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EDITED BY

Yong Song,
Michigan State University, United States

REVIEWED BY

Dalei Zhang,
Nanchang University, China
Sudipta Maitra,
Visva-Bharati University, India

*CORRESPONDENCE

Li Xiao,
✉ xiaoli2006929@126.com

†These authors have contributed equally to this work

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Fertility loss: negative effects of environmental toxicants on oogenesis

Xiaoxi Yao^{1,2†}, Weijing Liu^{3†}, Yidong Xie^{1,2}, Mingrong Xi^{1,2} and Li Xiao^{1,2*}

¹Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu, Sichuan, China, ²Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, China, ³Breast Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

There has been a global decline in fertility rates, with ovulatory disorders emerging as the leading cause, contributing to a global lifetime infertility prevalence of 17.5%. Formation of the primordial follicle pool during early and further development of oocytes after puberty is crucial in determining female fertility and reproductive quality. However, the increasing exposure to environmental toxins (through occupational exposure and ubiquitous chemicals) in daily life is a growing concern; these toxins have been identified as significant risk factors for oogenesis in women. In light of this concern, this review aims to enhance our understanding of female reproductive system diseases and their implications. Specifically, we summarized and categorized the environmental toxins that can affect oogenesis. Here, we provide an overview of oogenesis, highlighting specific stages that may be susceptible to the influence of environmental toxins. Furthermore, we discuss the genetic and molecular mechanisms by which various environmental toxins, including metals, cigarette smoke, and agricultural and industrial toxins, affect female oogenesis. Raising awareness about the potential risks associated with toxin exposure is crucial. However, further research is needed to fully comprehend the mechanisms underlying these effects, including the identification of biomarkers to assess exposure levels and predict reproductive outcomes. By providing a comprehensive overview, this review aims to contribute to a better understanding of the impact of environmental toxins on female oogenesis and guide future research in this field.

KEYWORDS

oogenesis, heavy metal, endocrine disruptors, smoke, agrochemicals

1 Introduction

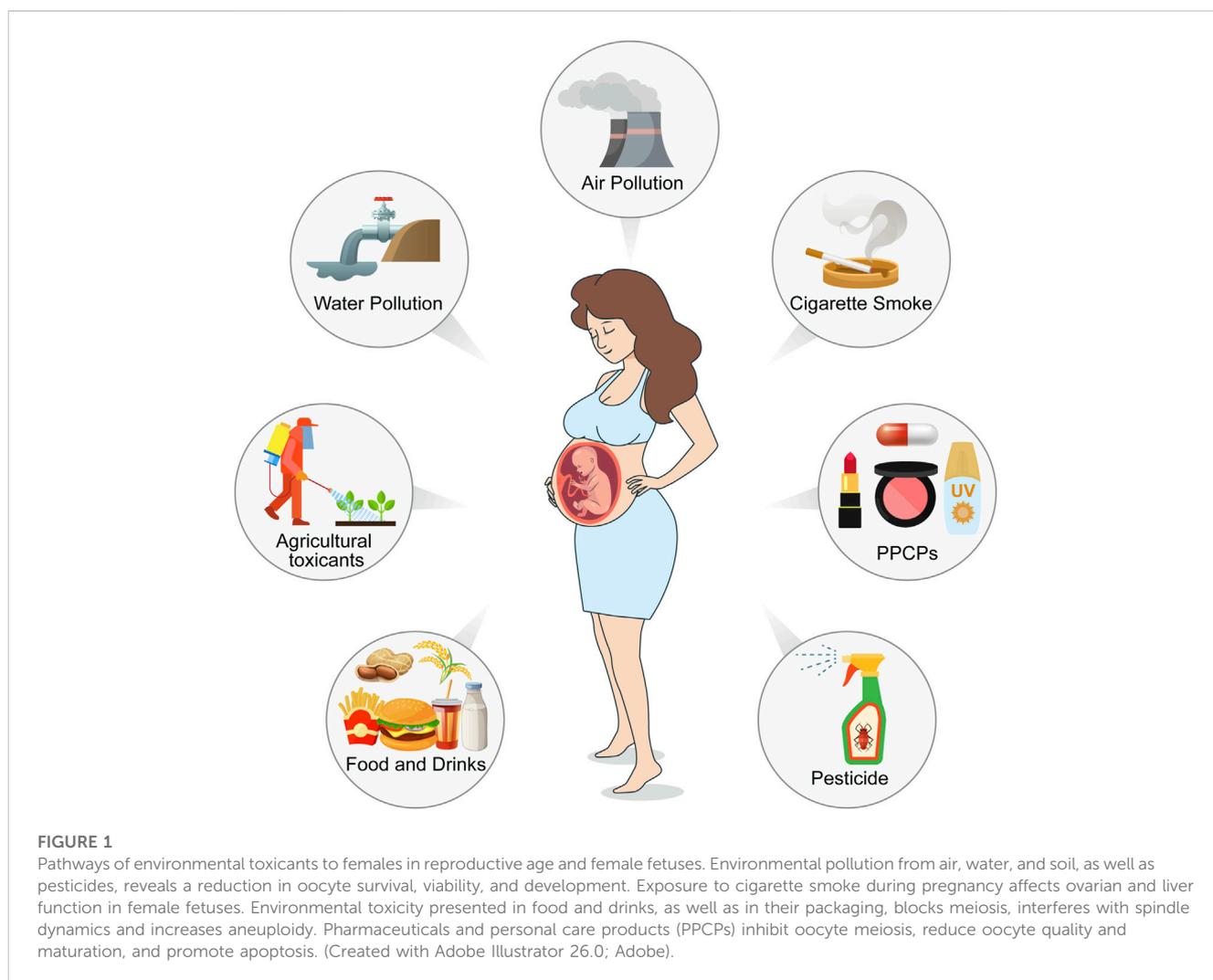
In recent years, a global decline in fertility rates and a high incidence of human infertility has been observed (GBD, 2019 Demographics Collaborators, 2020; Vollset et al., 2020). The World Health Organization (WHO, 2023) reported an estimated 17.5% lifetime prevalence of 2022 global infertility cases, and approximately one in six people experienced infertility at some stage in their lives; ovulatory disorders, the most common cause, account for approximately 25% of all infertility diagnoses (Carson and Kallen, 2021). Oogenesis is a crucial step in the development of female ovulatory function and is an important factor affecting fertility. Any abnormalities in either link can lead to defective oogenesis; for example, some environmental contaminants may interfere with

the development of oocytes at the premeiotic or early prophase periods, resulting in chromosomal aberrations in the ova and affecting women's reproductivity consequently (Foster and Hughes, 2011).

Environmental toxicants are a class of chemical or biological substances capable of compromising human health, including heavy metals, cigarette smoke, pesticides, plastic products, pharmaceuticals and personal care products (PPCPs), food toxicants, and fluorides. Females are exposed to these toxicants through environmental pollution, food, cosmetics, and agricultural and industrial products (Figure 1). These ubiquitous toxicants may be implicated in ovarian and oocyte development via anatomical abnormalities and endocrinological dysfunction. For example, some endocrine disruptors, such as bisphenol A (BPA), have been reported to be crucial risk factors for endometriosis, endometrial cancer, polycystic ovary syndrome, and other estrogen-dependent diseases (Kandaraki et al., 2011; Priya et al., 2021; Stavridis et al., 2022; Stephens et al., 2022); furthermore, it may affect oocyte maturity, fertilization, and implantation, leading to higher infertility and miscarriage

rates (Bloom et al., 2011; Ehrlich et al., 2012b; 2012a; Caserta et al., 2013). Heavy metal concentrations in the human body are associated with female reproductive disorders, preterm births, and stillbirths (Rzymiski et al., 2015). It has been shown that heavy metals, such as cadmium, accumulate in embryos from the four-cell stage and inhibit progression to the blastocyst at a higher dosage, which may reduce the possibility of a successful pregnancy (Thompson and Bannigan, 2008).

Pregnant women in the United States are reported to be exposed to 43 or more chemical toxins (Woodruff et al., 2011), which can elicit detrimental effects on fetal development and maternal health. Therefore, it is vital to investigate the effects of environmental toxicants on oogenesis. Because conditions such as polycystic ovary syndrome (PCOS) and premature ovarian insufficiency involve multiple risk factors, it is difficult to establish the role of toxicants. This review mainly focuses on the effects of environmental toxicants on female oogenesis, including the types of toxicants and the mechanisms that cause damage (Figure 2), in order to gain a better understanding and provide guidance for future research.



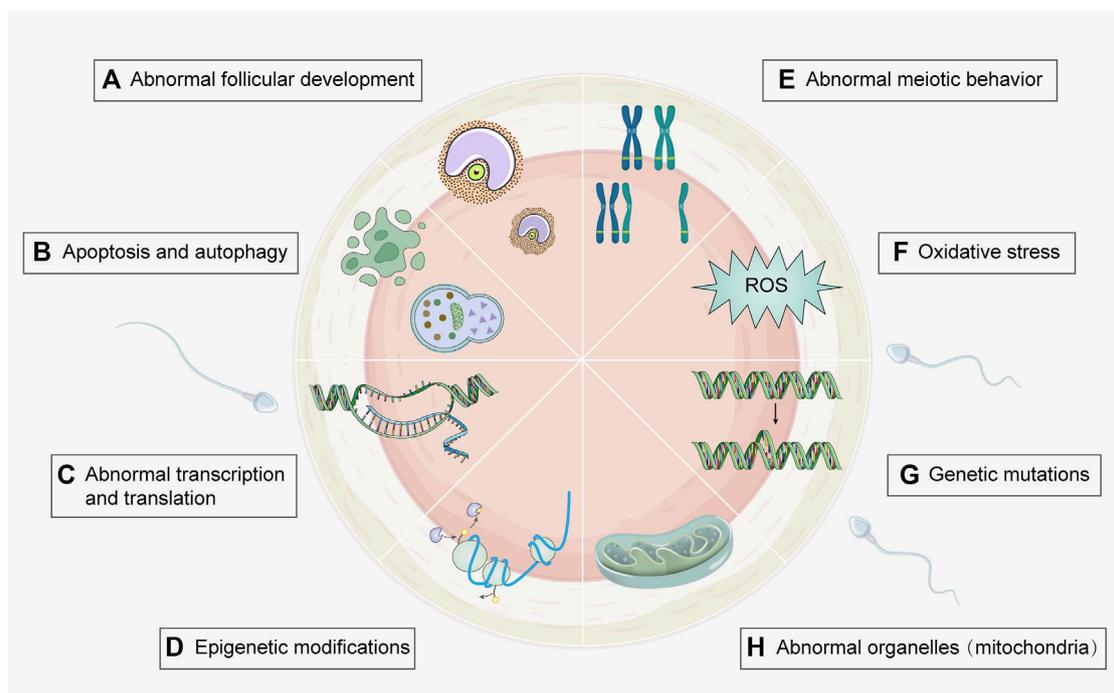


FIGURE 2

Toxic mechanisms of environmental toxicants on oogenesis process. Several genetic and molecular mechanisms involved in environmental toxicity can be underlying their effects on oogenesis. Associated mechanisms include **(A)** Abnormal follicular development (e.g., heavy metal, cigarette smoke, and PPCPs); **(B)** Apoptosis and autophagy (e.g., heavy metal, cigarette smoke, agricultural toxicants, food toxicant, and PPCPs); **(C)** Abnormal transcription and translation (e.g., agricultural toxicants); **(D)** Epigenetic modification (e.g., agricultural and food toxicants); **(E)** Abnormal meiotic behavior (e.g., heavy metal, cigarette smoke, agricultural and food toxicants); **(F)** Oxidative stress (e.g., heavy metal, cigarette smoke, food toxicants, and fluorides); **(G)** Genetic mutations (e.g., cigarette smoke and agricultural toxicants); **(H)** Abnormal organelles (e.g., agricultural and industrial toxicants). Detailed toxicants and associated mechanisms are provided in [Supplementary Table S1](#). (Created with Adobe Illustrator 26.0; Adobe).

2 The process and influencing factors of oogenesis

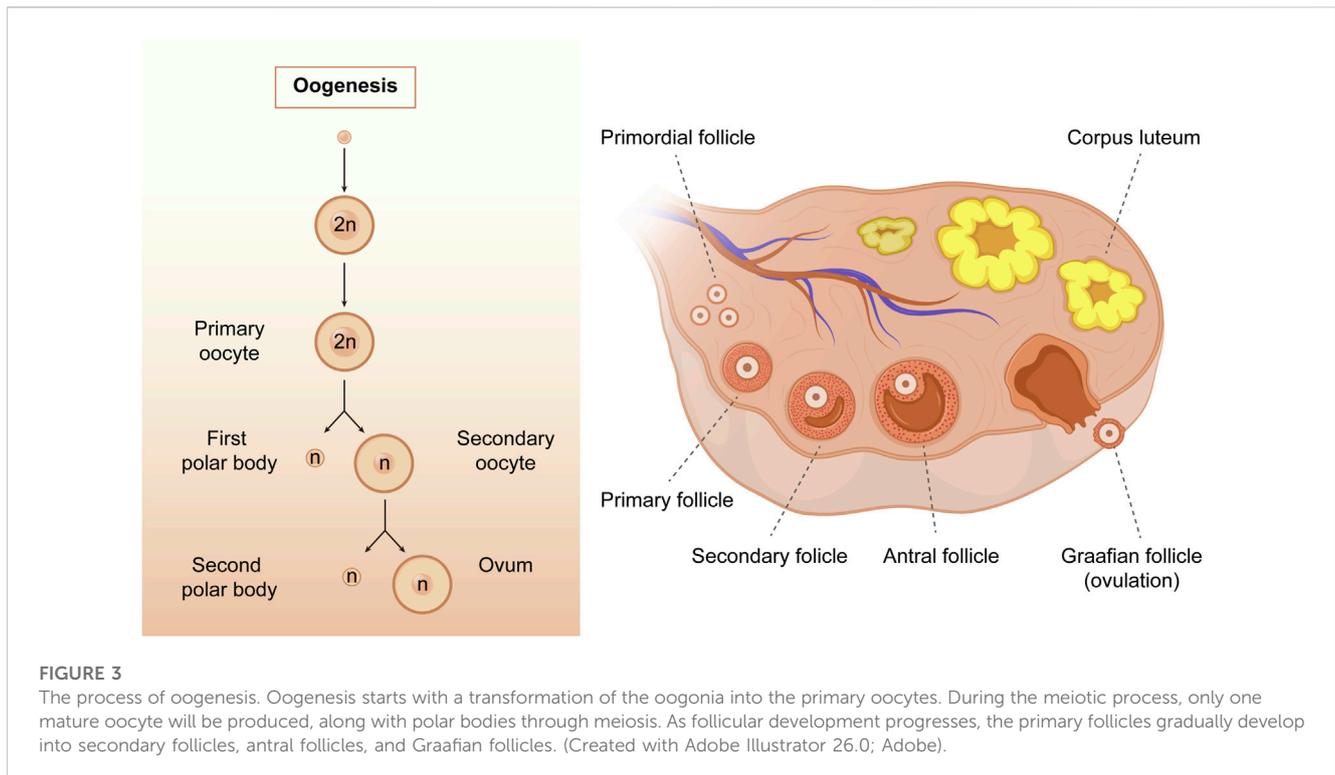
2.1 The multiplication, growth, and maturation of the oocyte

Oogenesis is a complex process by which female germ cells undergo a series of developmental changes to become mature oocytes. During the multiplication phase, primordial germ cells undergo mitotic division to form a large pool of oogonia that serve as precursors for primary oocytes (Gosden, 2002; Bukovsky et al., 2005). Oogonia multiplies mitotically and differentiates into primary oocytes, which are formed when oogonia undergo the first stage of meiosis. The growth phase is characterized by a significant increase in oocyte size, follicle formation, and accumulation of cytoplasmic components that support the growth and development of the embryo (Schultz et al., 1979). The hormonal regulation of oogenesis is critical, particularly during the growth phase of primary oocytes; the hypothalamus-pituitary-gonadal axis is activated during puberty, resulting in increased estrogen and follicle-stimulating hormone production (Spaziani et al., 2021). During the meiotic phase, primary oocytes undergo meiosis I and II. Meiosis I results in the formation of two haploid cells: a smaller first polar body (PB1) and a larger secondary oocyte. Meiosis II is arrested during metaphase II (MII) until

fertilization. Ultimately, the mature ovum and polar bodies were formed (Figure 3). The mature ovum is released during ovulation and can be fertilized by sperm to form a zygote.

2.2 Factors affecting the process

Metabolism plays a pivotal role in the absorption of chemicals, and alterations in metabolism during pregnancy may render the developing fetus susceptible to various environmental toxins (Singh L. et al., 2020). The early stage of pregnancy is particularly delicate; it represents a critical window for fetal organogenesis. Exposure to various environmental toxins can disrupt the delicate balance between signaling pathways and gene expression that regulates oogenesis (Sadeu and Foster, 2011b; Sánchez and Smitz, 2012). Environmental toxins, like heavy metals, pesticides, and endocrine disruptors, have been proven to interfere with the proliferation and differentiation of primordial germ cells during the multiplication phase of oogenesis. Exposure to certain pesticides is linked to a decrease in the number of primordial germ cells and the size of the primordial follicle pool (Legoff et al., 2019), ultimately reducing the number of oocytes available for ovulation. Additionally, endocrine disruptors such as BPA, phthalates, and polychlorinated biphenyls (PCBs) alter the balance of hormonal signaling pathways that regulate oogenesis (Liu S.-Z. et al., 2016; Wang et al., 2016; Gonsioroski et al., 2022).



During the growth phase, environmental toxicants disrupt the hormonal balance in the reproductive system, altering the time and progression of oogenesis; particularly, polycyclic aromatic hydrocarbons (PAHs) exposure can interfere with the proper functioning of the hypothalamic-pituitary-gonadal axis, which regulates the production and release of sex hormones (Bolden et al., 2017; Yin et al., 2017). This disruption can lead to delayed onset of puberty, changes in menstrual cycles, and impaired fertility.

Several studies have reported that exposure to environmental toxicants during the meiotic phase can cause chromosomal aberrations, meiotic spindle defects, and abnormal distribution of chromosomes during cell division, resulting in aneuploidy, which is the presence of an abnormal number of chromosomes in a cell (Coticchio et al., 2015; Ding et al., 2020; Zhang et al., 2020). Aneuploidy is a significant cause of pregnancy loss and developmental disorders such as Down syndrome (MacLennan et al., 2015). Environmental toxicants have harmful effects on oogenesis and meiosis, leading to adverse reproductive outcomes; therefore, it is essential to identify and minimize exposure to environmental toxicants to protect reproductive health and ensure reproduction.

3 Environmental toxicants and oogenesis

3.1 Heavy metals

Oogenesis requires the involvement of various enzymes and trace elements; therefore, metals such as zinc (Zn), iron (Fe), and copper (Cu) are essential in oogenesis. Notably, there are two sides to these essential metal ions; their high levels have toxic effects on

the oocytes (Cardoso-Jaime et al., 2022) and may be associated with female infertility (Li et al., 2020). Additionally, heavy metals, such as cadmium (Cd), lead (Pb), mercury (Hg), and Cu, can damage reproductive health as common environmental toxicants, and arsenic (As) is a heavy metal analog often included in studies. The mechanisms are summarized in [Supplementary Table S1](#).

3.1.1 Cadmium

Cd is a heavy metal endocrine disruptor. Numerous animal studies and epidemiological investigations have revealed that Cd abundance in the atmosphere, drinking water, food, and soil is hazardous to health and female fertility; it accumulates in the ovaries and affects ovarian function (Wang et al., 2015).

Research has revealed that Cd exposure reduces the number of oocytes, inhibits meiosis in oocytes, and reduces oocyte quality (Zhu et al., 2018). The underlying mechanisms include cytoskeletal organization, mitochondrial function, and histone modifications. Cd exposure inhibited meiosis by interfering with spindle assembly, chromosomal alignment, and actin cap development. Chronic Cd exposure has been found to disrupt chromosomal alignment and kinetochore-microtubule attachment, leading to the emergence of aneuploid oocytes, significantly reducing the ability of female mice to conceive (Dong et al., 2020).

Oocyte quality declines due to increased reactive oxygen species (ROS) levels and apoptosis induced by exposure to Cd. These changes resulted in abnormal mitochondrial distribution, a lack of energy, and DNA damage (Cheng et al., 2019). Additionally, Cd exposure affects the levels of global histone demethylation (H3K9me2), deacetylation (H4K12ac), lysine methylations (H3K9me3), acetylations (H3K9ac), and the global DNA methylation (5mC) in oocytes; these histone modifications are greatly associated with oocyte dysplasia and, consequently, the

failure of embryonic development (Zhu et al., 2018; Cheng et al., 2019). Furthermore, it is reported that Cd interferes with the cyclical changes in maturation promoting factor (MPF) activity by altering the expression of MPF-related genes, which delays meiosis in oocytes (Liu et al., 2018).

3.1.2 Arsenic

As and its compounds are extensively used in industry and agriculture (Chandravanshi et al., 2018). It is a toxic substance that affects the structure and function of female gonads, significantly reducing female fertility. The available results suggest that As inhibits oocyte meiosis and embryonic development. Numerous studies have demonstrated that arsenic trioxide significantly reduces mitochondrial DNA (mtDNA) copy number, causes mitochondrial damage, increases ROS levels, and decreases adenosine triphosphate (ATP) content (Zhang et al., 2011). Other studies have had similar results, and oocyte autophagy has been reported. These mechanisms can lead to a decrease in oocyte quality and quantity and cause embryonic arrest (Ommati et al., 2020; Kang et al., 2022). Additionally, aberrant expression of the global histone lysine trimethylation (H3K4me3), H3K9me3, and 5mC was observed in arsenic-exposed oocytes, indicating that As interferes with meiotic processes in oocytes by influencing DNA methylation and histone modifications. Studies have consistently reported that chronic As exposure in parental generations leads to cross-generational genotoxicity and global DNA methylation changes and is associated with reproductive defects in rats, implying that chronic As exposure may affect the health of offspring (Nava-Rivera et al., 2021).

3.1.3 Lead

Pb is a metal that enters the human body through various routes, including water, air, and soil contamination. It poisons the blood and the nervous system and is associated with lower live birth rates in women having assisted reproductive treatments (Butts et al., 2021). Few studies have investigated the effects of Pb exposure on the female reproductive system. A comparison of Cd with Pb revealed a reduction in oocyte viability and development; however, Pb was significantly less toxic than Cd (Nandi et al., 2010; Slaby et al., 2017). Furthermore, Pb exposure caused histopathological and ultrastructural changes in oocytes and ovarian tissues. Simultaneously, the activities of catalase, glutathione peroxidase, total superoxide dismutase, and glutathione-S-transferase decreased, and malondialdehyde levels increased in the ovaries of mice. Additionally, Pb activates the Nrf2/Keap1 pathway, inhibiting oocyte maturation and fertilization by inducing oxidative stress (Jiang X. et al., 2021). Notably, when the Pb level was increased to 10 µg/mL, over 50% of the oocytes died (Nandi et al., 2010).

3.1.4 Mercury

Hg is a common heavy metal used in industrial, household, and cosmetic products. Hg gas and its compounds are highly toxic and enter the body via respiratory inhalation, ingestion, and skin contact, causing systemic damage. Hg exposure can be assessed by measuring the levels of Hg in blood, urine, and hair; its exposure is strongly associated with biochemical pregnancy and live birth rates in women undergoing *in vitro* fertilization (IVF) (Butts et al., 2021).

Hg concentrations in hair may be negatively associated with human oocyte production; however, some studies have concluded that hair Hg levels are not associated with ovarian stimulation outcomes, IVF pregnancy, or live birth rates (Dickerson et al., 2011; Wright et al., 2015). Investigations in a zebrafish model demonstrated that zebrafish ovaries in the Hg-exposed group revealed a reduction in the number of previtellogenic and early vitellogenic oocytes and atresia of the previtellogenic oocytes; however, there was no effect on the size of mature oocytes, suggesting that the toxic effects of Hg on oocytes are in the early stages of adulthood (Patel et al., 2022). The histomorphology of the ovary was altered by Hg vapor inhalation, resulting in a reduction in the number of primordial, primary, and graafian follicles and a significant increase in the total volume of atretic follicles. Additionally, irregularities in follicle and oocyte boundaries and edematous degeneration of follicular granulosa cells have been observed in rats after Hg vapor intervention (Altunkaynak et al., 2016). Existing studies have demonstrated the effects of Hg exposure on oogenesis; however, the exact mechanism of its toxic effects is unclear. Further research is needed to assess the impact of Hg exposure levels on fertility outcomes in women during their fertile period.

3.1.5 Copper

Cu is an essential trace element in the human body. The Cu transport system is essential for follicular development in pigs, and copper deficiency negatively affects follicular development. In an *in vitro* experiment, administering appropriate concentrations of Cu reduced oxidative stress and apoptosis, promoted oocyte maturation, and improved oogenesis and blastocyst formation rates (Choi et al., 2021; 2022). However, a study revealed that increased Cu levels in the follicular fluid might induce abnormal steroid synthesis and affect follicular development in patients with PCOS (Sun et al., 2019). The toxicity of Cu in the female reproductive system is gradually being considered; high Cu levels damage oocyte chromosome structure and cause abnormal dynamics of actin distribution, activating the Nrf2 signaling pathway and leading to increased ROS levels; ultimately, this leads to reduced oocyte quality in pigs (Chen et al., 2021; Zhan et al., 2022). Similar results were obtained in experiments using copper sulfate to treat sheep oocytes; glutathione supplementation corrected copper-induced oocyte damage (Ren et al., 2023). Excess Cu has been shown to have a toxic effect on oogenesis in animal studies. However, there is a lack of evidence in humans.

3.1.6 Other metal

In addition to the common heavy metal toxins, there are a growing number of studies on the toxicity of other metals. Thallium may affect oogenesis and is associated with early embryonic abortion (Liang et al., 2022). Recently, metallic tin compounds have received attention as important environmental contaminants. Tributyltin oxide (TBTO) exposure impairs oocyte maturation by inducing intracellular ROS accumulation, causing mitochondrial dysfunction, and disrupting cellular iron homeostasis; consequently, this reduces oocyte quality and interferes with embryonic developmental capacity (Xiao et al., 2021). Hexavalent chromium (CrVI) promotes oocyte apoptosis and alters cell cycle regulatory genes and proteins. Chromium (Cr) exposure during gestation causes premature ovarian failure in offspring F1 rats (Stanley et al., 2015).

In addition to occupational exposure, heavy metal toxins exhibit numerous exposure pathways. The reduction in toxicity (due to exposure to heavy metals) in reproduction is gradually being investigated. For instance, blueberry extracts have been shown to reduce the adverse effects of Cd on the ovaries (Izaguirry et al., 2017). Additionally, quercetin inhibits oxidative stress in germ cells (Mao et al., 2018), and glutathione antagonizes As damage in goat oocytes by preserving or maintaining mitochondrial function, gene expression, and anti-oxidative products (Ren et al., 2022). These studies explored the antioxidant properties of these pharmaceuticals in terms of their ability to mitigate heavy metal toxicity. Therefore, more preventive measures that can alleviate heavy metal toxicity should be explored, especially in foods with antioxidant components without side effects on humans.

3.2 Cigarette smoke

The toxic effects of cigarette smoke and its components on the reproductive system are extensively recognized. Exposure to cigarettes during pregnancy can affect ovarian and liver functions in female fetuses (Talbot and Lin, 2011; Fowler et al., 2014). The harmful components include PAH, nicotine, benzo(a)pyrene (BaP), pyrazine, 2-ethylpyridine, and 3-ethylpyridine. Recently, in addition to cigarette smoke, smokeless tobacco (ST) has similar toxic components and effects on the reproductive system (Laldinsangi, 2022), as presented in Supplementary Table S1.

3.2.1 Smoke

Some observational studies in humans have concluded that smoking does not significantly affect oocyte quantity or quality (Budani et al., 2017; Fréour et al., 2018; Ozbakir and Tulay, 2020). However, smoking delays egg cleavage and affects early embryonic development. Additionally, researchers have identified an association between smoking and lower fertilization and pregnancy rates in women undergoing IVF (Fréour et al., 2013; Budani et al., 2017). In animal studies, cigarette smoke extracts have been found to cause premature luteinization of mouse follicles, reduced follicle survival, a diminished diameter of zona pellucida-free oocytes, and PB1 abnormalities in mice (Sadeu and Foster, 2011a; Mai et al., 2014). Impaired sinus follicle growth in mice exposed to cigarette smoke persists after smoking cessation (Paixão et al., 2012). Furthermore, although cigarette smoke exposure did not significantly reduce the number of oocytes, a thicker zona pellucida, and shorter and wider spindle bodies were observed (Jennings et al., 2011). If the parental generation is exposed to cigarettes during pregnancy, in that case, the F1 generation female mice show elevated levels of oxidative stress in somatic oocytes and changes in mid-term II spindle bodies, which is a hazard that persists into sexual maturity (Camlin et al., 2016). Changes in microRNAs (miRNAs) involved in the regulation of cell proliferation and apoptosis were observed in MII oocytes from cigarette smoke-exposed mice. Additionally, cigarette smoke exposure activated *CYP2E1* and oxidative stress, impairing oocyte development (Sobinoff et al., 2013; Budani et al., 2019). In addition to first-hand smoking, second-hand and third-hand smoke (THS) can harm women's reproductive health. THS is the residual tobacco smoke that remains on surfaces or in dust after smoking. The main

component, 1-(N-methyl-N-nitrosamino)1-(3-pyridinyl)-4-butanol (NNA), affects mouse oocyte survival; it alters epigenetic modifications by increasing the risk of DNA damage and abnormal spindle morphology, decreasing 5mC and histone lysine methylation (H3K4me2) levels, and inducing apoptosis through mitochondrial dysfunction and ROS accumulation (Liu et al., 2019b; 2019a).

3.2.2 Nicotine

Nicotine is the primary toxic component of cigarettes, and its metabolite is cotinine. In an experiment using human fetal ovaries, the addition of nicotine significantly reduced the number of oocytes in fetal ovaries, indicating that nicotine may directly induce oocyte apoptosis (Cheng et al., 2018). Nicotine exposure is associated with reduced expression of mouse oocyte-specific genes, such as *NOBOX*, *LHX8*, *FIGLA*, and *SOHLH2*. In addition, mice injected with nicotine showed increased levels of oxidative stress and autophagy markers in ovarian cells, including upregulation of AMPK α -1, increased protein light chain 3 (LC3)-II/LC3-I ratio, and downregulation of AKT and mTOR (Wang et al., 2018). The metabolic products of cotinine have been found to reduce oocyte quality (Cheng et al., 2022); luteinizing hormone and follicle-stimulating hormone antagonize this effect (Liu W.-X. et al., 2021). Additionally, it has been suggested that melatonin increases MnSOD expression, reduces nicotine-induced intracellular ROS production, and maintains normal H3K4 and H3K9 demethylation and trimethylation in zygotic ovaries. These mechanisms enable melatonin to counteract damage to oocytes caused by nicotine and its metabolites (Wang et al., 2018; Liu et al., 2020; Cheng et al., 2022).

3.2.3 Polycyclic aromatic hydrocarbons

PAHs originate from the incomplete combustion of many substances, and the main route of human exposure is cigarette smoke. PAHs inhibit meiosis and promote apoptosis of primary chicken germ cells (Ge et al., 2012). During the immature stage, PAH-exposed mice exhibit a significant increase in the number of luminal follicles and inhibit oocyte maturation and follicular atresia. Transcriptome analysis suggested that this may be related to the upregulation of the PI3K/Akt signaling pathway and disruption of the calcium signaling pathway (Guo et al., 2022). BaP is a PAH that is established to be carcinogenic and toxic to the reproductive system. BaP affects oocyte meiosis in mice and impairs the quantity and quality of oocytes in offspring (Zhang et al., 2018). Several studies have shown that BaP reduces mitochondrial content and ATPs synthesis and increases the accumulation of reactive oxidants and genomic DNA 5mC levels in offspring oocytes (Sadeu and Foster, 2011b; Sui et al., 2020; Malott et al., 2022). In addition, BaP exposure impairs the meiotic process in mouse oocytes by disrupting normal spindle assembly, chromosome arrangement, and mitotic microtubule attachment, leading to the production of aneuploid eggs. It significantly reduces fertilization rates in mice by reducing the number of sperm bound to the egg zona pellucida and interfering with the gamete fusion process (Einaudi et al., 2014; Zhang et al., 2018). Pyrazine, 2-ethylpyridine, and 3-ethylpyridine are harmful cigarette components, which inhibit oocyte maturation and affect sperm fertilization in women (Wu and Liu, 2012).

3.3 Agricultural and industrial toxicants

3.3.1 Herbicides

Glyphosate-based herbicides are common herbicides; however, whether they are carcinogenic to humans is controversial. Glyphosate exposure has been suggested to impair oocyte quality in mid-stage II mice by disrupting microtubule tissue centers and chromosomes, significant depletion of intracellular zinc bioavailability, and enhanced accumulation of reactive oxygen clusters (Spinaci et al., 2020; Yahfoufi et al., 2020; Zhang et al., 2021). Low doses of glyphosate adversely affect oocyte maturation and early embryonic oogenesis by increasing the levels of ROS, spindle defects, and chromosome misalignment (Cao et al., 2021). Its adjuvant is used to increase its herbicidal effect, and available studies indicate that the addition of an adjuvant enhances its toxicity and increases oocyte ROS levels (E et al., 2022). Fenoxaprop-ethyl is a post-emergence herbicide with an aryloxyphenoxypropionate moiety designed to prevent fatty acid synthesis by inhibiting acetyl coenzyme A carboxylase. Exposure to FE disrupts the oocyte cytoskeleton and induces ROS accumulation, affecting meiosis (He et al., 2019b). Atrazine is commonly used as a herbicide; exposure of embryos to Atrazine affects meiosis prophase I, reduces the number of primordial follicles, and increases the incidence of polyzygotic follicles in adult mice (Gely-Pernot et al., 2017). Furthermore, exposure to Atrazine significantly downregulates MLH1 in *Drosophila*, with transcriptional and translational defects, reduced double-strand breaks, and association complex formation; this leads to reduced fertility, reduced numbers of mature oocytes, abnormal ovarian follicle distribution, increased apoptosis, and abnormal embryonic development after fertilization in *Drosophila* (Vimal et al., 2019).

Generally, the toxic effects of herbicides on oocytes are evident. Some studies have investigated the drugs that can be used to treat this condition. Current evidence suggests that melatonin has a mitigating effect on the ototoxicity of glyphosate-based herbicides and fenoxaprop-ethyl, and its possible mechanisms include the prevention of glyphosate-based herbicides-induced oocyte deterioration and activation of its downstream signaling events (pERK/ERK) by protecting G-protein estrogen receptor (GPER/GPR30) expression and regulating the levels of regulatory hormones (He et al., 2019a; Cao et al., 2021; Zhang et al., 2021).

3.3.2 Pesticides

Pesticides are a class of endocrine disruptors extensively used in crop production. Common categories of pesticides include organophosphorus pesticides, neonicotinoids, formate insecticides, and pyrethroids.

The organophosphorus pesticide, malathion, significantly reduces oocyte survival and affects the regulation of genes for transcription, translation-related proteins, and mitochondrial function, affecting early oogenesis and oocyte viability (Bonilla et al., 2008; Flores et al., 2017). Methyl parathion (MP) is the most commonly used class of organophosphorus pesticide. MP exposure reduces the number of primordial follicles and increases DNA damage in granulosa cells. Additionally, it exerts a significant inhibitory effect on oocyte nuclear maturation and is associated with spindle malformation. Furthermore, MP-treated oocytes showed

higher cytoplasmic abnormalities and depleted glutathione levels (Nair et al., 2014; Satar et al., 2015). Gai et al. discovered that exposure to the organophosphorus pesticide diazinon (DZN) inhibited oocyte meiosis and reduced egg fertilization (Gai et al., 2022). Chlorpyrifos (CPF) is one of the most extensively used organophosphorus pesticides. Studies have shown that CPF exposure significantly reduces the extrusion rate of the PB1 and impaired MII oocytes. Exposure to 10 mM CPF disrupts meiotic cycle progression, leads to abnormal spindle and mitochondrial dysfunction and induces oxidative stress and apoptosis in porcine oocytes (Jiang Y. et al., 2021). 3-methyl-4-nitrophenol (PNMC), a degradation product of organophosphorus pesticides, significantly inhibits the resumption of meiosis in mouse oocytes (Han et al., 2018). Neonicotinoids are extensively utilized in modern agriculture. Additionally, thiamethoxam changes the expression of several oocyte genes associated with inflammation, apoptosis, and endoplasmic reticulum stress; it affects DNA integrity, promotes oxidative stress and endoplasmic reticulum stress, and induces apoptosis (Liu Y. et al., 2021). Acetamiprid (ACE) and imidacloprid are commonly used neonicotinoids. The effects of ACE and imidacloprid on porcine oocyte maturation *in vitro* have been reported previously. Irregular chromosomes were observed in the ACE- or imidacloprid-exposed groups and nuclear maturation rates were significantly reduced (Ishikawa et al., 2015). Formate insecticides are commonly used. Previous studies have shown that methomyl inhibits polar body extrusion in mouse oocytes. A significant increase in superoxide anion radicals in oocytes and a significant decrease in mitochondrial membrane potential in mid-stage II oocytes were observed in the methomyl-treated group, resulting in reduced mouse oocyte mass. After prolonged exposure to methomyl, mid-stage I mouse oocytes exhibit morphologically abnormal spindle bodies (He D. et al., 2022). Carbofuran (CF) has been banned in several countries and regions but remains an extensively used carbamate insecticide. CF induces programmed cell death dose-dependently and may alter spindle morphology by interacting with microtubules (MTs) assembly or impairing pericentriolar protein orientation. The inhibition concentration 50 (IC50) for 2000, 1,000, and 250 mM CF was calculated for the 6, 24, and 48 h incubation periods, respectively (Cinar et al., 2015). Pyrethroids are gradually replacing other insecticides. Cypermethrin, deltamethrin, and cyhalothrin are gradually replacing other insecticides, such as organophosphates. It is less toxic than traditional insecticides; however, it has been found to have adverse effects on animal fertility and may affect pregnancy outcomes in assisted reproduction (Tchounwou, 2004; Singh D. et al., 2020). Cypermethrin, deltamethrin, and cyhalothrin had no significant effect on oocyte survival at the concentrations tested. However, there was a concentration-dependent decrease in oocyte maturation rates in the experimental animals; additionally, abnormal spindle morphology and DNA double-strand breaks occurred. Furthermore, oxidative stress and apoptosis have been observed in the oocytes of mice exposed to deltamethrin (Petr et al., 2013; Jia Z.-Z. et al., 2019).

Specific types of insecticides have been found to affect egg cell production. Fipronil (FPN) is an extensively used phenylpyrazole insecticide that kills pests by blocking γ -aminobutyric acid (GABA)-gated chloride channels. FPN increases ROS levels and DNA

damage during porcine oocyte maturation and induces apoptosis and cell cycle arrest (Zhou et al., 2019). Methoxychlor (MXC) is a common cytotoxic and genotoxic organochlorine pesticide; MXC negatively affects oocyte meiotic maturation, primarily by cellular ROS metabolism impairment (Liu et al., 2016). Rotenone inhibited mitochondrial complex I. Rotenone treatment induced mitochondrial dysfunction and failure of mitochondrial biosynthesis and inhibited the maturation of porcine oocytes *in vitro* (Heo et al., 2022).

Pesticides include pesticidal agents used in agricultural production and varieties used in domestic mosquitoes and insect control, with more routes of exposure. Propolis has been suggested to alleviate the toxic effects of MXC, and its mechanism of action may be related to its antioxidant potential (El-Sharkawy et al., 2014). Notably, vitamin E has a protective effect in rats exposed to cypermethrin, increases glucose uptake in follicle cells and oocytes, and inhibits the biosynthesis of the pro-apoptotic protein caspase-3 (Molavi et al., 2016). Although pyrethroids have been extensively used as fewer toxic insecticides, the available evidence does not completely exclude the potential harm of such insecticides to female reproductive function or the female fetus, and further research is still needed in this area.

3.3.3 Fungicides

Fungicides are agricultural toxicants used in the cultivation of a wide range of crops. Dexamethasone zinc (MNZ) significantly reduced the number of oocytes, oocyte maturation rate, fertilization rate, fertility rate, fertility, and embryo development in F1 generation mouse pups (Esmail et al., 2019). As an endocrine disruptor, it has been suggested to induce progesterone secretion from granulosa cells, inhibiting the luteinizing hormone peak during ovulation (Dimisri et al., 2021). Captan alters the expression of multiple genes in oocytes; it triggers DNA damage, autophagy, and apoptosis, induces oxidative stress and mitochondrial dysfunction, disrupts mitochondrial structure and distribution, and depolarizes membrane potential (He Q.-K. et al., 2022). Azoxystrobin (AZO) is an extensively used fungicide that exerts fungicidal activity by inhibiting mitochondrial respiration. AZO exposure impairs oocyte maturation by increasing oxidative stress and mitochondrial dysfunction and reducing the integrity and spindle formation of microtubule organizing centers (MTOCs) and chromosome alignment (Gao et al., 2022).

3.3.4 Plasticizers

Plasticizers are increasingly used in domestic production. Di(2-ethylhexyl) phthalate (DEHP) is an extensively used plasticizer. As an endocrine disruptor, DEHP affects steroid production, sinus follicle growth, and primordial follicle production (Zhang et al., 2013; Zhou and Flaws, 2016; Gonsioroski et al., 2022). Animal studies have shown that DEHP exposure significantly reduces the number of primordial follicles during puberty and adulthood, possibly by accelerating the kinetic rate of follicle recruitment, decreasing or delaying imprinted gene methylation in oocytes, and increasing mid-term II spindle abnormalities in mature oocytes *in vitro* (Zhang et al., 2013). Maternal exposure to a mixture of phthalates affected folliculogenesis and steroidogenesis in F1 and F2 generation female rats and altered the expression of miRNAs in the F1 generation ovaries of female rats (Gonsioroski

et al., 2022). DEHP exposure alters ovarian miRNA expression in F1 generation rats and reduces the expression of H3K4me3, estrogen receptor (ER) VII, progesterone receptor (PR), and Notch2 signaling components (Mu et al., 2015; Gonsioroski et al., 2022; Li et al., 2023). Furthermore, it has been found that the combination of DEHP exposure and a high-fat diet has a synergistic effect, significantly increasing synaptic defects in meiosis and affecting folliculogenesis in the F1 generation (Mirihagalle et al., 2019).

Dibutyl benzodicyclohexylate (DBP) is an extensively used plasticizer that induces apoptosis in oocytes by increasing oxidative stress-induced DNA damage. DBP exposure during gestation disrupts the progression of meiotic prophase I in mouse oocytes, particularly from even-to coarse-lineage phases (Tu et al., 2019). In addition, DBP significantly reduced germinal vesicle breakdown and polar body extrusion in mouse oocytes and disrupted the cytoskeleton, and cortical granule-free domains of oocytes were disrupted (Li et al., 2019).

BPA is extensively used in the plastics industry, such as water bottles, containers, packaging, and toys, and is a common endocrine disruptor that causes delayed maturation of animal oocytes and significantly affects embryonic developmental potential (Ferris et al., 2016; Nakano et al., 2016; Saleh et al., 2021). Studies have shown that BPA affects the expression of AMH and AMH receptor II during oocyte maturation (Saleh et al., 2021). BPA activates the Gper/Egfr/Mapk3/1 pathway, which disrupts meiosis in zebrafish oocytes (Fitzgerald et al., 2015); it exerts toxic effects on oocytes by disrupting the cytoskeletal dynamics, inhibiting spindle stability, affecting epigenetic modifications, and inducing apoptosis and autophagy (Wang et al., 2016; Yang et al., 2020). In addition, BPA affects organelles in oocytes, causing mitochondrial dysfunction, abnormal mitochondrial distribution, abnormal endoplasmic reticulum distribution, abnormal Golgi apparatus structure, and lysosomal damage (Pan et al., 2021). Fluorene-9-bisphenol (BHFP), bisphenol S (BPS), and bisphenol AF (BPAF) are alternatives to BPA for the production of “BPA-free” plastics; however, they are harmful to living organisms. Studies have shown that BHFP inhibits the maturation of mouse oocytes *in vitro*, inhibits oocyte expansion at certain concentrations, and significantly reduces polar body excretion. Furthermore, they cause abnormal spindle assembly, reduced ATP levels, ROS accumulation, early apoptosis, and disturbed distribution of CGs in porcine oocytes (Ding et al., 2017; Jia Z. et al., 2019; Jiao et al., 2020). Similar to BPA, BPS can affect the expression of AMH and AMH receptors (Saleh et al., 2021). Notably, it may be not dose-dependent of the toxic effects of BPS, which affects the developmental quality of oocytes at a lower order of magnitude concentrations (Prokešová et al., 2020).

3.4 Pharmaceuticals and personal care products

3.4.1 Nanoparticle

Nanoparticles (NPs) are materials with at least one dimension less than 100 nm and are extensively used in cosmetics, food, health, and personal care products (Santacruz-Márquez et al., 2021).

Zinc oxide nanoparticles (ZnO NPs) are among the most widely used nanomaterials in industrial and commercial products (Huang et al., 2022). ZnO NPs inhibit oocyte meiosis, reduce oocyte quantity

and quality, and arrest early embryonic development by releasing zinc ions to produce cytotoxicity. ZnO NPs induce cytotoxicity by releasing zinc ions, which inhibit oocyte meiosis, reduce the number and quality of oocytes, and arrest early embryonic development. The mechanisms involved include mitochondrial and endoplasmic reticulum stress, leading to oocyte apoptosis and autophagy, disruption of the cytoskeletal structure, and a reduction in the extrusion rate of the PB1 (Zhai et al., 2018; Santacruz-Márquez et al., 2021; Huang et al., 2022). Animal experiments show the effects of ZnO exposure during gestation on DNA damage in mouse embryonic oocytes and ovarian reserve function in the offspring (Zhai et al., 2018). Notably, ZnO significantly affects cell-oocyte complex expansion; the toxicity of the NPs may be related to the release of ZnO ions and their internalization. Silicon dioxide coating reduces toxicity due to the expansion of the cumulus cell-oocyte complex (Camaioni et al., 2021).

3.4.2 Parabens

Parabens (PBs) are a family of alkyl esters, classified as methylparaben (MePB), ethylparaben (EP), propylparaben (PP), isobutylparaben (IBP), and butylparaben (BP) based on their alkyl chain, and are extensively used in cosmetics, food, and pharmaceuticals (Jeong et al., 2020).

MePB is primarily used in food, personal care, and baby care. A study of *in vitro* culture of porcine oocytes discovered that oocyte maturation was reduced; however, viability was not affected with a 50% lethal concentration (LC50) of 2028.38 μM and a 50% maturation inhibitory concentration (MIC50) of 780.31 μM (Barajas-Salinas et al., 2021). It inhibits oocyte maturation, possibly by inhibiting cumulus cell expansion and altering oocyte morphology (Barajas-Salinas et al., 2021).

IBP is extensively used in personal care products and cosmetics. *In vitro* studies in porcine oocytes showed that low concentrations (200 μM) of IBP significantly reduced the rate of PB1 expulsion but had no significant effect on oocyte expansion; however, high concentrations (400 μM) of IBP significantly affected both. Mechanistically, IBP-treated oocytes showed abnormal spindle bodies, chromosomal misalignment, abnormally distributed actin filaments, elevated levels of H3K9me3 and H3K27me3, and significantly increased oocyte ROS levels and apoptosis rates (Meng et al., 2020).

Additionally, BP is a common preservative, and *in vitro* oocyte cultures present with suppressed meiosis and reduced oocyte expansion, elevated ROS levels, abnormal mitochondrial distribution and function, DNA damage, apoptosis, autophagy, γ -H2AX, annexin V positivity, and significantly higher microtubule-associated LC3 expression (Jeong et al., 2020).

3.4.3 Other toxicants in personal care products

In addition to the substances mentioned above, there are ingredients in personal care products, such as antioxidants, stains, and antibacterial agents, which have been investigated and proven to have harmful effects on oocytes. Para-phenylenediamine (PPD), a common component of hair dyes, has significant toxic effects on human health (Dressler and Appelqvist, 2006). In mice, abnormal oocyte development and reduced fertilization ability with irregular distribution or absence of Juno proteins have been observed. PPD may affect spindle morphology and chromosome

aggregation in oocytes and may disrupt oocyte mitochondrial function, promote oxidative stress, and induce early apoptosis (Wang X. et al., 2022). Propyl gallate (PG), an antioxidant commonly used in personal care products, induces DNA damage and oxidative stress, affecting oocyte proliferation and development. Additionally, PG exposure increased histone methylation (H3K27me2 and H3K27me3) in oocytes (Yang et al., 2023).

Organic ultraviolet filters, including oxybenzone (OBZ), benzophenone-3 (BP3), octocrylene (OCL), etc., which are found in human breast milk, amniotic fluid, urine, and blood plasma, are extensively used in personal care products (Ruszkiewicz et al., 2017). They inhibit meiosis and development in animal oocytes by promoting mitochondrial stress and affecting the normal function of the cytoskeleton (Jin et al., 2021; Chang et al., 2022; Tao et al., 2023).

3.4.4 Pharmaceuticals

As environmental toxicants, which have received increasing attention in recent years, PPCPs are derived from various prescription and over-the-counter drugs, antibiotics, hormones, and their metabolites (Qin et al., 2023). Few studies have investigated the effects of these pharmaceuticals on oocytes. *In vitro*-fertilized women of childbearing age were analyzed for oocyte maturation and embryo quality, and it was concluded that ibuprofen had no effect on oocyte or embryo quality (Schwartz and Burkard, 2020). However, negative effects of hormones on oogenesis have been reported. For example, 17 α -ethynylestradiol (EE2) can reduce the abundance of Juno protein and increase ROS levels to promote oocyte apoptosis, which can be inhibited by melatonin (Dai et al., 2020).

3.5 Food toxicants

Reproductive toxicity is present in foods; some toxicants, such as mycotoxins, sprouted potatoes, and arecoline, are often ignored.

3.5.1 Mycotoxins

Fusarium mycotoxins include deoxynivalenol (DON), fumonisin B1 (FB1), nivalenol (NIV), beauvericin (BEA), and zearalenone (ZEN); they are primarily produced by fusarium mycotoxins and are commonly detected in agricultural staples such as corn, wheat, oats, barley, peanuts, peas, and many oil grains. They are mainly produced on farmland and may be recontaminated during storage (Hou et al., 2014; Han et al., 2016; Schoevers et al., 2016; Wang et al., 2021a; 2021b). Mycotoxins significantly inhibit the maturation of porcine oocytes by reducing p-MAPK protein levels and disrupting meiosis, delaying cell cycle progression. DON treatment of porcine oocytes with upregulated LC3 protein expression and abnormal Lamp2, LC3, and mTOR mRNA expression induced autophagy and apoptosis. DON exposure increases oocyte DNA methylation by altering DNMT3A mRNA levels. Additionally, histone methylation levels were altered, with increased H3K27me3 and H3K4me2 proteins and related methyltransferase gene mRNA levels (Han et al., 2016). Notably, failure of PB1 extrusion and organelle dysfunction were discovered, with mycotoxin causing impaired PB1 expulsion at concentrations of

30–50 μM and toxic effects on embryos, oocytes, and cumulus cells at concentrations above 50 μM (Schoevers et al., 2016; Wang et al., 2021b). ZEN, a metabolite of *Fusarium* mycotoxin, acts as a xenoestrogen and is considered cytotoxic, histotoxic, and genotoxic (Hou et al., 2015). ZEN-treated oocytes showed reduced *in vitro* culture maturation rates, impaired mitochondrial membrane potential, and disrupted Golgi apparatus function. In porcine oocytes, ZEN exposure altered ER stress levels, and GRP78 expression was reduced (Hou et al., 2015; Wang Y. et al., 2022).

Ochratoxin A (OTA) is a fungal toxin primarily produced by *Aspergillus* and *Penicillium* and is commonly detected in pulses, cereals, grains, spices, and processed products (Huang and Chan, 2016). OTA reduces oocyte quality and quantity by disrupting oocyte meiosis and development, spindle and chromosome arrangement, and extrusion rate of the PB1 (Jia et al., 2020). In addition, OTA induces oxidative stress by inducing the accumulation of ROS during meiosis and the depletion of antioxidants, leading to oocyte apoptosis. Notably, epigenetic modifications in mouse oocytes were affected, as evidenced by the altered levels of 5mC, the global DNA hydroxymethylation (5hmC), H3K9ac, and H3K9me3 (Huang and Chan, 2016; Jia et al., 2020); melatonin has a protective impact against OTA exposure (Lan et al., 2020).

3.5.2 Other food toxicants

4-Methylimidazole (4-MI) is a simple, nitrogen-containing heterocyclic compound. It is commonly used to produce baked goods, soups, beer, and soft drinks. It affects the quality of oocytes by affecting their meiotic ability and fertility. Its toxic effects include mitochondrial dysfunction and meiosis-related cytoskeletal abnormalities (Lu et al., 2022). Solanine is a natural toxin in potato sprouts and often in long-stored potatoes. It was discovered that in porcine oocytes cultured *in vitro*, α -solanine (10 μM) interfered with meiotic progression, increased autophagy-related genes (*LC3*, *ATG7*, and *LAMP2*) and apoptosis-related genes (*BAX* and *CASP3*), and significantly increased the levels of H3K36me3 and H3K27me3 compared to the untreated group (Lin et al., 2018). Arecoline, the primary bioactive substance extracted from betel nuts, affects actin filament kinetics, spindle assembly, and microtubule attachment stability in mouse oocytes, leading to aneuploidy and meiotic arrest. In addition, arecoline treatment disrupts mitochondrial distribution, reduces ATP production, increases oxidative stress, and ultimately induces oocyte apoptosis; metformin has been shown to reverse betaine toxicity (Li et al., 2020).

3.6 Fluoride

Fluoride is used globally as an emulsifier in cleaning products, pesticides, food containers, shampoos, toothpaste, etc. (Renner, 2001). A study showed that women with high levels of perfluorinated compounds in their follicular fluid had lower fertilization rates when undergoing *in vitro* fertilization and embryo transplantation (IVF-ET) (Governini et al., 2011).

Exposure to fluoride salt blocks meiosis in porcine oocytes, interferes with spindle dynamics, and increases aneuploidy. It

interferes with oocyte mitochondrial function, triggers the DNA damage response, and induces early apoptosis (Liang et al., 2017). In addition, fluoride salt intervention reduced the expression of oocyte-specific genes involved in oocyte growth and induced acrosome response in a dose-dependent manner. Fluorine treatment resulted in lower levels of H3K9ac and H3K18ac in the experimental group than in the control group (Liang et al., 2016).

Perfluorinated compounds are important industrial products extensively used in agricultural activities, the textile industry, food packaging, and cosmetics (Wei et al., 2021). Perfluorodecanoic acid is a synthetic perfluorinated compound that has a significant negative effect on oocyte survival (LC50 = 7.8 μM) and maturation (IM50 = 3.8 μM) by disrupting oocyte calcium homeostasis and gap-junctional intercellular communication (Domínguez et al., 2019). Perfluorohexane sulfonate had a moderate gap-junctional lethal concentration (LC50 = 39.1 μM) of cytotoxicity and inhibited oocyte maturation (MIC50 = 91.68 μM), and had a toxic effect on intercellular communication (Martínez-Quezada et al., 2021). Perfluorooctane sulfonate, a surfactant extensively used in agriculture, causes cytoskeletal abnormalities in oocytes, disrupts mitochondrial function, induces oxidative stress, and triggers early apoptosis. Studies have shown that 600 μM perfluorooctane sulfonate significantly reduces the polar body extrusion rate in mouse oocytes (Wei et al., 2021).

In general, fluorinated compounds have significant reproductive toxicity in animal studies and have been validated in observational studies in humans, although the number of cases is small. However, this evidence indicates that fluorinated compounds should be avoided, especially in mother and child products, food, and personal care products.

4 Concluding remarks and future directions

In summary, we have provided an overview of the effects of environmental toxicants on oogenesis and female fertility; this suggests that exposure to heavy metals, cigarette smoke, and agrochemicals can have detrimental effects on oocyte multiplication, growth, and maturation. Several measures can be used to mitigate the effects of environmental toxicants on reproductive health. The primary step involves minimizing or eliminating exposure to toxicants by identifying and avoiding specific sources known to contribute to reproductive toxicity, such as chemicals, pollutants, or occupational hazards. Detoxification and antioxidant strategies help remove toxins from the body and enhance reproductive health. Drinking abundant water and consuming a healthy diet can accelerate liver detoxification. Some antioxidants, including blueberry extracts, glutathione, and melatonin, have been reported to be beneficial for reproductive health. Additionally, consuming foods that support liver function, such as cruciferous vegetables (broccoli, kale, and cabbage), may be beneficial. Guidance from healthcare professionals specializing in reproductive health or environmental medicine is crucial, as they can provide personalized recommendations and suggest targeted therapies or interventions based on an individual's specific circumstances.

The experimental animal models used in the original studies were primarily rats, pigs, ewes, sheep, and zebrafish. These experimental approaches are limited in their ability to accurately restore the concentration distribution and metabolic processes of environmental toxicants in the human body, which may result in higher doses that amplify toxic effects or inaccurate dose control due to inter-species differences in body size. Furthermore, ethical and feasibility considerations have limited the use of human oocytes as experimental subjects. Despite recent advances in 3D culture and organoid technologies, their application in studying environmental toxins in oocytes remains limited. Therefore, future studies should incorporate models that closely resemble the structure and physiological functions of the human ovary.

Raising awareness of the potential risks of toxin exposure is crucial for promoting public health and preventing adverse reproductive outcomes. To effectively mitigate these risks, it is essential to understand the mechanisms underlying the effects of environmental toxins on reproductive health, which includes the identification of biomarkers that can accurately assess exposure levels and predict reproductive outcomes. Further research is necessary to develop effective strategies for safeguarding the reproductive health of women and their offspring. By advancing our knowledge of the impact of environmental toxins on reproductive health, proactive steps can be taken toward reducing exposure levels and improving overall reproductive outcomes.

Effective prevention and intervention strategies may involve reducing exposure levels and fertility damage by regulating industrial practices or novel treatments for infertility or miscarriages. Furthermore, it is important to provide special protection for women with occupational exposure to the reproductive hazards of environmental toxins, and women of childbearing age should be aware that exposure to environmental toxins can cause damage to oogenesis and the female reproductive system; consequently, safety measures may involve lifestyle changes, such as smoking cessation or dietary modifications. Regarding alleviating exposure to environmental toxins, foods and supplements with antioxidant potential may be effective in protecting the development of oocytes; however, the current evidence is mainly from animal studies, which do not provide significant confidence for their efficacy in humans.

Overall, this study provides evidence for the deleterious effects of environmental toxins on female reproductive health. Further research is warranted to better understand the mechanisms

underlying toxicity and the potential protective strategies for oogenesis.

Author contributions

XY and WL performed the literature search and drafted the manuscript. LX, YX, and MX reviewed and revised the draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

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Glossary

4-MI	4-methylimidazole	MNZ	Dexamethasone zinc
ACE	Acetamidrid	MP	Methyl parathion
As	Arsenic	MPF	Maturation promoting factor
ATP	Adenosine triphosphate	MTOCs	Microtubule organizing centers
AZO	Azoxystrobin	MTs	Microtubules
BaP	Benzo(a)pyrene	MXC	Methoxychlor
BEA	Beauvericin	NIV	Nivalenol
BHPF	Fuorene-9-bisphenol	NNA	1-(N-methyl-N-nitrosamino)1-(3-pyridinyl)-4-butanal
BP	Butylparaben	NPs	Nanoparticles
BP3	Benzophenone-3	OBZ	Oxybenzone
BPA	Bisphenol A	OCL	Octocrylene
BPAF	Bisphenol AF	OTA	Ochratoxin A
BPS	Isphenol S	PAHs	Polycyclic aromatic hydrocarbons
Cd	Cadmium	Pb	lead
CF	Carbofuran	PB1	First polar body
CPF	Chlorpyrifos	PBs	Parabens
Cr	Chromium	PCBs	Polychlorinated biphenyls
CrVI	Hexavalent chromium	PCOS	Polycystic ovary syndrome
Cu	Copper	PG	Propyl gallate
DBP	Dibutyl benzodicarboxylate	PNMC	3-methyl-4-nitrophenol
DEHP	Di(2-ethylhexyl) phthalate	PP	Propylparaben
DON	Deoxynivalenol	PPCPs	Pharmaceuticals and personal care products
DZN	Diazinon	PPD	Para-phenylenediamine
EE2	17 α -ethynylestradiol	PR	Progesterone receptor
EP	Ethylparaben	ROS	Reactive oxygen species
ER	Estrogen receptor	ST	Smokeless tobacco
FB1	Fumonisin B1	TBTO	Tributyltin oxide
Fe	Iron	THS	Third-hand smoke
FPN	Fipronil	ZEN	Zearalenone
Hg	Mercury	Zn	Zinc
IBP	Isobutylparaben	ZnO NPs	Zinc oxide nanoparticles
IC50	Inhibition concentration 50		
IVF	<i>In vitro</i> fertilization		
IVF-ET	<i>In vitro</i> fertilization and embryo transplantation		
LC3	Protein light chain 3		
LC50	50% Lethal concentration		
MePB	Methylparaben		
MIC50	50% Maturation inhibitory concentration		
MII	Metaphase II		
miRNAs	microRNAs		