not only the production and maintenance of oocytes, but also uterine health, oocyte fertilization and implantation, and normal gestation to accomplish successful reproduction. Mammalian females are born with a finite number of oocytes that must be carefully maintained *via* endocrine regulation for future successful fertilization, implantation, and gestation. Therefore, damage to the menstrual cycle, ovaries, and uterus will be detrimental to reproduction. Females can be exposed to non-essential metals, such as arsenic, cadmium, lead and nickel through contaminated air and water, which compromise female fertility.

Arsenic (As) is a toxic, heavy metal often present in contaminated drinking water [13, 14] and fine particulate matter in ambient air [15, 16]. While ingestion of As is often associated with cancer and inflammatory disease, As also alters female reproductive health resulting in miscarriages, still birth, and gestational abnormalities [17, 18]. These reproductive failures following As exposure may be compromising the integrity of the ovum, uterus, and fetus. *In vitro* analysis demonstrated that oocytes exposed to 2 μg/mL of As for 2 hours resulted in chromosome misalignments during a disrupted meiosis I and severe chromosome spreading during disrupted meiosis II [19]. *In vivo* experiments also demonstrate the dangers of As on uterine health. In a study where rats were exposed to various doses of As (50, 100, and 200 ppm) *via* drinking water, the animals exposed to high As doses (100 and 200 ppm) exhibited a thinning of the uterine horns compared to the lowest As dose used and non-exposed animals, with the thinning more severe in the 200 ppm group compared to 100 ppm [20]. Moreover, gross anatomy and H&E analysis of uterine cross sections from all four groups showed that As exposure decreased the overall weight and size of the uterus, and altered epithelium invagination [20]. Further analysis demonstrated that As exposure also altered endometrium and myometrium thickness and morphology in a dose dependent manner [20]. With increased As doses, there was also a dose-dependent decrease in plasma levels of important hormones that govern the menstrual cycle and uterine health, estradiol, progesterone, FSH, and LH [20]. Exposure to As also affects embryo viability and implantation. Embryos cultured with As doses higher than 250 nM result in poor survival after 72 hr [21]. Moreover, embryos cultured in 500 nM of As for 72 hr exhibited a high number of blastomere cells containing fragmented DNA resulting in apoptosis [21], a phenomenon that may explain how As exposure at low levels in the uterine lumen may promote miscarriage, congenital defects, and still birth.

Cadmium (Cd), found in rocks and soils [22], is often found in agricultural products, such as rice and seafood [23, 24]. Cd accumulates in the body [25] and may affect reproductive health *via* its ability to interfere with Zinc homeostasis *via* displacement [26]. Cd can be excreted from the body through urine and feces, but at very low rates and is therefore predominantly stored in the body [24]. Cd is tightly bound to metallothionein and can remain in the human body for over 10 years. Exposure to Cd via drinking water (32 mg/L for 35 days) resulted in reduced ovulated oocytes and a lower percentage of oocytes in meiosis II compared to control [27]. By altering oocyte maturation, the Cd exposure rendered these

oocytes incompetent by impairing embryonic development from single cell to blastocyst [27]. Damage to the oocytes and embryonic development following Cd exposure was likely caused by the disruption in alpha-tubulin, actin, and increased H3K9me2 and H4K12ac levels [27]. Cd also affects the integrity of the uterus and ovaries. Caucasian and Asian females often suffer from uterine fibroids that may lead to uterine bleeding and pelvic pain [28]. In a study examining age and metal exposure through a rice-fish diet, women with uterine fibroids presented with higher levels of Cd in their blood compared to women without fibroids [28]. Interestingly, higher blood concentrations of Cd correlated to higher fibroid volumes [28]. Similarly, analysis of uterine morphology demonstrated that oral Cd administration increased the endometrial thickness in Wistar rats [29]. Cd-exposed mice also presented with degeneration loci in the corpora luteum of the ovaries as well as evidence of damaged oocytes [29]. Cd-induced damage to the oocytes, ovaries, and the uterus can all contribute to poor reproductive health.

Chromium (Cr) is commonly found as trivalent Cr and hexavalent Cr. While trivalent Cr is considered a nutritional supplement found in foods and health supplements safe for human consumption [30], hexavalent Cr exposure results in DNA damage, such as DNA strand breaks, DNA protein cross links, and Cr-DNA adducts [31] that may contribute to carcinogenesis [31, 32] and adverse effects to reproductive health [31]. Numerous Willits residents reported adverse health outcomes following exposure to hexavalent Cr waste from a machine plant in Willits (a town in Mendocino County, CA) that was dumped into local creeks and contaminated the ground water [31]. Examination of the longitudinal hospital data demonstrated a much lower birth rate in Willits compared to the rest of the county (ROC) that did not improve until 12 years after the plant was closed, and therefore was associated with the contamination emanating from the plant [31]. Willits residents also experienced a higher incidence of abnormal birth weight and birth defects compared to ROC, which also improved following the plant closure [31]. Unfortunately, there were some persistent adverse effects, such as higher risk of miscarriage, damage to reproductive organs, and development of neoplasms compared to ROC [31]. The reason reproductive damage persisted past a generation following the plant closure may result from the effects of hexavalent Cr on fetal ovarian development. To study the adverse effects of Cr to the development of ovarian tissue, Stanley *et al*. exposed ovaries from rat embryos to hexavalent Cr [33]. Their study demonstrated that while control ovaries contained tightly packed germ cells in germ cell nests (GCN), the hexavalent Cr exposure had damaged the GCN resulting in damaged and dead oocytes and granulosa cells [33]. Examination of the primordial and primary follicles showed degeneration that may result in an inability to ovulate during the menstrual cycle [33]. After 9 days of hexavalent Cr exposure, the embryonic rat ovarian tissue presented high levels of Caspase 3, BAX, and p53, as well as downregulation of oocyte-specific proteins BMP-15, GDF-9 and cKit [33] that together contribute to lack of mature oocytes during ovulation that would be successfully fertilized. The high risk of miscarriage and diminished birth rate observed in areas with high ambient Cr (as found in Willits [31]), may not be solely due to damage on the ovarian tissue, but also the uterus. Histological analyses of uterine tissue isolated from rats exposed to Cr demonstrated atrophy of endometrial glands, accumulation of fibrous tissue, and hyperplasia of the uterine epithelium [34] that may affect successful implantation or gestation, which may contribute to the increased risk of miscarriage observed in humans.

Metal pollutants and male fertility

Mammalian male fertility is also affected by diet and environment. Successful fertility depends on the integrity of the testicular tissue, generation of quality sperm (numerous and motile), various genetic predispositions. Upon reaching puberty, mammalian males can generate several million sperm per day. The number and motility of sperm, as well as the genetic content in the sperm can be altered by various external stimuli. For example, injury to testicles by change in temperature or mechanical injury can affect quality of sperm. Here we will present how exposure to non-essential metals in the ambient environments may affect testicular tissue and generation of healthy, functional sperm.

Epidemiological studies examining environmental exposure to As and various aspects of male infertility

demonstrated that men exposed to As exhibited chromosomal alterations in sperm [35] and erectile dysfunction [36]. In a study examining semen quality with concentration of various As species in the urine, higher urine levels of inorganic As and total As were found in males exhibiting "unexplained infertility" compared to fertile males [37]. Rats treated with As resulted in decreased testes weight compared to control rats [38]. The As exposure reduced testosterone levels in the serum and within the testicles [38]. Moreover, compared to control rats, the testes in the As-treated rats also have lower levels of LDH, ALP, and ACP, which are markers of normal testicular activity [38]. Maintenance of testicular tissue is an important part of producing healthy sperm. Exposure to As was shown to diminish the number of sperm within the testicles and epididymis [38], which contain reserve sperm and the daily produced sperm. These diminished numbers of sperm also had limited motility and presented with increased sperm abnormalities [38]. Diminished sperm number and increased sperm abnormalities were induced by As genotoxicity. Analysis of Comet assay demonstrated that rats exposed to As exhibited damaged spermatozoa DNA [39]. Arsenic can also cause these sperm abnormalities *via* altered expression of 70 proteins (36 up-regulated and 34 down-regulated) and 13 metabolites (8 increased and 5 decreased) [40]. Among these, 19 proteins and 2 metabolites were specifically related with spermatogenesis, sperm function, and fertilization [40]. The As-mediated damage to testes and sperm quality contributes to the observed decreased fertility in mammalian males.

Cd exposure is also deleterious to male fertility. In a study, fifty healthy male volunteers were recruited and provided semen and blood samples. Examinations showed that the mean concentrations of Cd was 8.18 ± 1.6 ng/ml in blood samples and 2.56 ± 0.9 ng/ml in semen samples [25]. Additionally, a significant positive correlation was demonstrated between Cd blood levels, number of immotile spermatozoa, and teratozoospermia index (TZI) [25]. In 1957, Pařízek demonstrated that rats administered Cd salts exhibited damage of the testes, the seminiferous epithelium, and interstitial tissue [41], which essentially mimicked castration. Treatment with Zinc prevented the Cd-mediated damage [41]. Cd exposure in various animals also caused testicular damage resulting in diminished weight, tissue edema, areas of hemorrhage, necrosis, and loss of germ cells [42] that may all contribute to sterility. After Cd enters testicular tissue, it then accumulates in spermatogonia, spermatocytes, spermatid and spermatozoa [43]. In rats, the accumulation of Cd in the spermatogonia and spermatocytes leads to a decrease in both cells types [43]. Elevated administration of Cd and prolonged exposure results in reduced sperm concentration due to increased apoptosis of sperm cells that is comparable to what is observed in cigarette smokers (as cigarette smoke contains high levels of Cd) [43]. Cd exposure not only reduces the number of sperm in semen, but also affects sperm motility. Sperm motility is essential for travel through the female reproductive tract in order to fertilize an ovulated ovum. Sperm analyzed from rats exposed to Cd displayed a significant reduction in motility, distance travelled, and velocity [44], all of which would contribute to semen unable to achieve fertilization of ovum. Moreover, the sperm from the rats treated with Cd contained a significantly lower percentage of sperm with normal morphology, with a majority displaying sperm head defects and flagellum described as "knob-wisted" [44].

The Cr-mediated low birth rate and gestational defects observed in the Willits residents [31] may also be due to damage in male reproductive health. Occupational exposure present with decreased sperm count and motility [45]. Examination of trace metals in seminal fluid demonstrated a correlation of elevated Cr levels to donors presenting with oligospermia (few sperm in semen) and azoospermia (no sperm in semen) compared to males with normal sperm number [46]. These sperm abnormalities may be due to increased apoptosis and DNA fragmentation found in the testes [45]. The reproductive abnormalities can also persist in the second generation of males. Pregnant rats treated with Cr from gestational day 12 to 21.5 produced males with reduced fetal Leydig cells and their proliferative potential [47]. Due to advancements of *in vitro* fertilization, reproductive science may overcome low, immobile sperm. However, Cr exposure may also induce cytotoxicity thus reducing successful fertilization and embryo development [48]. Sperm isolated from healthy mice were treated

with increasing doses of Cr for 3 hours prior to fertilization [48]. Following Cr exposure, analysis showed that higher Cr doses correlated with diminished live sperm and more dead sperm [48]. Live sperm from Cr-treated samples also exhibited decreased acrosome reaction (the sperm's penetration of the ovum), resulting in less fertilized eggs [48]. Blastocyst generated by Cr-exposed sperm limited cell proliferation compared to blastocyst from untreated sperm [48]. Further analysis of the blastocysts demonstrated that the Cr-exposed sperm also diminish expression of pluripotent cell markers (sox2, pou5f1, and klf4) and trophectroderm gene expression (eomes, cdx2, and krt8) [48]. All together these studies demonstrate the detrimental effects of Cr exposure on various aspects of male reproductive health.

Metal-mediated pathways associated with cancer in reproductive health

As, Cd, and Cr are toxic metals that induce cytotoxic and genotoxic injury that transform epithelial cells to adopt cancer cell phenotypes, such as anchorage-independent growth through upregulation of SATB2 [49-51]. SATB2 (special AT-rich sequence-binding protein 2) regulates gene expression by changing chromatin structure [49-51]. Aberrant SATB2 expression is also associated with pathologies of reproductive tissue, such as ovarian cancer [52], uterine fibroids [53, 54], and neuroendocrine prostate tumors [55]. Exposure to these metals during implantation and gestation may aberrantly upregulate SATB2 in the embryo resulting in the development of teratomas resulting in miscarriage or still birth.

As exposure downregulates the microRNA miR-31 in epithelial cells undergoing transformation [50]. miR-31 regulates different cellular processes by targeting genes controlling cell proliferation, apoptosis, differentiation, and cell motility [56]. Thus, it is plausible that miR-31 also plays important role in various aspects of reproductive health. Interestingly, patients with germ cell aplasia (male infertility due to sole presence of Sertoli cells in semniferous tubules) expressed less miR-31 in their testes compared to healthy men [56], which may suggest miR-31 regulates pathways necessary for early sperm development. The endometrium of the uterus undergoes elevated levels of miR-31 during embryonic implantation and it is postulated that the miR-31 expression plays a role in immune-tolerance thereby securing successful implantation and decreasing risk of miscarriage [56].

All together, these various studies suggest that the alterations ambient, non-essential metals induce to promote carcinogenesis may also contribute to the observed reproductive adversities observed in patients and in animal studies. Understanding shared pathways may aid in improving fertility and prevention of metal-induced carcinogenesis.

CONFLICT OF INTEREST STATEMENT

Neither author has any conflicts of interest to report.

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