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Endocrine Disruptors And Ovarian Dysfunction: Mechanisms And Adverse Reproductive Outcomes

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Summary
Endocrine disruptors (EDs) are external chemical substances, widely present in the environment and in consumer products, capable of interfering with the normal functions of the endocrine system through various mechanisms. This systematic review addresses their effects on female ovarian health. Human exposure occurs through ingestion, inhalation, and dermal absorption, leading to tissue accumulation and proven detrimental effects on folliculogenesis, steroidogenesis, oocyte quality, and ovarian cell viability. Among the main EDs studied are bisphenol A and analogues, phthalates, PFAS, persistent organic pollutants (such as PCBs, dioxins, and organochlorine pesticides), and heavy metals. The literature demonstrates consistent associations between these exposures and adverse reproductive outcomes, such as reduced ovarian reserve, features of polycystic ovary syndrome, premature ovarian failure, infertility, and poorer performance in assisted reproductive techniques. The mechanisms of toxicity include alterations in steroidogenesis, follicular maturation dysfunction, oxidative stress, apoptosis of oocytes and follicular cells, as well as lasting epigenetic modifications that can affect future generations. The review reinforces the urgent need for stricter regulations, public awareness, continued translational research, and the development of therapeutic strategies to protect female reproductive function in the face of increasing environmental chemical pollution.

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I. Introduction

Endocrine disruptors constitute a heterogeneous and problematic class of exogenous chemical substances that interfere with the normal functioning of the endocrine system through various mechanisms, including alteration of endogenous hormone synthesis, modification of hormone transport via transporter protein ligands, disruption of hormone metabolism through enzymatic alterations, and impediment of adequate hormone elimination, consequently resulting in altered circulating hormone status and tissue hormone action. The World Health Organization, in cooperation with the United Nations Environment Programme, established a comprehensive operational definition in 2012, characterizing endocrine disruptors as exogenous substances or mixtures that alter the functions of the endocrine system and consequently cause adverse health effects in intact organisms, their offspring, or (sub)populations. (Tzouma et al., 2025; Diamanti et al., 2025)

Human exposure to endocrine disruptors is virtually universal and continuous, occurring through multiple, complementary absorption routes. Primary sources of exposure include manufactured consumer goods that frequently come into dermal or oral contact with consumers, particularly polycarbonate and polyvinyl chloride plastics, food packaging including the inner linings of metal cans, personal care and cosmetic products containing phthalates as fragrance solvents, detergents and household cleaning products, children's toys containing plasticizers, as well as environmental contaminants from industrial, agricultural and combustion processes that are distributed through air, water and contaminated food. (Tzouma et al., 2025)

The female reproductive system, particularly the ovaries, represents a particularly vulnerable and susceptible target to the deleterious effects of endocrine disruptors. The ovaries, as the organ responsible for the production of viable female gametes and the synthesis of essential reproductive hormones, depend on an extraordinarily complex and finely balanced hormonal regulation involving multiple layers of control, from hypothalamic neural signals to pituitary endocrine feedback and local intercellular communication via gap junctions. This regulatory complexity confers upon the ovaries a particular vulnerability to disturbances caused by endocrine disruptors that can interfere at any level of this control hierarchy. (Patel et al., 2015; Flaws et al., 2015)

Documented clinical consequences of exposure to endocrine disruptors include multifactorial infertility, premature ovarian failure with early menopause, polycystic ovary syndrome with hyperandrogenic manifestations and associated metabolic dysfunction, significant alterations in circulating and tissue sex steroid hormone levels,

significant impairment of assisted reproductive technology outcomes including reduced egg retrieval and worsened embryo quality, as well as manifestations of inflammation and oxidative stress in ovarian tissue. These reproductive health problems constitute significant global public health concerns, affecting millions of women of reproductive and post-reproductive age, substantially reducing quality of life with profound economic and psychosocial consequences. (Patel et al., 2015; Ding et al., 2020)

II. Main Endocrine Disruptors, Sources Of Exposure And Environmental Distribution

Bisphenol A (BPA) and its analogues

Bisphenol A (BPA) undoubtedly represents one of the most extensively studied and widely distributed endocrine disruptors globally in the environment and human tissues. Annual industrial production of BPA exceeds six million pounds globally, making it the third most important environmental contaminant according to US environmental protection agencies. BPA is predominantly used as a plasticizer in polycarbonate polymers for food and liquid storage applications, in the internal epoxy coatings of metal cans for food and beverages, in paper thermal receipts used at points of sale, in dental restorative materials, in medical devices and implants, as well as in various other consumer products widely used in domestic and occupational settings. (Patel et al., 2015)

Human exposure to BPA is ubiquitous and essentially continuous, occurring predominantly through oral routes via ingestion of contaminated food and beverages stored in materials containing BPA, dermal routes particularly through contact with thermal paper receipts that release substantial amounts of BPA that penetrate the skin, and potentially through inhalation of particles in occupational settings. Biomonitoring studies conducted by the Centers for Disease Control and Prevention (CDC) show this to be the most reliable indicator of BPA exposure. Control and Prevention has documented the detectability of BPA in biological samples from over 90% of the sampled population in the United States, confirming the ubiquity of this exposure. BPA has been consistently detected in samples of serum, plasma, urine, sweat, breast milk, amniotic fluid, placental tissue, and even umbilical cord blood from globally studied human populations, definitively confirming the penetration and systemic distribution of this substance. (Patel et al., 2015; Urbanetz et al., 2024)

Epidemiological studies in women with polycystic ovary syndrome have consistently revealed that serum BPA levels were significantly higher in those diagnosed with polycystic ovary syndrome compared to those without the condition, suggesting a possible association between cumulative BPA exposure and the development or progression of the syndrome. BPA exposure has been consistently associated with clinically significant reduction in ovarian reserve, with women with higher exposure showing higher urinary BPA levels alongside reduced levels of anti-Müllerian hormone, a critical and well-validated marker of ovarian reserve. (Zhang et al., 2024; Tzouma et al., 2025)

Phthalates and Plastic Esters

Phthalates constitute a broad class of chemical plasticizing compounds widely used industrially in applications requiring the flexibility and durability of plastic polymers. Over eighteen billion pounds of phthalates are used annually on a global scale, predominantly as plasticizers in manufactured polyvinyl chloride (PVC) products intended for consumer applications including shower curtains, rainwear, footwear, personal care products, and the structural integrity of capsule medications. The phthalates most commonly studied in reproductive toxicity research include di- (2-ethylhexyl) phthalate (DEHP), the most widely used plasticizer, dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), and diethyl phthalate (DEP), all produced in extremely high industrial volumes and ubiquitously detectable in environments and consumer products. (Patel et al., 2015; Hlisníková et al., 2020)

Estimated daily exposure to DEHP in the general population ranges from 0.71 to 4.6 micrograms per kilogram of body weight per day, while exposure to DBP ranges from 0.84 to 5.22 micrograms per kilogram of body weight per day, representing continuous and cumulative exposures. In particular, occupationally exposed populations, such as workers in plastic factories and beauty professionals who handle products containing phthalates, may experience significantly higher exposures. Although phthalates have a relatively short biological half-life in the human body of approximately twelve hours, frequent daily exposure through ingestion of food stored in plastic packaging containing phthalates, inhalation of vapors in contaminated environments, and dermal absorption through dermal contact with products containing phthalates results in progressive accumulation and long-lasting cumulative adverse effects. (Tzouma et al., 2025; Hlisníková et al., 2020)

Exposure to phthalates has been consistently associated with reduced fertility in women attempting to conceive naturally, and specifically with poorer clinical outcomes in in vitro fertilization cycles, including a clinically significant decrease in the number of eggs retrieved during follicular aspiration, demonstrable impairment of oocyte quality based on morphological criteria, and a statistically significant reduction in embryo implantation rates. Studies demonstrate that phthalates directly affect ovulation rates by blocking the surge of luteinizing hormone and impair meiotic maturation of the oocyte through mechanisms involving cell cycle disruption. (Ding et al., 2020; Hlisníková et al., 2020)

Long-Chain Per- and Polyfluoroalkyl Substances (PFAS)

polyfluoroalkyl substances (PFAS) constitute an emerging and problematic class of synthetic chemical compounds notable for their extraordinary environmental and biological stability conferred by their extremely stable carbon-fluorine bonds. These substances exhibit environmental half-lives exceeding fifty years in soil and water, and human biological half-lives ranging from three to eight and a half years in the body, earning them the designation of "eternal chemicals" by the scientific community, as they essentially never fully degrade. The most studied long-chain PFAS include perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDoA), all of which demonstrate significant endocrine-disrupting potential. (Ding et al., 2020; An et al., 2025)

PFAS are used in the production of manufactured materials that require notable hydrophobic and lipophobic properties , including oil- and water-resistant food packaging particularly used for reheated foods such as microwave popcorn and fast foods, non-stick coated cookware and utensils (commercially known as Teflon), coatings and resistant fabrics in waterproof clothing, foams and fire-retardant compounds widely used in military bases and airports, as well as filter paper in coffee machines. National biomonitoring studies demonstrate that at least one type of PFAS has been detected in the blood of approximately ninety-seven percent of the sampled population, confirming virtually universal exposure. (Ding et al., 2020; An et al., 2025)

Clinical evidence demonstrates that long-chain PFAS substances can cross the blood-follicular barrier separating blood from follicular fluid within ovarian follicles, and their presence has been detected in follicular fluid collected during oocyte retrieval in assisted reproductive cycles, confirming direct access to germ cells and follicular support cells. Exposure to long-chain PFAS has been associated with delayed menarche occurring one to two years later than controls, chronically irregular menstrual cycles with increased variability in cycle length, significantly earlier age of natural menopause occurring from one virgin and eight months to three years and eight months earlier than the control, as well as reduced circulating levels of estrogens and androgens. (Ding et al., 2020; An et al., 2025)

Persistent Organic Pollutants and Heavy Metals

Persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), dibenzo - p-dioxin and dibenzofuran dioxins , as well as organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), hexachlorocyclohexane (lindane), and other chlorinated compounds, as well as biologically relevant heavy metals such as cadmium, arsenic, mercury, and lead, represent significant environmental sources of exposure through multiple pathways. POPs enter the environment through past and present industrial releases, agricultural pesticide applications that persist decades after their ban in many jurisdictions, and combustion processes of contaminated materials in incinerators, resulting in global environmental distribution via long-distance atmospheric transport. (Patel et al., 2015; Pan et al., 2019)

Human exposure to POPs and heavy metals occurs predominantly through the ingestion of contaminated food, including fish and other aquatic organisms that bioaccumulate these compounds in concentrations that increase successively along food chains, as well as through inhalation of air pollution in industrialized urban environments. Exposure to heavy metals, particularly cadmium through inhalation of environmental or occupational cigarette smoke, and arsenic through contaminated drinking water in specific geographic regions, has been consistently associated with significantly lower levels of anti-Müllerian hormone and clinically relevant reduction in ovarian reserve, even in women with occupational exposure considered "moderate" by regulatory agencies. (Pan et al., 2019; An et al., 2025)

III. Molecular Mechanisms Of Ovarian Toxicity

Interference with Ovarian Steroidogenesis through Disruption of Critical Gene Pathways

Ovarian steroidogenesis is a critical physiological process requiring the coordinated activation of multiple specialized cytochrome P450 enzymes and essential cofactors for the successive synthesis of sex steroid hormones from the precursor molecule cholesterol. This complex process can be profoundly disrupted by exposure to endocrine disruptors through multiple molecular mechanisms affecting gene transcription, protein translation, enzymatic activity, and cellular compartmentalization dynamics. Endocrine disruptors exert particularly pronounced effects on ovarian theca cells and granulosa cells, the two main somatic cell types responsible for the cooperative synthesis of androgens and estrogens.

Bisphenol A (BPA), due to its remarkable structural similarity to endogenous estradiol, functions as a potent xenoestrogen that can bind to both genomic and non- genomic estrogen receptors present in ovarian tissues. BPA binds to estrogen receptors alpha (ERα) and estrogen receptors beta (ERβ) in ovarian cells, causing activation of signaling pathways that result in significant metabolic and hormonal changes. In addition to its action through classical estrogen receptors, BPA additionally binds to estrogen-related gamma receptors (ERRγ), which are

expressed at particularly high concentrations in ovarian tissue as follicular differentiation progresses. (Urbanetz et al., 2024)

Exposure to BPA promotes measurable changes in the gene expression of key steroidogenic enzymes , particularly increasing the expression of 17α-hydroxylase (CYP17A1), an enzyme that catalyzes the conversion of pregnenolone to 17-OH-pregnenolone and progesterone to 17-OH-progesterone, critical steps in androgen synthesis. This increased expression of CYP17A1 leads to the hyperandrogenism characteristic of multiple female reproductive disorders, including polycystic ovary syndrome. Simultaneously, BPA promotes a significant reduction in the expression of the steroidogenic acute regulatory protein (StAR), which mediates the rate-limiting step in steroidogenesis, namely, the transport of cholesterol across the outer mitochondrial membrane to the inner mitochondrial membrane where the P450scc enzyme (cytochrome P450, cleaver side) can access it to initiate steroidogenic synthesis . (Patel et al., 2015; Urbanetz et al., 2024)

In vitro studies using isolated and cultured ovarian granulosa and theca cells demonstrate that BPA potently inhibits the enzymatic activity of aromatase (CYP19A1), the enzyme responsible for the final conversion of testosterone to estradiol and androstenedione to estrone in ovarian tissues, resulting in a significant increase in testosterone levels and a corresponding reduction in estradiol. This aromatase inhibition by BPA operates through multiple mechanisms including depletion of essential cofactors such as NADPH, alteration of CYP19A1 gene expression, and possible direct inhibition of enzymatic activity. Additionally, BPA may interact with the sex hormone- binding globulin (SHBG) transport protein, increasing the amount of biologically available circulating free testosterone. (Patel et al., 2015; Urbanetz et al., 2024)

In experimental animal models, particularly in isolated antral follicles from mice exposed to BPA, an acute and dose-dependent decrease in the expression of Cyp11a1 (P450 cleaver side) occurs, leading to a progressive reduction in pregnenolone, androstenedione, testosterone, and estradiol levels. These findings in animal models were subsequently validated in primary culture systems of human ovarian cells, where BPA at environmentally found concentrations and at clinically relevant concentrations demonstrated similar inhibitory effects on multiple critical steroidogenic enzymes . (Patel et al., 2015; Urbanetz et al., 2024)

polyfluoroalkyl substances (PFAS) modulate ovarian steroidogenesis primarily through the activation of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs), particularly PPAR-α and PPAR-γ , which are expressed at relevant levels in ovarian cells during folliculogenesis . Mechanistic studies demonstrate that long-chain PFAS block ovarian steroid hormone synthesis by critically interfering with the expression of transcriptional factors and regulatory proteins involved in steroidogenic pathways , particularly through a pronounced reduction in the expression of steroidogenic acute regulatory protein (STAR), whose product is absolutely essential for mitochondrial cholesterol transfer. Research with PFOS has demonstrated that chronic exposure of adult female rats to PFOS at environmentally relevant concentrations suppresses estradiol biosynthesis, possibly through reduced STAR expression mediated by reduced histone acetylation, an additional epigenetic mechanism described below. (Ding et al., 2020; Shi et al., 2009; Feng et al., 2015)

Research on phthalate exposure reveals that these compounds decrease ovarian estradiol levels by significantly reducing gene expression in multiple critical genes in the estradiol biosynthesis pathway, including Cyp19a1, Cyp17a1, Cyp11a1, Star, 17β- hydroxysteroid dehydrogenase-1 (Hsd17b1), and 3β- hydroxysteroid dehydrogenase-1 (Hsd3b1). This pattern of coordinated reduction of multiple steroidogenic enzymes by di- (2-ethylhexyl) phthalate (DEHP) has been documented in both primary ovarian cell culture systems and intact ovarian follicles. (Patel et al., 2015; Hlisníková et al., 2020)

Persistent organic pollutants, particularly DDT and its metabolite DDE, exert significant disruptive effects on steroidogenesis. In vivo studies have demonstrated that exposure of female rats to o,p' -DDT at doses of 0.1 to 1 milligram per kilogram reduced ovarian production of prostaglandin E2 (PGE2) in a dose-dependent manner, a lipid mediator critical for successful ovulation. In vitro studies using primary cultures of bovine granulosa cells and luteinized cells revealed that exposure to DDT and DDE increased the secretion of oxytocin, a peptide hormone involved in the regulation of follicular growth and luteinization. Specifically, lindane, another organochlorine compound, when applied to cultured mouse antral follicles, resulted in inhibition of progesterone synthesis in granulosa cells, induction of anti-Müllerian hormone production in rat granulosa cells, and a generalized reduction in estradiol, testosterone, and androstenedione levels. (Wang et al., 2025; Shibayama et al., oral presentation; Wang et al., 2025)

Heavy metals such as cadmium and lead interfere with steroidogenesis through additional mechanisms, particularly by inducing oxidative damage that impairs the function of the complex mitochondrial enzymatic machinery involved in steroidogenic synthesis. Cadmium, in particular, can substitute for iron and copper ions in metal-containing proteins, altering critical protein structural conformations and generating toxic hydroxyl radicals through Fenton-like reactions, resulting in amplified oxidative damage to mitochondria-localized steroidogenic enzymes.

Multifactorial Disruption of Ovarian Folliculogenesis

Folliculogenesis , a complex process involving the recruitment of primordial follicles stored since fetal life, their progressive growth through multiple distinct stages of development, proliferation and differentiation of follicular somatic cells, expansion of oocyte volume , and finally maturation to ovulation, constitutes an extraordinarily refined physiological process that can be fundamentally disrupted by exposure to endocrine disruptors at any stage of its development. Endocrine disruptors can interfere with folliculogenesis through multiple distinct molecular mechanisms that often interact synergistically.

Exposure to hexyl diethyl phthalate (HEHP) accelerates the recruitment of stored primordial follicles through overactivation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway, a crucial intracellular signaling pathway that, when constitutively activated, promotes the transient transfer of follicles from the primordial reserve population to the growing follicle pool. This acceleration of premature follicular recruitment results in accelerated and significant depletion of the finite ovarian reserve established during gestation, explaining the epidemiological observations of reduced ovarian reserve in women with higher phthalate exposure. Dibutyl phthalate (DBP), another widely used phthalate, inhibits antral follicle growth through cell cycle disruption by decreasing the expression of critical cell cycle regulatory proteins such as cyclin D2 (Ccnd2) and cyclin -dependent kinase 4 (Cdk4), effectively blocking progression through the G1/S restriction point of the cell cycle. (Patel et al., 2015; Hlisníková et al., 2020)

polyfluoroalkyl substances interfere with gonadotropin-dependent follicular maturation, luteinizing hormone (LH)-stimulated ovulation, and follicular hormone secretion through multiple convergent mechanisms. Mechanistic studies have revealed that PFAS act as agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ) in granulosa cells, critically impairing follicle-stimulating hormone (FSH)-dependent follicular maturation and LH-stimulated ovulation. PFAS activation of PPAR-γ in granulosa cells interferes with FSH signaling pathways, particularly blocking the cAMP signaling cascade that is critical for an appropriate follicular response to FSH. (Ding et al., 2020; previous publication 2024 in preparation)

Recent experimental research using bovine oocytes cultured in vitro has demonstrated that the administration of perfluorononanoic acid... The use of phospholipid bicarbonate (PFNA) at a concentration of 10 microliters per milliliter for a period of twenty-two hours in culture had a significant negative effect on oocyte developmental competence during meiotic maturation. This decrease in oocyte survival was mechanistically attributed to PPAR-α activation, leading to disruption of lipid metabolism and excessive lipid accumulation in oocytes and ovaries. Convergent research has shown that the presence of excessive lipids in the ooplasm correlates with impaired oocyte developmental competence and decreased oocyte survival rates. (Hallberg et al., 2019)

Oxidative Stress and Apoptosis of Oocytes and Somatic Follicular Cells

Oxidative stress, defined as an imbalance between the generation of reactive oxygen species (ROS) such as superoxide radicals and hydrogen peroxide, versus the ability of antioxidant defenses to decompose and neutralize these reactive species , constitutes a central mechanism through which endocrine disruptors exert ovarian toxicity with significant consequences for oocyte quality, follicular somatic cell viability, and overall reproductive function.

Exposure to BPA causes substantial oxidative damage to ovarian tissues through increased production of reactive oxygen species and simultaneous impairment of mitochondrial function, particularly in oocytes and granulosa cells. In isolated antral follicles from mice exposed to BPA, there is a significant and dose-dependent increase in the Bax:Bcl-2 ratio, with increased expression of the pro-apoptotic protein Bax and simultaneous decrease in the expression of the anti-apoptotic protein Bcl-2, leading to activation of the intrinsic mitochondrial apoptotic cascade and resulting in programmed follicular atresia. Simultaneously, the expression of transformation-related protein 53 (Trp53), a critical transcription factor in cellular apoptosis, increases, further amplifying apoptotic signals. (Patel et al., 2015; Gao et al., 2015) polyfluoroalkyl substances (PFAS) induce excessive and uncontrolled production of reactive oxygen species (ROS) and trigger the cellular apoptotic cascade via the mitochondria-dependent intrinsic pathway, particularly in oocytes and granulosa cells. This heightened oxidative stress compromises mitochondrial function by disrupting the mitochondrial membrane potential gradient, reducing adenosine triphosphate (ATP) synthesis, and altering mitochondrial dynamics, including fragmentation and abnormal redistribution. The resulting damage compromises the structural stability of the oocyte-cumulus cell complex by disrupting gap junctions, eventually leading to apoptosis and oocyte necrosis. (Ding et al., 2020; An et al., 2025)

Studies using occupational exposure to atrazine , a widely used herbicide classified as an endocrine disruptor, have revealed that exposure stimulates a significant increase in the production of reactive oxygen species, ovarian inflammation with an increase in pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and nitrification oxidative synthase (iNOS), as well as increased expression and activation of caspase-3, a critical protease in the apoptotic cascade. Additionally, atrazine exposure resulted in an increased BAX:BCL-2 ratio and activation of signaling through the NRF-

2/NQO1 pathway, suggesting activation of adaptive stress responses that eventually become insufficient. (Zhao et al., 2024)

Heavy metals such as arsenic and cadmium exert oocyte toxicity through ROS generation and direct mitochondrial dysfunction. Exposure of meiosis II mouse oocytes to arsenite resulted in decreased mitochondrial membrane potential at one hour of exposure, with a subsequent increase in significantly elevated ROS at two hours of exposure. These effects were completely reversible by co-treatment with N- acetylcysteine , a precursor of reduced glutathione, confirming an oxidative stress mechanism. Maternal exposure to arsenite in mice resulted in a significantly elevated incidence of meiotic spindle abnormalities in harvested oocytes, and zygotes derived from exposed animals exhibited significantly reduced cleavage and in vitro development rates compared to controls. (Malott et al., 2021; Zhu et al., previous review)

Exposure to cadmium in meiosis II oocytes resulted in significant depletion of adenosine triphosphate content and aberrant mitochondrial distribution. Additionally, cadmium exposure disrupted meiotic spindle assembly and chromosome alignment, both energy-intensive ATP-dependent processes, leading to increased ROS, abnormal mitochondrial distribution within oocytes, and decreased levels of the epigenetic modifications 5-methylcytosine, histone 3 lysine 9 trimethylation (H3K9me3), and histone 3 lysine 9 acetylation (H3K9ac), processes that depend on mitochondrial energy. (Malott et al., 2021)

Long-Lasting Epigenetic Modifications with Transgenerational Potential

Endocrine disruptors induce long-lasting epigenetic changes that affect reproductive function not only in the exposed individual, but potentially in successive generations through heritable transmission of epigenetic modifications that occur in the germline. Epigenetics refers to regulatory mechanisms of gene expression that modify phenotype without altering the underlying DNA sequence, including cytosine dinucleotide methylation. CpG , post- translational histone modifications , nucleosome repositioning , and regulation by non-coding microRNAs .

DNA methylation and histone modifications represent fundamentally important epigenetic mechanisms in the regulation of genes associated with fertility, folliculogenesis , oocyte quality, and recruitment of dormant primordial follicles . Exposure to endocrine disruptors during critical periods of development, particularly during fetal gonadal organogenesis in the second and third trimesters of gestation and during gonadal sex determination, can permanently reprogram DNA methylation and alter the expression of steroid hormone receptors through epigenetic mechanisms. (Tzouma et al., 2025; Voros et al., 2025)

Epidemiological studies demonstrate that perinatal and fetal exposure to endocrine disruptors can contribute to altered fetal programming and, consequently, lead to the subsequent development of polycystic ovary syndrome, premature ovarian failure, and other reproductive disorders through persistent epigenetic modifications established during critical fetal development. These fetal programming effects may not manifest phenotypically until individuals reach reproductive age, explaining the latency between fetal exposure and clinical manifestation of disease. Genes with modified DNA methylation are primarily involved in hormonal regulation and inflammatory pathways, as well as energy metabolism and insulin sensitivity. (Tzouma et al., 2025)

Histone modifications, particularly histone acetylation, represent a critical mechanism through which endocrine disruptors can alter the expression of genes critical for ovarian function. Histone acetylation is mediated by histone acetyltransferases (HATs), which add acetyl groups to lysine residues in histone tails , neutralizing positive charges and resulting in an open chromatin conformation that promotes transcription. In contrast, histone deacetylases (HDACs) remove acetyl groups, causing chromatin condensation and gene silencing. Histone acetylation at specific sites in ovarian granulosa cells has been correlated with increased expression of genes that control estrogen synthesis and follicular development, including CYP19A1, which encodes aromatase. (Voros et al., 2025; Olsen et al., 2021)

Studies demonstrating that deficient acetylation at H3K9 and H3K27 in aged oocytes causes chromosomal instability, failed meiotic progression , and deficient meiotic spindle assembly, leading to increased aneuploidy and oocyte degeneration. Loss of histone acetylation at H3K9 and H3K27 sites causes heterochromatin compaction, which silences important meiotic genes and impairs cumulus-oocyte communication. Additionally, HDAC-mediated deacetylation disrupts mitochondrial function by inhibiting mitochondrial transcription factor A (TFAM), a protein absolutely necessary for mitochondrial biogenesis and ATP generation in mature oocytes. (Sindik et al., 2024)

Exposure to endocrine disruptors can alter histone methylation dynamics, particularly by increasing histone H3 trimethylation at lysine 27 (H3K27me3), a chromatin repressive mark associated with gene silencing. Studies of embryos derived from assisted reproductive techniques have identified persistent H3K27me3 hypermethylation associated with delayed embryonic genome activation, decreased blastocyst formation, and reduced implantation potential, findings suggesting that assisted reproductive techniques or culture contamination by endocrine disruptors may inadvertently affect histone methylation dynamics. (Sciorio et al., 2022)

Intercellular Communication Disruption and Gap Junctions

Intercellular communication through gap junctions composed predominantly of connexin proteins represents a critical mechanism through which granulosa cells communicate with each other and with the oocyte, transferring essential small molecules, nutrients, and signaling molecules. Genetic studies in knockout mice deficient in connexin 43 (Cx43), the main component of gap junctions between granulosa cells, revealed that Cx43-deficient follicles arrest at early preantral stages and produce meiotically incompetent oocytes incapable of fertilization. Electrophysiological patch- clamp studies revealed that the conductance between Cx43-deficient granulosa cells was virtually zero (2.6 ± 0.8 nanosiemens) compared to wild-type cells (84.1 ± 28.6 nanosiemens), confirming ablation of intercellular communication. (Ackert et al., 2001; Kidder et al., 2002; Tong et al., 2006)

Connexin 37 (Cx37) is another critical connexin specifically expressed in oocytes that mediates oocyte-granulosa cell communication. Cx37-deficient knockout mice exhibit impaired follicular development with arrest at the early secondary follicle stage, demonstrating the critical importance of this gap junction for successful follicular progression. PFAS can interfere with intercellular communication by disrupting gap junction dynamics, potentially through alterations in connexin gene expression or disruption of biophysical properties of cell membranes that affect gap junction stability and function. (Ackert et al., 2001)

IV. Clinical Impacts Of Exposure To Endocrine Disruptors On Female Reproductive Health

Reduction of Ovarian Reserve and Its Clinical Manifestations

Ovarian reserve, defined as the total number of functionally competent oocytes stored within the ovaries, is established solely during fetal life in the second trimester of gestation when the population of primordial germ cells undergoes final differentiation and formation of primordial follicles. This process of primordial follicle formation occurs approximately between the eighth and twentieth weeks of gestation, making it absolutely critical that exposure to toxic substances be minimized during this critical period of development. After birth, no oocyte neogenesis occurs, so ovarian reserve is simply determined during fetal life and only progressively decreases throughout adult life through repeated monthly ovulation and continuous basal cell death. This irreversible nature of ovarian reserve makes intrauterine exposure to endocrine disruptors particularly deleterious, as any reduction in oocytes during fetal life cannot be reversed or compensated for later. (Ding et al., 2020)

Robust evidence from experimental animal studies demonstrates that intrauterine exposure to endocrine disruptors can significantly compromise this critical reserve, decreasing the number of primordial follicles from birth through multiple mechanisms including induction of accelerated atresia, acceleration of primordial follicle recruitment for premature growth, and induction of germ apoptosis . Differentiating cells . Epidemiological studies in women of reproductive age have revealed that urinary BPA levels were significantly higher in the group with diminished ovarian reserve (defined as anti-Müllerian hormone below the 25th percentile for age) compared to the group with normal ovarian reserve. Multivariate logistic regression analysis adjusting for age, oral contraceptive use, age at menarche, parity, and waist circumference revealed a significant increase in infertility in the group with high BPA exposure compared to the group with low exposure. (Tzouma et al., 2025)

European epidemiological research demonstrates that women residing in geographic areas with high atmospheric levels of particulate pollutants (PM 2.5 and PM 10) have a significantly increased risk of significant reduction in ovarian reserve, with the risk increased two to three times compared to women in areas with low air pollution. The prospective study directly correlated measured levels of anti-Müllerian hormone with objective measurements of air pollution in the woman's place of residence, confirming a linear dose-response relationship: the higher the air pollution in the region of residence, the lower the measurable levels of AMH and the reduced ovarian reserve. (Pan et al., 2019; An et al., 2025)

Polycystic Ovary Syndrome and Associated Hyperandrogenism

Polycystic ovary syndrome (PCOS), the most common endocrinopathy among women of childbearing age, affecting approximately five to ten percent of this population, has a consistent and clinically relevant epidemiological association with exposure to multiple endocrine disruptors. PCOS is characterized by clinical hyperandrogenism (hirsutism, acne, alopecia) or biochemical hyperandrogenism (elevated free or total testosterone), irregular menstrual cycles or amenorrhea, findings of enlarged ovaries with multiple small antral follicles on ultrasound, and frequently insulin resistance with compensatory hyperinsulinemia.

Case-control studies reveal an association between a significantly increased prevalence of polycystic ovary syndrome in women of reproductive age and greater exposure to per- and polyfluoroalkyl substances (PFAS) and bisphenol A, with analyses adjusted for potential confounders revealing odds... Increased rates of PCOS diagnosis were observed in the highest quartiles of PFAS and BPA exposure. Bisphenol A may act through multiple distinct but convergent molecular mechanisms in the pathogenesis of polycystic ovary syndrome. These mechanisms include altered gene expression of genes specifically related to PCOS and systemic dysregulation of the hypothalamic-pituitary-ovarian axis (HPO axis). (Zhang et al., 2023; Zhan et al., 2023) dysregulation caused by BPA exposure affects function at both the hypothalamic and pituitary levels, with profound consequences for

the ovary . Excessive activation of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus induces a steady increase in luteinizing hormone (LH) secreted by the anterior pituitary and a concomitant decline in follicle-stimulating hormone (FSH) secreted by the pituitary, impairing normal follicular development and increasing ovarian androgen production. BPA can directly alter the expression of ovarian steroidogenesis genes by increasing mRNA expression of key enzymes such as 17α-hydroxylase, leading to pronounced hyperandrogenism and ovulatory dysfunction. BPA can also alter the expression of genes encoding enzymes such as epoxide hydrolase 1, which reduces the conversion of testosterone to estradiol, further contributing to hyperandrogenism. (Patel et al., 2015; Urbanetz et al., 2024)

BPA can directly stimulate androgen production in ovarian theca cells, causing direct hyperandrogenism, as well as interact with receptors in peripheral adipose tissue and stimulate pancreatic beta cells to produce insulin, leading to compensatory hyperinsulinemia. The subsequent hyperinsulinemia results in lipid accumulation in adipose tissue and systemic insulin resistance, adversely affecting ovarian folliculogenesis and precipitating anovulation, favoring the development of PCOS phenotype. (Urbanetz et al., 2024)

Premature Ovarian Failure and Early Menopause

Premature ovarian insufficiency (POI), formerly known as "premature ovarian failure," is a serious gynecological endocrine condition characterized by the cessation of menstruation before the age of forty, with elevated levels of follicle-stimulating hormone (FSH > 40 mIU /ml on two occasions with a minimum interval of one month) and reduced levels of estradiol (< 20 pg /ml), frequently accompanied by primary infertility.

Epidemiological studies identify a statistically significant association between exposure to multiple classes of endocrine disruptors, including pesticides, alkylphenols , polycyclic aromatic compounds , toxic metals, and phytoestrogens, with an increased risk of premature ovarian failure and premature ovarian insufficiency. Prospective analyses in cohorts of menopausal women reveal that participants with higher serum concentrations of per- and polyfluoroalkyl substances (PFAS) have a significantly shorter time since natural menopause, with menopause occurring one year and eight months to three years and eight months earlier compared to women with lower PFAS exposure. Mediation analyses suggest that follicle-stimulating hormone (FSH) acts as a key mediator in this association, suggesting that PFAS induce FSH elevation that precipitates accelerated depletion of ovarian reserve. (Ding et al., 2020; An et al., 2025)

Adverse Outcomes in Assisted Reproduction

Exposure to endocrine disruptors significantly and clinically impairs the outcomes of assisted reproductive technologies, including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Studies demonstrate that BPA exposure is negatively associated with peak serum estradiol levels during ovarian stimulation with gonadotropins, the absolute number of oocytes retrieved during follicular aspiration, the number of normally fertilized oocytes (2 pronuclei fertilization), and embryo implantation rates after embryo transfer. BPA has also been linked to a measurable decrease in basal antral follicle counts in infertile women with polycystic ovary syndrome, suggesting an important role for BPA in compromising ovarian reserve. (Tzouma et al., 2025; Urbanetz et al., 2024)

Exposure of women undergoing in vitro fertilization cycles to higher levels of PFAS in blood and follicular fluid was associated with slightly higher basal antral follicle counts (a finding that may reflect accelerated premature recruitment), but a lower chance of obtaining embryos of high morphological quality based on embryo grading criteria. Additionally, higher phthalate exposure is associated with a statistically significant reduction in fertility in women attempting natural conception, poorer outcomes in IVF cycles including decreased egg retrieval, decreased oocyte morphological quality, and reduced rates of appropriate fertilization and embryonic development. (Ding et al., 2020; Tzouma et al., 2025)

Specific Effects of Bisphenol A on Meiotic Competence and Oocyte Quality

Bisphenol A (BPA) demonstrates particularly deleterious and well-documented effects on oocyte quality and reproductive competence at multiple levels of biological organization. Hunt and colleagues were the first to unequivocally establish a causal link between meiotic aneuploidy in mammals and accidental exposure to a specific environmental chemical contaminant, identifying that BPA exposure causes measurable meiotic defects in oocytes harvested from exposed mice, including specific alterations in chromosome segregation and increased chromosomal nondisjunction during meiosis I. (Hunt et al., 2003; Hunt et al., 2012)

Exposure to BPA induces specific epigenetic alterations in developing oocytes that can lead to meiotic errors and increased aneuploidy. Subsequent studies by Trapphoff et al. demonstrated that BPA affects the architecture of the meiotic spindle, causes abnormalities in chromosome condensation, and induces aneuploidy through errors in meiotic division I. BPA also significantly reduces the amount of hyaluronic acid present in the extracellular matrix of the oocyte cumulus , a critical structure that facilitates communication between the oocyte and cumulus cells and is absolutely necessary for proper cumulus expansion during meiotic maturation.

Additionally, BPA adversely affects oocyte meiotic maturation through mechanisms involving disruption of meiotic spindle dynamics and proper progression through meiosis I and II (Trapphoff et al., 2012; Patel et al., 2015).

V. Final Considerations And Summary Of Evidence

The body of scientific evidence accumulated over two decades of intensive research consistently, replicably, and mechanistically plausibly demonstrates that endocrine disruptors represent a significant and ubiquitous threat to ovarian health and female reproductive capacity. The molecular mechanisms through which these environmental contaminants exert ovarian toxicity are multifactorial and often overlapping, involving interference with steroidogenesis through alterations in gene expression of critical enzymes, multidimensional disruption of folliculogenesis through multiple simultaneously operating mechanisms, induction of oxidative stress with an uncontrolled increase in reactive oxygen species, activation of apoptotic cascades in oocytes and follicular somatic cells, as well as lasting epigenetic modifications that can affect successive generations not yet exposed. (Patel et al., 2015; Ding et al., 2020; Tzouma et al., 2025)

The particular vulnerability of the female reproductive system to exposure to endocrine disruptors stems from multiple biological characteristics: the extraordinary complexity of ovarian processes involving multiple specialized cell types and signaling pathways; the extraordinarily refined hormonal regulation necessary for normal reproductive function; the extended duration of oocyte development , beginning during fetal life in the second trimester of gestation and continuing until potential ovulation in adulthood, conferring critical periods of vulnerability to toxic exposure; the irreversible nature of the ovarian reserve established during fetal life; and the fact that meiotic processes involved in oocyte maturation are energetically intensive and particularly sensitive to metabolic disturbances caused by oxidative stress. (Patel et al., 2015; Flaws et al., 2015)

Epidemiological data consistently converge to demonstrate that exposure to endocrine disruptors is significantly associated with multiple clinically relevant adverse reproductive outcomes. Key documented epidemiological associations include measurable and clinically significant reduction in ovarian reserve with a reduction in the number of primordial and antral follicles , polycystic ovary syndrome with associated hyperandrogenic manifestations , premature ovarian failure with natural menopause occurring many years earlier, infertility of multiple etiologies, and significantly compromised outcomes in assisted reproductive cycles including a lower number of oocytes retrieved and decreased embryo quality. (Tzouma et al., 2025; Ding et al., 2020; Pan et al., 2019)

The ubiquity of human exposure to these chemical contaminants, through everyday consumer products repeatedly in contact with contaminants, food consumed daily in packaging that releases contaminants, contaminated drinking water in specific geographic regions, and ubiquitous air pollution in urban and peri-urban environments , makes the urgent implementation of mitigation and prevention strategies operating simultaneously at multiple levels of society and government imperative. (Tzouma et al., 2025)

It is strongly recommended that substantially more stringent regulatory policies based on sound biological mechanisms be implemented to significantly restrict or completely eliminate the use of known and suspected endocrine disruptors in manufactured consumer products, with a particular focus on products that come into prolonged contact with food or that are used by vulnerable populations, including children and women of childbearing age. (Tzouma et al., 2025; An et al., 2025)

Systematically increasing public awareness and education about common and ubiquitous sources of exposure to endocrine disruptors, and practical, implementable strategies for reducing personal exposure, is an essential component of an integrated public health approach. Simple dietary changes, including avoiding foods in plastic packaging or epoxy-coated metal cans, reducing consumption of processed foods often packaged in contaminated materials, increasing consumption of fresh, organically grown foods when possible, and carefully selecting personal care, cosmetic, and household cleaning products that are explicitly free of phthalates, parabens, and other known endocrine-disrupting chemicals, can substantially reduce individual exposure. (Tzouma et al., 2025)

Future scientific research should urgently prioritize large-scale prospective longitudinal studies that assess the cumulative effects of chronic exposure to endocrine disruptors on human fertility across multiple time points. Well-designed prospective cohort studies are urgently needed to elucidate dose-response relationships, assess long-term and potentially transgenerational effects, explore differential susceptibility in specialized populations, and develop and validate promising therapeutic intervention strategies. (Ding et al., 2020; Tzouma et al., 2025)

The development of pharmacological and behavioral therapies aimed at mitigating hidden damage induced by endocrine disruptors constitutes an extraordinarily promising area for future translational research. Therapeutic strategies under development include the use of potent antioxidants to combat induced oxidative stress, modulators of cell signaling pathways to restore gonadotropin sensitivity, and epigenetic regulators potentially capable of reversing deleterious epigenetic modifications. Additionally, the implementation of natural

cycle assisted reproductive techniques with minimal gonadotropin stimulation and other personalized approaches may represent valuable alternatives for women whose reproductive systems have been damaged by exposure to endocrine disruptors. (Patel et al., 2015; Tzouma et al., 2025)

A thorough understanding of the specific molecular mechanisms through which endocrine disruptors interfere with normal female reproductive function can facilitate the development of environmental policies grounded in solid, translational scientific evidence, as well as personalized clinical interventions based on biomarkers of exposure and genetic susceptibility. The rigorous implementation of these scientific and public health recommendations is imperative, urgent, and necessary to adequately safeguard the reproductive health of current and future generations of women of reproductive age in the face of the growing and ongoing challenge of ubiquitous anthropogenic environmental chemical pollution.

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