Chapter 3
The Influence of Environmental Factors on Ovarian Function, Follicular Genesis, and Oocyte Quality

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Abstract Endocrine-disrupting chemicals (EDCs) exist ubiquitously in the environment. Epidemiological data suggest that the increasing prevalence of infertility may be related to the numerous chemicals. Exposure to EDCs may have significant adverse impacts on the reproductive system including fertility, ovarian reserve, and sex steroid hormone levels. This chapter covers the common exposure ways, the origins of EDCs, and their effects on ovarian function, follicular genesis, and oocyte quality. Furthermore, we will review the origin and the physiology of ovarian development, as well as explore the mechanisms in which EDCs act on the ovary from human and animal data. And then, we will focus on the bisphenol A (BPA), which has been shown to reduce fertility and ovarian reserve, as well as disrupt steroidogenesis in animal and human models. Finally, we will discuss the future direction of prevention and solution methods.

Keywords Endocrine-disrupting chemicals (EDCs) · Bisphenol A (BPA) · Folliculogenesis · Oocyte · Steroidogenesis

3.1 The Common Exposure Ways, the Origins of EDCs, and their Effects on Ovarian Function, Follicular Genesis, and Oocyte Quality

Endocrine-disrupting chemicals (EDCs) are extrinsic chemicals that can interfere with the processes regulated by endogenous hormones. EDC was defined as "an exogenous chemical or mixture of chemicals that interferes with any aspect of hormone action"[1] in 2012 by the Endocrine Society. They emphasized that very low dose EDC exposures during the developmental stage might have potent and

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Fig. 3.1 Common exposure origins of endocrine disrupting chemicals

irreversible effects. The female reproductive system is regulated by hormones which means it would be the target of EDCs. Ovary is an important assurance for fertility and performs normal functions of oocyte/follicular quality, folliculogenesis, or steroidogenesis, which is also a target constitution assaulted by EDCs. As a result, EDCs exposure may disrupt folliculogenesis, oocyte quality as well as steroidogenesis.

EDCs are ubiquitous in the environment, and a recent report has indicated that there are more than 800 chemicals with endocrine-disrupting properties been used in daily life [2]. People and animals tend to exposure to EDCs by various routes, such as direct contact, inhalation, ingestion, maternal-fetal transfer, or intravenous administration [3]. Generally, there are two categories of EDCs: One is naturalistic EDCs such as phytoestrogen, genistein, and coumestrol found in natural food. The other one is synthetic EDCs which can be further divided into the following groups: Dioxins, polybrominated biphenyls (PBBs), and polychlorinated biphenyls (PCBs) that are found in industrial synthetic chemicals and their by-products; Bisphenol A (BPA) and phthalate in plastics; Methoxychlor (MXC) and dichlorodiphenyltrichloroethane (DDT) in pesticides; Vinclozolin in fungicide and diethylstilbestrol (DES) in some pharmaceutical agents [4] (Fig. 3.1).

Epidemiological data have suggested that EDCs may accumulate in human body and the environment. BPA and four phthalate metabolites (mono-(2-ethylhexyl) phthalate (MEHP), monomethyl phthalate (MMP), monoisobutyl phthalate (MiBP), monoethyl phthalate (MEP)) could be detected in nearly all 1016

participants aged 70[5]. A Spanish cohort study in 2011 discovered that phthalate and phenol were commonly found in the urine of young children and pregnant women, with the urinary concentrations higher in children than in pregnant women [6]. Research in 2015 indicated that organochlorine pesticides, 13.4% of which was MXC, could be detected in follicular fluid of women from central China [7]. Besides, BPA and its derivatives can be detected in serum from second-trimester umbilical cord [8], which indicates that EDCs can be passed from mother to fetus through placenta and concentrated in fetal body. Furthermore, EDCs are difficult to be eradicated by biodegradation. For instance, MXC is persistent in soil, and its residues are present even 18 months after the soil treatment with microorganisms [9].

EDCs are prone to expose and accumulate in human body, and they can be detected in people of all ages. In addition, the existence of EDCs in follicular fluid raises a concern that EDCs may affect the reproductive system and even cause epigenetic modification of gametes. What's more, the accumulation of EDCs in the environment is difficult to be eradicated by biodegradation, having a long-lasting impact on human health.

Researches have disclosed that EDCs adversely affect the ovary by disrupting folliculogenesis, oocyte development, and ovarian function. For instance, numerous studies have elucidated that EDCs interfered with folliculogenesis and oocyte development. Mixtures of EDCs (BPA, pesticides, phthalates, butylparaben, paracetamol, and UV-filters.) exposed to rats before puberty cause a significant reduction in primordial follicle quantities and plasma levels of prolactin [10]. Prenatal treatment of caiman latirostris with 17β-estradiol (E2), BPA, or atrazine (ATZ) can increase type III follicles, and treatment with BPA or E2 also presents higher proportioned multi-oocyte follicles [11]. Di(2-ethylhexyl) phthalate (DEHP) and MEHP can inhibit antral follicle growth via reducing estradiol production and decreasing the expression of cell cycle regulators [12]. DEHP has been proved to inhibit follicle growth and induce antral follicle atresia via dysregulation of cell cycle and apoptosis regulators [13]. Furthermore, EDCs have negative impacts on oocyte development. Female adult South African clawed toads (Xenopus laevis) that were exposed to tamoxifen (TAM) and methyldihydrotestosterone (MDHT) showed oocyte atresia in a previous study [14]. EDCs can disrupt the oocyte meiotic progression of in vitro cultured porcine oocyte cumulus complexes (OCC). BPA and 4-chloro-3-methyl phenol (CMP) exposure reduces numbers of oocytes undergoing germinal vesicle breakdown (GVBD) or reached metaphase II stage (MII) via meiotic maturation disturbance. Besides, BPA and CMP can reduce the synthesis of extracellular matrix (ECM) by altering the process of cumulus expansion [15].

Multiple studies have also consistently shown that EDCs exposure disrupted ovarian function. For example, the serum level of BPA, octylphenol (OP), and 4-nonylphenol (4-NP) is significantly elevated in precocious girls. Prepubertal exposure to EDCs including genistein, zearalenone, zeranol, and DES results in acceleration of puberty earlier onset, prolonged estrous cycle, and anovulatory period [16]. Besides, BPA and OP levels are positively correlated with the volume of the uterus and ovary [17]. Prenatal ewes exposure to mixture EDCs reduces ovarian reserve, greatly increasing the number of altered fetal ovarian genes and proteins [18]. Zama et al. [19] have suggested that transient exposure to MXC during

fetal and neonatal development results in ovarian dysfunction via significant hypermethylation in the ERβ promoter regions and increase of DNMT3B. Further studies have revealed that transient exposure to MXC results in epigenetic modification in ovaries via specific signaling pathways such as IGF-1 signaling, PTEN signaling, and rapid estrogen signaling [20].

3.2 The Origin and the Physiology of Ovarian Development, as well as Briefly Introduce the Mechanisms in which EDCs Act on the Ovary

Ovary is a complex organ that is responsible for gametogenesis and steroidogenesis. And ovary is one of the most important target organs of endocrine disruptor chemicals. The oogonia develop from the yolk sac and then migrate to the ovary, which are proliferated by mitosis until about gestation age 28–30 weeks, and then start meiosis. The oogonia differentiate into primary oocytes, which progress into the prophase of the first meiotic division and then become dormant until puberty. The number of oocytes comes to a climax around six to seven million at gestation age 25–28 weeks, which and then starts a steady decline because of atresia. There are approximately 700,000 to two million germ cells in the neonatal period and about 300,000 to 500,000 primordial follicles at the time of puberty. For females reaching 37 years old, the numbers of primordial follicles decline to 25,000. There are about only 1000 primordial follicles reserved for peri-menopausal women (Fig. 3.2). At the period of fetus and child, the follicles hardly reach maturation. After puberty, with the stimulation of gonadotropin secreted by the pituitary gland, there is a follicle maturation every month and then about 14 days before the onset of the next menstruation cycle. In a female's whole life, there are only 400 eggs successfully ovulated. And the rest of the follicles degenerate into atretic follicles. Follicles
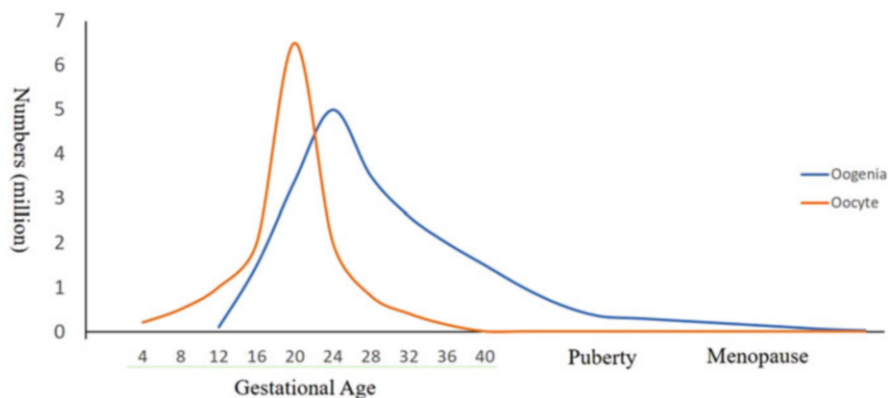

Fig. 3.2 The change of gamete numbers along with age

consist of granulosa cells surrounding an oocyte. The follicular development in a continual process of four stages, including primordial follicles, primary follicles, secondary follicles, and mature follicles, has a series of structural and physiological changes (Table 3.1).

After introducing the basic physiology of ovary, we would briefly introduce the underlying mechanisms by EDCs working on ovary as follows.

EDCs are commonly identified as compounds that can interact with androgen or estrogen receptors and thus act as antagonists or agonists of endogenous hormones. EDCs disrupt the interference with hormone by mimicking or opposing actions and the hormonal and homeostatic systems [21]. In addition, the reproductive system is vulnerable to endocrine, especially during the early stage of life. Therefore, exposure to endocrine disruptors during development may lead to disease in children or adults and even to the next generations because of epigenetic modification [21].

3.2.1 Oxidative Stress

Reactive oxygen species (ROS) such as hydrogen peroxide, superoxide, and hydroxyl radical are the by-products during natural oxygen metabolism, which can induce cellular damage and death and thus cause a wide range of diseases [22]. When ROS are excessively produced, or body clearance ability deficiency such as deficiency of antioxidants, oxidative stress will occur [23]. Oxidative stress is involved in ovarian toxicity caused by a variety of EDCs. It is well documented that ROS are involved in the initiation of apoptosis in follicular cells, poor quality of oocytes, and so on [23]. For instance, DEHP (10 μg/ml) has been proved to inhibit antral follicle growth by increasing ROS levels and reducing the expression and the activity of one of the critical antioxidant enzyme Cu/Zn superoxide dismutase (SOD) [1, 24]. MXC (1–100 μg/ml) can induce antral follicle atresia by decreasing the enzymatic activity and mRNA expression of antioxidant catalase Cu/Zn SOD1, glutathione peroxidase (GPX), and catalase [25]. In addition, neonatal exposure to EDCs (4-vinylcyclohexene diepoxide (VCD): 40–80 mg/kg/day, MXC: 50–100 mg/kg/day, and menadione: 7.5–15 mg/kg/day) can increase oocyte lipid peroxidation by ROS and thus induce permanent oocyte damage [26].

3.2.2 Disturbance of Steroidogenesis

Ovary is essential for the synthesis of steroid hormones. The "two-cell, two-gonadotropin" theory proposed by Armstrong et al. in 1979 demonstrates that granulosa cells express follicle-stimulating hormone (FSH) receptors, which stimulate aromatase activity, while theca cells possess luteinizing hormone (LH) receptors which stimulate androgen synthesis [27, 28]. During the process of ovarian steroidogenesis, LH stimulates the activation of 17α-hydroxylase to convert cholesterol and

Table 3.1 Characteristics of follicles in different stages

		Primordial follicle	Primary follicle	Secondary follicle	Antral follicle	Growing follicle		Preovulatory follicle	Corpus luteum
						Early	Late		
Diameter (mm)		0.03–0.06	>0.06	<0.12	>0.2	7–10	>10	16–20	–
Granulosa cell	Morphology	Simple squamous GC	Simple cuboidal GC	$<6*10^2$ cuboidal GC	$>(3\text{-}5)*10^3$ cuboidal GC	$>19*10^6$ cuboidal GC	$>94*10^6$ cuboidal GC	$>47*10^6$ cuboidal GC	–
	FSHR	–	–	–	+	+	+	+++	++++
	Hormone production	–	–	–	–	–	E_2	E_2	P, E_2
Theca cell	LHR	–	–	–	+	+	+	+++	++++
	Hormone production	–	–	–	P	P, ASD	P, ASD	P	ASD

pregnenolone to androgens in the cal cells. Later the androgens diffuse to the granulosa cells and are transformed into estrogens under the catalysis of cytochrome P450 aromatase, which is stimulated by FSH [29, 30].

Researches have indicated that EDCs can inhibit ovarian steroidogenesis. For example, neonatal female caiman exposed to E2 or BPA presents higher estrogen serum levels [11]. DES, BP, and OP reduce estradiol and testosterone levels, and GEN causes a decline in testosterone levels and cAMP by stimulating the activity of aromatase enzyme [31]. DEHP inhibits the production of progesterone, androstenedione, testosterone, and estradiol from antral follicles, by inhibiting the expression of side-chain cleavage related enzymes such as 17α-hydroxylase-17,20-desmolase, 17β-hydroxysteroid dehydrogenase, and aromatase [13]. Cytochrome P450 aromatase is the critical steroidogenic enzyme that is responsible for the conversion of androgens to estrogens. EDCs disrupt steroidogenesis by interfering with the gene expression of cytochrome P450 aromatase. Varieties of EDCs have been proved to potentially disturb reproductive function by dysregulating the expression of CYP19 genes through differential transcriptional modulation [32, 33]. Zebrafishes exposed to an estrogenic mixture of 11 EDCs can be observed an alteration of CYP19A1 activity and Mtf-1 and tfap2c transcription factor [34]. Furthermore, Benzo[α] pyrene (B[α]P) alters the expression of CYP2N23. BPA changes CYP2P18, CYP2P19, and 4-OP and disturbs CYP2AD12 [35]. DES and tetrabromobisphenol A suppress CYP17 but not CYP19 activity, indicating different mechanisms of different EDCs acting on these cytochrome p450 aromatase [36].

EDCs not only can alter the enzymatic activity of cytochrome p450 aromatase, but also can interfere with the gonadotropin receptor signaling second messengers such as cAMP or modulate the Ca^{2+} associated metabolic pathway. For example, 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), a metabolite of DDT, suppresses progesterone synthesis through inhibiting the generation of gonadotropin receptor signaling second messengers cAMP [37], and also decreases the gene expression of P450 cholesterol side-chain cleavage (P450scc) [38]. Furthermore, Younglai et al. [39] have found elevations of [Ca(2+)](cyt) in granulosa-lutein cells, suggesting DDT can also modulate $Ca2^{+}$-dependent pathways.

3.2.3 Nuclear Receptor Signaling

There are a variety of mechanisms in which EDCs exert harmful effects, one of which is attributed to the interaction with nuclear hormone receptors (NHRs). EDCs interfere with genomic and non-genomic estrogen receptor (ER) activity via directly binding with two ERs (ERα and ERβ), by the assistance of transcription factors like the aryl hydrocarbon receptor (AhR) or through modulation of critical enzymes during estrogen synthesis or metabolism [40]. Estrogenic signal networks are divided into the intracellular and the extracellular pathways. The intracellular pathways include the genomic pathway and the non-genomic pathway, involving in

the transcription of target genes and signal transductions via binding with membrane receptors, respectively. The extracellular pathways involve other modulating factors such as other growth factors, cytokines, and hormones [40, 41]. Not only the estrogenic or androgenic receptors, multiple studies have indicated that activity of the constitutive androstane receptor (CAR), the pregnane X receptor (PXR), the thyroid hormone receptors (TRs), the retinoid X receptors (RXRs), the estrogen related receptors (ERRs), or the peroxisome proliferator-activated receptors (PPARs) could also be affected by EDCs, reviewed by Albane et al. [42].

Different kinds of EDCs exhibit different ER responsive properties. For example, kaempferol, coumestrol, daidzein, and genistein can mediate both ERα and ERβ ERE-mediated activities, while 2-2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane, bisphenol AF, and BPA activate the ERα pathway. Besides, only a few kinds of EDCs activate the tethered mechanism through ERα or ERβ [43]. In addition, Sheikh et al. [44] have elucidated that BPA, MBP (4-Methyl-2, 4-bis (4-hydroxyphenyl) pent-1-ene), 4-tert-OP, and 4-NP exhibited high binding affinity with sex hormone-binding globulin (SHBG), indicating that these EDCs can potentially interfere or disrupt the steroid-binding function.

3.2.4   Epigenetic Modification

As we have mentioned above, the reproductive system is sensitive to EDCs, especially during the early critical development window, which may lead to subtle epigenetic alteration and thus cause permanent or even multigenerational or transgenerational changes [45–48]. The epigenetic modification of the germline includes histone modifications, DNA methylation, non-coding RNAs, or alterations in chromatin structure [49, 50]. For example, prenatal exposure to the environmental doses of phthalate mixture induced multigenerational and transgenerational effects on female reproduction [51]. Brehm et al. [52] have suggested that prenatal DEHP exposure (750 mg/kg/d) can alter estrous cyclicity, augment estradiol levels (F1 and F3), increase the presence of ovarian cysts (F1), decreased testosterone levels and folliculogenesis (F1, F2, and F3), reduce progesterone levels (F2), decrease inhibin B levels (F1 and F3), and change gonadotropin hormone levels (F1 and F3). We will discuss it further in the later section.

3.3 BPA Reduces Fertility Ability, Reduces the Primordial Follicle Pool Reserve, Leads to Premature Ovarian Failure, Disturbs the Estrous Cycle, and Disrupts Steroidogenesis in Different Animal and Human Models

In this section, we will focus on BPA, which is a plasticizer used commonly and widely in food and drink containers, plastic products, epoxy resins [53], and dental materials [54]. BPA can leach out from several products in the condition of high temperatures, acidic or alkaline environment, UV rays, or repeated use [55]. BPA can be detected in plasma, serum, sweat, urine, breast milk, placental tissue, umbilical cords, amniotic fluid, and fetal serum [56]. More importantly, BPA is considered a reproductive toxicant because it can be detected in various reproductive tissues [57]. Controversially, however, Teeguarden et al. [58] summarized methods of serum BPA measurement but they found that BPA serum concentrations in humans were unmeasurable, and contributed limited or no estrogenicity.

According to the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO), the human exposure levels to BPA are estimated to be $0.4 \sim 1.4$ mg/kg bw/d [59]. Although the safe reference dose of BPA proposed by the US Environmental Protection Agency is 50 mg/kg bw/d [60], previous studies have indicated that BPA has potentially negative impacts even at much lower doses in a non-monotonic dose-response manner [61–63].

A study has revealed that BPA can be measured in the urine of almost all the women undergoing IVF treatment, of which the concentrations are negatively associated with the ovarian response, including peak estradiol levels and the number of oocytes retrieved [64]. Besides, the plasma concentrations of BPA are transient with short half-lives (< 2 h) in pregnant women, while sustained in fetal plasma [65]. Furthermore, BPA concentrations in serum of women carrying fetuses with abnormal karyotypes in the early second trimester are higher than the control group [66], which raises concerns about the adverse impacts of BPA on human development.

Human and animal studies have illustrated that BPA exposure will reduce fertility ability by disrupting the primordial follicle pool, interfering with oogenesis, and disturbing ovary functions such as steroidogenesis and the estrous cycle. Worse still, BPA was proved to have transgenic effects that may have impacts on offspring.

Researches on infertility women have revealed that higher urinary BPA concentrations are correlated with lower antral follicle counts [67]. In animal models, scientists have obtained consistent results. In rat models, BPA exposure (2.5 and 250 mg/kg bw/d) at PND 21 can reduce the numbers of primordial, primary, preantral, and total healthy follicle numbers [55]. Atretic follicles, cysts formation, and separation of granulosa cells can be observed in rats' ovaries after exposure to BPA orally for 4 weeks [68]. Perinatal exposure to BPA by the oral route during gestation and breastfeeding can decrease recruitment of primordial follicles, increase the number of corpora lutea, and ovulate oocytes in rats ovaries [69]. Neonatal rats subcutaneous exposed to BPA (1 mg/kg) exhibits multiple cystic follicles and

decreased area of corpora lutea (CL) in the ovary [70]. In mice models, BPA can facilitate the transition from primordial to primary follicles, accelerate the dissipation of the primordial follicle pool, and inhibit meiosis I by abnormal spindle assembly [71]. BPA (10 or 100 μM) exposure to neonatal mice isolated ovaries significantly reduces germ nest breakdown and primordial follicle assembly [72]. Besides, BPA (30 M) exposure to in vitro mice oocytes during follicular development shows the reduction of granulosa cell proliferation and total estrogen production, but it still can develop and form antral-like cavities [73]. In lambs models, prenatal low dose BPA (50 μg/kg/day) exposure affects the ovarian follicular dynamics by reducing primordial follicle pool reserve and stimulating follicular recruitment and development [74]. Veiga-Lopez et al. [75] have also proved that prenatal BPA treatment causes ovarian follicular dynamics disruption on sheep. BPA exposure can shorten the time interval between the estradiol rise and the preovulatory LH surge, and disturb follicular count trajectories. Besides, BPA early exposure results in the augmentation of the number of multi-oocyte follicles (MOFs), granulosa/theca cells in antral follicles as well as antral atretic follicles, because folliculogenesis acceleration increases the incidence of atretic follicles [74]. What's more, Gieske et al. [76] have also suggested that prenatal and postnatal exposure to BPA results in increased formation of MOFs and antral follicles in the primate model. One of the underlying mechanisms is that BPA disrupts the follicular progression. BPA induces follicular atresia via disrupting the follicular progress by interfering with the previtellogenic and vitellogenic phases. BPA exposure may stimulate follicular recruitment of the primary follicular recruitment on the primary stage and then forces the follicular transition from stage III to IV with enlarged stage IV follicles, thereby inducing atresia [77]. What's more, BPA affects follicle numbers and constituent via interfering with the follicle development-related genes such as down-regulation of the expression of oocyte-specific histone H1 variant (H1FOO) and factor in the germline alpha (FIGLA) genes, and up-regulation of anti-Mullerian hormone (AMH) genes expression [78]. In addition, BPA may impair folliculogenesis by increasing the expression of oocytes specific genes such as Sohlh2 (spermatogenesis and oogenesis helix-loop-helix), Nobox (newborn ovary homeobox), Lhx8 (LIM homeobox 8), and FIGLA. BPA disturbs the normal process of folliculogenesis by blocking the demethylation of CpG sites of the Lhx8 gene in oocytes [72]. Furthermore, postnatal exposure to BPA can dose-dependently disturb the early ovary development by disrupting the Notch signaling pathway [79].

BPA orally exposure to young adult mice (50 μg/kg bw/day) has been shown to reduce the fertilization ability of oocytes rather than affect ovulation [80]. Acute low doses exposure of BPA (3, 5 mg/L) to zebrafish can disrupt oogenesis, displaying severe deterioration of ovarian tissue with distorted and immature oocytes, and the increased number of atretic oocytes [81]. Persistent unenclosed oocytes in the medullary region and small non-growing oocytes in secondary and antral follicles have been presented in rhesus monkeys when continuously exposed to BPA before birth [82]. Consistently, BPA exposure to human oocytes shows decreased oocyte survival, increased oocyte degeneration, and increased MLH1 (crossover marker) foci number, which indicates BPA can act as a toxic substance and affect meiotic

prophase such as pairing-synapsis and recombination processes, as well as decrease oocyte survival [83]. Numerous previous studies have attempted to explain the underlying mechanisms of the impacts of BPA on oocyte development. Researches have suggested there is lipid droplet accumulation, chromatin condensation in the nuclei of granulosa cells, and autophagosomes in rats' ovaries at 4 weeks post-exposure to BPA [68]. Exposure to BPA during early gestation age may have adverse impacts on meiosis, thus disrupts the development of the oocytes. For example, low dose BPA exposures during mid-gestation lead to oocytes displaying gross aberrations in the meiotic prophase, including enhanced levels of recombination and synaptic defects, and an increase in aneuploid eggs and embryos in rats [84]. In isolated mice ovaries model, BPA exposure (30 M) has adverse effects on the meiotic spindle, thereby hindering meiosis progression [73]. Besides, BPA exposures to rhesus monkeys during middle and gestational age can induce chromosome segregation disturbances and MOFs increase, respectively [82]. Also, BPA has been proven to have genotoxic and cytogenetic, but not mutagenic effects. BPA can interfere with the gene expressions related to meiosis. Prenatal exposure to low dose BPA may have impacts on early oogenesis by disturbing the gene expression, especially that correlated with the onset of meiosis [85]. BPA exposure to mice results in more oocytes in germ cell cyst and less primordial follicle counts through inhibiting the meiotic progression of oocytes, via down-regulated mRNA expression of specific meiotic genes, including Dmc1, Stra8, Scp3, and Rec8 [86]. BPA exposure to in vitro embryonic stem (ES) cells significantly upregulates the expression of the meiotic entry gene Stra8, accompanied by aggregated Sycp3 signal localized in nuclei and up-regulation of ovarian markers (Foxl2 and Wnt4), which can help to explain how BPA affects germ cell differentiation [87]. Furthermore, BPA can deteriorate egg quality through decreasing HDAC7 expression in mice ovary and eggs, while increasing H3K9 and H4K16 acetylation [88]. Besides, BPA exposure to ovaries induces a significant elevation in micronucleus frequency, and conventional chromosome aberrations such as breaks, gaps, and fragments increased [89]. Furthermore, BPA exposure leads to chromosome synapsis impairment and disturbance of meiotic double-strand break repair (DSBR) progression, which is essential to genomic integrity maintenance during meiosis [90]. Oocytes exposed to BPA show a significant increment of Rpa, Spo11, H2ax, and Blm genes involved in DSB generation, signaling, and repair, as well as up-regulation of Erα, Erβ, and Errγ genes related to estrogen receptor [91]. Ganesan et al. [92] have demonstrated that BPA can induce ovarian DNA damage, with significant increased DNA DSB marker cH2AX and ATM before follicle loss. Besides, they have observed ovary that may activate DNA repairment and xenobiotic biotransformation to protect oocyte from damage, or activate cell death signaling to deplete follicles.

Previous researches have indicated that BPA adversely affects ovarian functions, including disturbing estrous cycle and steroidogenesis. Neonatal period exposure to BPA causes advanced puberty onset [70] and irregular estrous cycle [70]. Prepubertal exposure to BPA in mice will present advanced puberty onset [93, 94], ovary weight reduction [78, 93, 74], disturb estrous cycle and duration [93, 94], lower E2 response during in vitro fertilization (IVF) [95], and diminish ovarian reserve [96]. Exposure

to BPA during the implantation period may have potential effects on adverse pregnancy outcomes and reduction of litter size or implantation rate [97].

In vitro experiments in isolated porcine granulosa cells have illustrated that BPA exposure can disturb steroidogenesis with the progesterone level decreased [98]. However, BPA exhibits non-monotonic dose effects on ovarian steroidogenesis, which may be attributed to different alteration properties of steroidogenic enzymes. For instance, steroidogenic gene expressions are promoted by BPA at lower concentrations (5 and 15 μg/L) while inhibited at higher concentrations (50 μg/L) [99]. The basal progesterone level elevates when BPA is at 10^{-8} M to 10^{-5} M, and FSH-stimulated progesterone level is promoted when BPA is at 10^{-7} M and 10^{-6} M. In comparison, BPA at 10^{-4} M inhibits the basal and gonadotropin-stimulated progesterone production [100]. Besides, BPA increases progesterone levels and elevates mRNA expression of steroidogenic acute regulatory protein (StAR) and P450scc at 10^{-7} to 10^{-5} M. In contrast, progesterone levels and P450scc expression are decreased, and StAR expression is increased at 10^{-4} M. BPA exposure at the concentrations of 10^{-6} to 10^{-4} M inhibits estradiol levels and P450 aromatase expression in a dose-dependent manner [101]. BPA exposure (10^{-7} to 10^{-4} M) shows enhancive testosterone synthesis, augmentation of mRNA expression of cholesterol side-chain cleavage enzyme (P450scc), 17- hydroxylase (P450c17), and StAR in rat ovarian theca-interstitial cells. BPA (20 mg/ml) disturbs progesterone and estradiol synthesis via down-regulated gene expression of 3b-hydroxysteroid dehydrogenase (3b-HSD), cytochrome P450 side-chain cleavage (CYP11A1) and CYP19A1 related to encode steroidogenesis enzymes [102]. In the studies of isolated human luteinized granulosa cells, BPA exposure (10, 100 μg/mL) lessens the expression of steroidogenic enzyme Cyp11A1 and StAR in mice antral follicles in vitro, causing a reduction of steroidogenesis including progesterone, androstenedione, testosterone, and estradiol. However, these effects can be reversed by the removal of BPA in acute exposure [103]. Perinatal rats exposed to BPA (0.5, 50 μg/kg day) exhibit higher levels of mRNA expression of 3-β-hydroxysteroid dehydrogenase and serum progesterone, and lower levels of androgen receptor (AR) [69]. Banerjee et al. have elucidated that catalase mediated reproductive damage to granulosa cells in rats after BPA exposure. BPA exposure results in the elevation of nitric oxide, lipid peroxidation, pro-inflammatory cytokine, serum FSH and LH levels, as well as reduction of the catalase expression and estrogen or progesterone levels, of which the effects can be augmented by pretreatment with catalase blocker [104]. Zhang et al. have also revealed that BPA action may involve epigenetic regulation, as well as ER and AR signaling, nuclear receptor subfamily 5, group A, number 1 (Nr5a1) pathway [99].

We have reviewed that BPA exposure has effects on follicular formation, oocyte development, and steroidogenesis based on human and animal studies. Various studies have also observed that BPA has transgenerational effects on steroidogenesis and folliculogenesis. In utero low doses of BPA exposure will affect early ovarian development and reduce the fecundity of females in the subsequent generations.

BPA exposure (20 μg/L) to zebrafish can diminish female adult fertility up to F2 [105]. A further study [106] has shown that in utero BPA exposure not only affects

F1 but also reduces fecundity on the subsequent three generations. Wang et al. [107] have indicated that F1 female mice exposed to low doses of BPA exhibit various fertility problems, significantly increased dead pups and estrus cycle disturbance. In vivo [107] and in vitro [108] studies have reached a consistent result that BPA exposure may inhibit germ cell nest breakdown via altering the expression of critical ovarian apoptotic genes, such as decreasing expression of pro-apoptotic factors and increasing expression of anti-apoptotic factors. Shi et al. [94] also have found transgenerational effects of BPA on the earlier onset of puberty, estrous cyclicity disturbance, fertility problem, serum testosterone elevation, and primary and secondary follicle counts reduction. Early BPA exposure to F1 might reduce the relative ovary weight in F2. However, they did not observe that BPA exposure affected germ cell nest breakdown, primordial, primary, or secondary follicles in F3 ovaries on PND 4, whereas exposure to BP tended to increase germ cells in nests. Likewise, Berger et al. [109] have shown no transgenerational effects on germ cell nest breakdown and gene expression on PND 4. Collectively, these data have suggested that BPA directly targets the ovary to inhibit germ cell nest breakdown in the F1 generation, but not the subsequent generations.

One of the reasons to explain BPA exposure affecting female germ cells is that BPA may change the gene expression pattern. Liu et al. [110] have elucidated that BPA exposure to zebrafish can result in the global DNA demethylation in the ovary via altering transcripts of DNA methylation/demethylation-associated genes: glycine N-methyltransferase (GNMT), DNA methyltransferase (DNMTs), and ten-eleven translocation. The global DNA methylation level is significantly elevated in the ovary, which can be affected by DNMTs expression alteration [111]. BPA exposure can affect the DNA methylation of imprinting genes by decreasing gene expressions of Igf2r, Peg3, and H19, and curtailing mRNA expressions of specific meiotic genes, as well as increasing Nobox mRNA expression in fetal mouse germ cells [112]. Chao et al. [71] have illustrated that BPA exposure to CD-1 mice results in reduced imprinting gene expressions of Igf2r and Peg3 via the ER signaling pathway during oogenesis. A study conducted on zebrafish has demonstrated that exposure to 5 μg/L BPA may promote apoptosis in mature follicles and downregulate oocyte maturation-promoting signals, probably via alterations in the chromatin structure mediated by histone modifications [113]. Collectively, these data have indicated that the detrimental impacts of BPA on the female reproductive system may be due to the deregulation of epigenetic mechanisms.

In addition to the transgenic effects on germ cell development, BPA can also affect the sex hormone production on subsequent generations. In utero, BPA exposure will reduce cytochrome P450 aromatase mRNA levels, estradiol levels, and preantral follicle numbers in the F1 generation. On the other hand, it may decrease testosterone levels and alter mRNA expression of cytochrome P450 cholesterol side-chain cleavage, cytochrome P450 aromatase, 3β-hydroxysteroid dehydrogenase 1, and steroidogenic acute regulatory protein in the F2 generation [114]. Moustafa et al. [115] have illustrated that exposure to BPA (50 and 200 mg/kg), especially at 200 mg/kg, results in a clear marked DNA fragmentation and an increase in ER expression in the ovary, as well as serum estrogen elevation of both dam and F1

female rats. The methylation level of ovarian cytochrome P450 aromatase gene (CYP19A1A) is drastically reduced and increased, respectively, by 7- and 35-day BPA exposure. CYP19A1A mRNA expression in the ovary is reversely correlated to methylation levels of the four CpGs at the 5-flanking region [111]. These results suggest that the alteration of CYP19A1A expression can be related to the modification of DNA methylation status.

Although we have presented the human and animal data of the pernicious effects of BPA, the experiment doses of BPA are higher than the environmental doses. One study [116] has illustrated that there was no significant alteration in transcriptome and ovarian morphology in sheep ovaries when in vitro exposure to BPA at environmental doses (10^{-7} M and 10^{-8} M). Therefore, we are not sure about the exact doses of BPA which can exert its harmful effects. Further studies to prove different dose effects of BPA are needed.

3.4 The Future Direction of Prevention and Solution Methods

Due to the adverse health impacts caused by BPA exposure, BPA has begun to be eliminated from various consumer products or be replaced by substitutes such as bisphenol S (BPS), which is structurally similar to BPA. However, the structural similarity implicates that BPS may have analogical adverse effects. For instance, neonatal exposure to BPS (5 and 50 mg/kg) causes BPA like endocrine and structural changes in female rats [117]. Prenatal BPS exposure alters the expression of estrogen-responsive genes in both the uterus and ovary, displaying heightened responses in the uterus and diminished responses in the ovary, respectively [118]. Besides, BPS exposure can accelerate ovarian follicular development in prepubertal female mice. BPS causes significant germline apoptosis and embryonic lethality in the genetic model system Caenorhabditis elegans [119]. BPS administration in low or high doses can lead to female reproductive toxicities and oxidative stress in mice [120]. In consequence, these findings urge more researches and safe novel alternatives to BPA.

In addition to looking for new alternatives, studies also attempt to discover new therapies that can reverse the harmful effects of BPA. For example, Tualang honey has a protective effect on minimizing BPA-induced ovarian toxicity by modifying the estrous cycle and reducing numbers of atretic follicles [121]. Further study suggests that Tualang honey can change the ERα, ERβ, and C3 expressions and distribution in BPA-treated rats [122]. High doses of BPA (100 mg/kg/day) were pernicious to ovaries, and vitamins may have protective effects [123]. Vitamin C can be a potential antidote in a condition of ovarian toxification by BPA exposure [124]. 1,25-dihydroxyvitamin D3 (1,25D3) may reverse the detrimental effect of BPA by increasing mtDNA content, attenuating mtDNA deletion, inhibiting reduction in E2 secretion and COXI expression. Besides, 1,25D3 can increase

mitochondrial biogenesis-related proteins by PI3K-Akt signaling and elevate cellular oxygen consumption rate and ATP production [125]. What's more, Ficus deltoidea may protect against BPA-induced toxicity of the pituitary-ovarian axis in prepubertal female rats. It can restore normal estrous cycle, normalize FSH and progesterone levels, as well as reduce the number of atretic follicles [126].

Because humans are exposed to low doses and mixtures of various kinds of EDCs at different life stages, exploration of the exact effects of EDCs on human life turns to be complicated. This means that rather than the investigation of single-exposure, dose-response effects of pure chemical, we need new strategies to conduct a risk assessment on mixtures of daily EDCs such as the safe exposure threshold of mixtures rather than single pure compounds. Besides, EDCs are ubiquitous in the environment hence humans in different life stages from embryo, fetus, infant, child to adolescence, adulthood, and aging are vulnerable to EDCs. Therefore, researches on EDCs should not only focus on the dose effects, but also the timing effects. In conclusion, EDCs have been proven to be of significant adverse effects on human life. In order to diminish even reverse the harmful impacts of EDCs, we still need further researches.

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