

ENDOCRINE DISRUPTOR CHEMICALS

Beatrice Anne M.D., D.M., Assistant Professor, Department of Endocrinology, Nizam's Institute of Medical Sciences, Hyderabad. maglarne@yahoo.com **Ruby Raphael, M.D.**, Senior Resident, Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad. drrubyraphael@gmail.com

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ABSTRACT

Endocrine Disrupting Chemicals (EDCs) impact health and disease. Scientific research conducted over the last few decades has solidified our knowledge of the health impacts of these chemicals. Intrauterine exposure of EDCs can have transgenerational effects, thus laying the foundation for disease in later life, when exposure may not be documentable. The meticulously orchestrated endocrine system is often a target for these chemicals. As the endocrine system is central to the body's physiological and biological functions, EDCs can lead to perturbations in the functioning of an individual. Exposure to EDCs can occur right from children's products to personal care products, food containers to pesticides and herbicides. Moreover, there are many unsuspected chemicals which may be contributing to the disease burden in the society, which have never been studied. The dose response relationship may not always be predictable for the different EDCs as even low-level exposures that may occur in everyday life can have significant effects in a susceptible individual. Although individual compounds have been studied in detail, the effects of a combination of these chemicals are yet to be studied in order to understand the real-life situation, where human beings are exposed to a cocktail of these EDCs. This chapter aims to summarize the available literature regarding these EDCs and their effects on endocrine physiology.

INTRODUCTION

Endocrine Disrupting Chemicals (EDCs) are a ubiquitous problem. This is a global issue and health hazard not well addressed due to lack of evidence and testing. Only a few EDCs are known and the others are suspected or yet to be explored (1). EDCs represent a broad class of natural or synthetic chemicals which are widely dispersed in the environment. This can be ingested or consumed or inhaled and may be found in larger quantities or trace amounts in serum, placenta, fat, umbilical cord blood etc. Exposure to EDCs can occur as early as in gestational period or childhood and can impact later stages of life. EDCs can alter normal physiological mechanisms in our body leading to a myriad of endocrinological problems both in children and adults.

The Endocrine Society defined EDC as "an exogenous chemical, or mixture of chemicals, that interfere with any aspect of hormone action." In other words, the chemical substances that can affect the endocrine system resulting in adverse effects are called Endocrine Disruptor Chemicals (EDCs) (2). These chemicals often bind to the endogenous receptors (e.g.: estrogen receptor, steroid receptor) and interfere with the normal function of brain, reproductive organs, development, immune system, and other organs (3).

The common EDCs are bisphenol A (BPA), perchlorate, dioxins, phthalates, phytoestrogens, polychlorinated biphenyls (PCB), polybrominated diphenyl ethers (PBDE), triclosan, perfluoroalkyl and polyfluoroalkyl substances (PFAS), pesticides like dichlorodiphenyldichloroethylene (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), organophosphorus compounds, alkylphenols(surfactants), parabans, methoxychlor, diethylstilbestrol (DES), fungicide vinclozolin, and natural hormones (2) (4) (5). Among these, BPA is the most commonly encountered EDC, which has both estrogenic and antiandrogenic properties. EDCs are mostly lipophilic in nature and resistant to metabolism (6). EDCs are usually present in food, beverages, pesticides, or air. People who get exposed to any of these EDCs may have hormonal imbalance. Even a small amount of EDC consumed can result in hormonal imbalance especially in children (2). Sometimes they are stored in body fats, and transferred to the developing fetus via the placenta (6).

Studies on animal models and humans reveal that the mechanisms through which the EDCs act involve divergent pathways. The EDC's can act like endogenous hormones and thereby increase or decrease the cellular response. Also, they can block the effects of hormones and stimulate or inhibit the production of hormones. They can thus interfere with synthesis, transport, action, and degradation of hormones (7). EDCs can act via nuclear receptors,

nonsteroidal receptors, transcription coactivators, and certain enzymatic pathways (5).

HISTORY OF EDCs

The effect of EDCs was first noticed by pig farmers in USA. Farmers observed pigs fed on moldy grain did not reproduce. Later it was found that moldy grain contained mycoestrogens. Several other incidents with such EDCs were noticed by farmers in other parts of the world. In 1940, diethylstilbestestrol (DES), a synthetic estrogen, was prescribed to women in their first trimester of pregnancy to prevent threatened miscarriage. Later in 1971, a rare vaginal cancer in daughters born to mothers who had taken DES was noted. All these events inspired Rachel Carlson to write a book named 'Silent Spring'. In this book the author warned about long- term consequences of the use of pesticides and herbicides. In another book 'Our Stolen Future 'by Theo Colbron, Dianne Dumankosi, and John Peterson Meyers additional evidence on EDC was described. The hypothesis and evidence generated by this book was used for future research on EDC. This booked paved the path for the US regulators to create the United States Environment Protect Agency.

ARE HORMONES AND EDCs THE SAME?

EDCs are not the same as hormones but they can mimic hormones, and produce ill effects in the body.

Table 1. The Difference Between Hormone and Endocrine Disruptor Chemicals. (4)(8)		
Hormones	EDCs	
(1) These are chemical substances produced	(1) Exogenous substance that alters function(s)	
by the body and transported via bloodstream to	of the endocrine system and consequently	
the cells and organs which carry receptors for	causes adverse effects in an intact organism, or	
the hormone and on which it has a specific	its progeny, or populations.	
regulatory effect.		
(2) They act via specific receptors and produces	(2) They act via hormone and other receptors	
class effects	and produces abnormal functions and	
	interactions.	

(3) No bio accumulation	(3) Results in bioaccumulation
(4) Non-linear dose response with saturable	(4) Non-linear dose response with saturable
kinetics	kinetics
E.g.; steroid hormones, thyroid hormones	E.g.; Perchlorate, Dioxins, Phthalates

EDCs AND HUMAN HEALTH

EDCs can affect several systems in our body resulting in many ill health effects. There is evidence showing various diseases are linked to EDCs as shown in Table 2.

Table 2. Examples of EDCs and Their Possible Mechanisms Resulting in Clinical Conditions. (4)(9)(10)			
EDCs	Main Sources	Possible Mechanism	Clinical condition
Alkylphenols	Detergents Shampoos Pesticide	Mimics estrogen	Breast cancer
Phthalates	Plastic products Personal care products (perfume, moisturizer)	Not yet known	Testicular and ovarian toxicants
Polychlorinated biphenyls (chlorinated/ halogenated/ TBBPA)	Paints Plastics Lubricants Electrical applications	Estrogenic and anti- androgenic activity Indirectly regulate circulating gonadal hormones. Inducers of CYP1A and CYPIIB Decreased NMDA receptor binding in striatum, frontal cortex and hippocampus, cerebellum Reduced glutamate and dopamine Acts at AhR signaling pathways resulting in cytotoxic effects	Neurobehavioral defects like cognitive deficits in children Neurotoxicity Thyroid toxicity Susceptibility to infections Cancers (especially Breast Cancer) Infertility

TBBPA- Tetrabromobisphenol A, CYP - cytochrome P450 enzymes, NMDA- N-methyl-D-aspartate, AhR - aryl hydrocarbon receptor

EFFECT OF EDCs ON ENDOCRINE SYSTEM

Neuro- Hypothalamic Effects

According to recent studies one in eight children 2-9 years of age suffer from neurodevelopmental disorders (NDDs) in India. NDDs include speech and language disorders, autism, cerebral palsy, epilepsy, vision impairment, ADHD, learning disorders, etc. EDCs are one among other risk factors associated with development of NDDs in children. NDD burden can be lessened by eliminating the causative factors or by preventing exposure to them. The major EDCs associated with NDDs are PCB and polybrominated diphenyl ethers (PBDEs). Other EDCs that are linked to NDDs but lack firm evidence are brominated flame retardants, perfluorinated compounds, and pesticides. Animal studies reveal that EDCs can alter or affect development. svnaptic neuronal organization. neurotransmitter synthesis and release, and structural development of the brain (11). Studies of pregnant women who lived near Lake Michigan, with high levels of exposure to PCBs, revealed that children of mothers with the highest exposure levels were much more likely to have lower average IQ levels and poorer performance on reading comprehension (12). BPA and phthalates have also been shown to be associated with behavioral problems in children, including anxiety and depression (13,14). Prenatal pesticide exposure has been linked to increased likelihood of children having autism spectrum disorder or developmental delay (15).

EDCs can cause perturbations of the neuroendocrine processes originating in the hypothalamus, and can also act on the steroid hormone receptors and other signaling pathways that occur widely throughout the brain. The critical period of exposure is important because even minor alterations in hormones can alter the neurobiological outcome during development. Our knowledge in this area is predominantly derived from animal studies as human studies (postmortem studies, accurate measurement of hypothalamic releasing hormones) are not feasible. Animal studies have shown the variable effects of BPA exposure on ER α and β protein and mRNA expression in different areas of the brain (16,17,18,19). Treatment of adult male and female rats for 4 days with low-dose BPA had significant effects on mRNAs for aromatase (increased in both sexes) and 5α -reductase 1 (decreased in females) in the prefrontal cortex (20). Although we know that developmental EDC exposure can alter the expression of genes and proteins for steroid hormone receptors, we cannot draw generalized conclusions from these animal models and future research should target especially this area of early EDC exposure.

EDC exposure can also have neuroendocrine effects. Animal studies have reported on the stimulatory as well as inhibitory actions of BPA on GnRH and kisspeptin systems (21,22). Studies on PCBs and phthalates have shown mixed results. Animal studies have shed some light on the effect of EDCs on the developing hypothalamic pituitary adrenal (HPA) axis. BPA exposure has been found to be associated with an increase in adrenal weight and an attenuated stress response (23). Basal corticosterone, as well as CRH- or ACTH-induced corticosterone release, has been found to be significantly suppressed in PCB exposed rats (24). These effects of EDCs on the HPA axis leading to aberrant stress response needs to be evaluated further in humans. Animal studies have opened up some new and interesting possibilities of EDC exposure with changes in AVP and oxytocin levels and social behavior (25,26).

Thyroid Function

EDCs can interfere with thyroid hormone synthesis, release, transport, metabolism and clearance.

Table 3. EDCs Effect on Thyroid Function (27,28)		
EDC	Source	Possible Outcome
Perchlorate	Oxidant in solid rocket propellants, fireworks, airbag deployment systems, etc.	Interferes with the uptake of iodide into the thyrocyte by sodium/iodide symporter (NIS)
Thiocyanates	Cigarettes	Interferes with the uptake of iodide
lsoflavones (Phytoestrogens)	Soy protein	TPO inhibitors resulting in goiter in children
PCB	Paints Plastics	They can act as TR agonist or antagonist, or reduce circulating levels of T4 resulting in relative hypothyroidism, increase in expression of glial fibrillar acidic protein leading to neurotoxicity in children.
BPA	Plastics Food cans Dental sealants	Binds to TR β and antagonizesT3 activation. It can block T3-induced oligodendrocyte development from precursor cells, resulting in ADHD. Halogenated BPA can act as TR agonists, TBBPA bind to TR and induces GH3 cell proliferation and GH production.

PCB - Polychlorinated biphenyls, BPA - Bisphenol A, ADHD- Attention Deficit Hyperactivity Disorder, TBBPA - Tetrabromobisphenol A, T4 - tetraiodothyronine (thyroxine), T3 - triiodothyronine, TPO – Thyroperoxidase, TR – Thyroid Receptor, TH - Thyroid hormone, GH- Growth Hormone

Adipose Tissue and Metabolic Disorders

OBESITY

Obesity can result in the metabolic syndrome, reproductive problems, and cardiovascular risk factors. "Obesogens" are defined as "xenobiotic chemicals that can disrupt the normal developmental and homeostatic controls over adipogenesis and/or energy balance" (29). The "obesogen hypothesis" suggests that prenatal or early-life exposure to certain EDCs compounded by sedentary lifestyle and improper nutrition predisposes certain individuals to become obese later in life (30).

In DES exposed mice an increase in body fat, leptin, adiponectin, interleukin (IL) - 6, triglyceride (TG) was observed. EDCs cause upregulation of gene expression involved in adipocyte differentiation and lipid metabolism resulting in fat accumulation (31). PPAR γ (peroxisome proliferator-activated receptors), a major regulator of adipogenesis, are expressed in adipocytes. It promotes adipocyte differentiation and the induction of lipogenic enzymes. During activation, PPAR γ along with retinoid X receptor (RXR), forms a heterodimer complex which then binds to PPAR response elements for regulation of fatty acids and repression of lipolysis. EDCs like tributyltin (TBT) and triphenyltin acts as PPAR γ and RXR agonists and increases adipose tissue mass. Phytoestrogens mimic endogenous estrogens and exert various biological actions. They can bind to estrogen receptor (ER) α and estrogen receptor (ER) β and influence lipogenesis. One of the major sources of phytoestrogens is soy protein which contains genistein, a phytoestrogen. At low doses genistein inhibits lipogenesis whereas at high doses it can promote lipogenesis (27). EDCs like BPA, phthalates, dioxins perfluorinated compounds, and some pesticides are emerging as potential obesogens warranting further research.

Table 4. Potential Obesogenic Actions of EDCs

- Agonist at PPAR_ν and RXRα (32)
- Promotion of adipogenesis through ERs (33)
- Increase in enzymatic activity of 11-β hydroxysteroid dehydrogenase type 1 (11-β HSD type 1) (34)
- Increase in insulin stimulated lipogenesis (35)
- Alterations in blood levels of insulin, leptin, and adiponectin (36)
- Alteration of central energy regulatory pathways (37)
- Decreased TRH expression and type 4 melanocortin receptors in the paraventricular nucleus of the hypothalamus and stimulation of orexigenic pathways (38)
- Epigenetic transgenerational inheritance of adult-onset obesity (39)

DIABETES AND GLUCOSE HOMEOSTASIS

EDCs can disrupt glucose homeostasis in our body by affecting both insulin- and glucagon-secretory cells. Any toxic chemical that kills β cells or disrupts their function has been termed a "diabetogen". The "diabetogen hypothesis" suggests that "every EDC circulating in plasma able to produce insulin resistance, independently of its obesogenic potential and its accumulation in adipocytes, may be considered a risk factor for metabolic syndrome and type 2 diabetes" (40). The obesogenic EDCs are risk factors for type 2 diabetes as well and lead to the dangerous combination of obesity and diabetes or "Diabesity". However, certain EDCs may directly cause insulin resistance and defects in insulin production and secretion, without significantly affecting the weight of the individual. Studies have shown that acute treatment with BPA causes a temporary hyperinsulinemia, whereas longer-term exposure suppresses adiponectin release, and aggravates insulin resistance, obesity related syndromes, and development of diabetes mellitus. The hyperinsulinemia is attributed to the very rapid closure of ATP-sensitive K+ channels, potentiation of glucose-stimulated Ca2+ signals, and release of insulin via binding at extranuclear ER (41). Low doses of DES have been shown to impair the molecular signaling that regulates glucagon production through non genomic mechanism (27). POPs have been demonstrated to have direct effects on insulin signaling (42). They can lead to insulin resistance by causing adipose tissue inflammation. Heavy metals such as arsenic and mercury have also been considered as potential diabetogens. Intake of a high fat diet along with exposure to a cocktail of these EDCs (DEHP, BPA, PCB153, and TCDD) has been found to have sex specific alterations in the metabolic milieu in offspring. In males, there was alteration in the cholesterol metabolism whereas in females, there was pronounced effect on the glucose metabolism through a decrease in ER α expression and estrogen target genes (43).

The causal relationship between EDCs and type 1 diabetes is an area warranting research as animal studies have shown exposure to EDCs associated with insulitis (44).

Reproductive System

Over the past few decades there has been a surge in the incidence of reproductive system related disorders among both the males and females. EDCs can be attributed to this surge. Exposure to EDCs especially phytoestrogens have resulted in early menarche and polycystic ovarian diseases (PCODs) in adolescent girls. Infertility affects up to 15% of couples in the reproductive age group worldwide. The EDCs and their effect on reproductive system is summarized in Table 5.

Table 5. Effects of EDCs on the Reproductive System (27)(9)			
EDC	Possible Mechanism	Possible Clinical Condition	
		Males	Females
Vinclozolin	Epigenetic (altered DNA methylation in germ cell lines) AR antagonism	Hypospadias Undescended testes Delayed puberty Prostate disease/cancer	Dysregulates the gland development Formation of mammary tumor
DES	Increased ER expression in Epididymis Epigenetic silencing of mRNA	Hypospadias Cryptorchidism Micropenis Epididymal cysts	Vaginal adenocarcinoma Ectopic pregnancy Infertility
DDT/DDE	Antiandrogen Antiprogestin Induction of aromatase Reduced insulin-like factor	Cryptorchidism Infertility	Risk of breast cancer in females Precocious and early puberty Infertility
РСВ	Estrogen agonist / Estrogen antagonist / antiandrogenic activity	Prostate cancer	Early onset of menarche Delayed pubertal development Accumulates in breast adipose tissue
Phthalates	ER agonist/antagonist Antiandrogen and decreases testosterone synthesis	Reduced anogenital distance and Leydig cell function Hypospadias Cryptorchidism	Increased cell proliferation in the breast
ВРА	ER agonist Antiandrogen Inhibition of apoptotic activity in breast	Prostate cancer Testicular cancer in fetus	Altered breast development Early puberty

	Increased number of progesterone receptor positive epithelial cells Nongenomic activation of ERK1/2 Reduced sulfotransferase inactivation of estradiol		
Dioxins	ER agonist Antiandrogen Interfere with sex-steroid synthesis Inhibition of cyclooxygenase2 via AhR	Cryptorchidism	Premature thelarche Endometriosis Breast cancer

DES – Diethylstilbestrol, DDT – dichlorodiphenyldichloroethylene, DDE - dichlorodiphenyldichloroethylen, DNA – Deoxyribonucleicacid, AR – Androgen Receptor, ER – Estrogen Receptor, AhR - aryl hydrocarbon receptor, ERK1/2 - extracellular signal-regulated kinase 2, mRNA – messenger RNA

EFFECTS ON THE FEMALE REPRODUCTIVE SYSTEM

In vivo animal studies and thereafter in vitro studies indicate that exposure to BPA (1–30M) impairs meiotic progression in human fetal oocytes, increased levels of recombination, and induces epigenetic changes that may contribute to chromosome congression failure (45,46). Studies in rats have shown that neonatal BPA exposure decreased the numbers of all follicle types and increased atretic follicles during adulthood (47). In vitro animal studies have demonstrated the toxic effect of phthalates on the follicle growth and inhibition of estradiol production (48). Similar toxic effects of pesticides and environmental pollutants on gene expression, follicle growth and oocyte quality have been confirmed in animal studies. BPA and phthalates have also been implicated in altered steroidogenesis in the gonads (49). Findings of alteration in uterine structure and function after exposure to EDCs is more concerning as it may lead to abnormalities in implantation and recurrent abortions (50). BPA exposure has been associated with increased risk of implantation failure and miscarriages (51). Animal studies have also pointed towards the transgenerational effect of prenatal BPA exposure on female fertility (52). Experimental studies have shown an association between phthalate exposure and reduced fertility (53). The findings of these studies need to be confirmed in the human ovary to fully understand the impact of these EDCs on fertility and reproductive health as well as the transgenerational impact. EDCs have also been found to have adverse effects on menstrual cyclicity in women. Fungicide exposure has been associated with a significant decrease in bleeding (54). BPA and pesticides may accelerate ovarian failure and may lead to premature menopause in women (55). In utero exposure to DES increases the lifetime risk of premature menopause (56). Propyl paraben, a preservative in personal care product, was associated with lower antral follicle counts as well as higher day-3 FSH levels indicating accelerated ovarian aging (57). It may not be exposure to just a single EDC and more often than not it may be a cocktail of these that could lead to early reproductive senescence. In animal studies, late gestational exposure to DES causes ovarian hyperandrogenism and menstrual abnormalities similar to those in women with PCOS (58). A few epidemiological studies have pointed

towards an association between phthalate exposure and risk of endometriosis, possibly due to increased viability of cells (59). 2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD) exposure may disrupt cannabinoid signaling in the human endometrium and lead to increased inflammation in the endometrium (60). TCCD exposure can cause a progesterone-resistant phenotype that may persist over multiple generations, suggesting that TCDD exposure has transgenerational effects on endometriosis (61). TCDD increases the expression of thymus-expressed chemokine and promotes the invasiveness of endometrial stromal cells by increasing the expression of matrix metalloproteinase-2 and -9(62). TCDD also reduces the expression of CD82 (a wide-spectrum tumor metastasis suppressor that inhibits the mobility and invasiveness of cells), and increases the of CCL2-CCR2. expression which recruits macrophages and further down-regulates CD82 (63). Pesticides like fenvalerate stimulate the growth of uterine fibroid cells by enhancing cell cycle progression and inhibiting apoptosis through an ERindependent pathway (64). DES exposure has been shown to increase the occurrence of early onset fibroids in the Sister Study and Nurses' Health Study II (65,66). Given the multiplicity of effects of EDCs on the female reproductive system, there remains an urgent need for future studies to confirm the findings of experimental and animal studies and understand the underlying mechanisms.

EFFECTS ON THE MALE REPRODUCTIVE SYSTEM

EDCs, by virtue of their antiandrogenic and estrogenic effects can have a profound influence on the male reproductive physiology. Studies on the causative effect of EDCs on hypospadias have not given consistent results due to the small number of subjects studied. Levels of chlorinated pesticides have been found to be higher in breast milk of mothers with cryptorchid boys (77). Studies on the incidence of cryptorchidism with xenoestrogen exposure showed detectable levels of lindane and mirex in placenta with higher cryptorchidism risk (78). Higher dioxin levels in breast milk and dibutyltin concentrations in placenta were associated with cryptorchidism in Danish boys (79). Dioxins may have estrogenic effects through interaction of the dioxin-AhR nuclear translocator complex with estrogen receptor. High exposure to DDE and PCBs also has a higher risk of cryptorchidism (80). Environmental factors play an important role in the development of testicular cancers. Cryptorchidism and hypospadias are wellcharacterized risk factors of testicular germ cell cancers (TGCC). Although TGCC is probably a condition with fetal origins, it has been practically difficult to prove the association between pre and postnatal exposure of EDCs and TGCC, given the long lag time between exposure and effect. A positive association of TGCC with DDE (81) and chlordane exposure (cis-nonachlor and trans-nonachlor) has been found (82). Intra uterine exposure to EDCs that affect the spermatogonial stem cells or Sertoli cells, can cause irreversible changes that result in permanently low adult sperm number. PCB exposure may affect sperm DNA integrity and motility (83). DDE exposure has been inversely associated with sperm motility and total sperm count (84), and positively correlated with defects in sperm chromatin condensation and morphology (85). Fetal and perinatal exposure via breast-feeding to dioxin in the Seveso accident was associated with reductions in sperm concentration, number of motile sperm, and total sperm number (86). PBDEs used as flame retardants have been found to negatively affect sperm concentration, testicular size and sperm motility (87). The major impediment to establishing a causal role of these effects of EDCs is the long lag time between the critical exposure and the manifestation of the adverse outcomes.

EFFECTS ON PUBERTY

There has been a decrease in the age of breast development but the age of menarche has not

changed significantly. This finding alerted researchers about the possible interfering role of EDCs in pubertal mechanisms. Results of epidemiological studies have been equivocal on the effects of BPA and phthalates on pubertal onset (67,68). Studies have pointed towards higher kisspeptin levels in girls exposed to phthalates, which may promote precocious puberty (69). There have been inconsistencies between animal and human studies and hence, inconclusive data on the effects of other EDCs like pesticides and environmental contaminants on puberty. Apparently innocuous substances like lavender oil and tea tree oil present in lotions and creams can lead to prepubertal gynecomastia by their estrogenic effects (70). A very interesting hypothesis has been put forward to explain the role of EDCs in precocious puberty seen in immigrant girls from developing countries. Early and temporary exposure to weakly estrogenic dichlorodiphenyltrichloroethane (DDT) in developing countries, where the exposure is still high, could stimulate hypothalamic maturation while the pituitary gonadotrophins are inhibited via a negative feedback that prevents manifestation of central maturation. This negative feedback disappears after withdrawal from the exposure, as happens when the child migrates to a different environment. This could precipitate precocious puberty in these migrant children (71). High exposure to endosulfan has been shown to be associated with pubertal delay. due to its antisteroidogenic properties (72). Dioxins act through aryl hydrocarbon receptors and thereby interact with other nuclear receptors. Exposure in boys has been associated with delayed puberty and in girls with delayed thelarche due to its antiestrogenic effects (73,74). Lead exposure has been implicated in delayed puberty in both boys and girls (75,76). Endocrine disrupters may alter the levels of endogenous hormones and their ratios by influencing their production, secretion, binding to carriers, metabolism and excretion. When studying these compounds, one needs to keep in mind about their active metabolites and the multiplicity of effects on the complex endocrine milieu.

Hormone Responsive Cancer

Most cancer occur due to genetic predisposition or exposure to environmental or occupational hazards. EDCs can alter the genes and result in uncontrolled proliferation of cells. Almost all the EDCs identified are known to cause cancer. People working in certain industries like coal, steel, rubber, textile, paper manufacturing, paint are at higher risk of developing cancers due to increased exposure to these EDCs. Studies have shown that early exposure to these EDCs BPA, PCBs, perflourinated compounds, phthalates, and some pesticides can increase cancer risk(1). Several EDCs that mimic endogenous estrogens are potential carcinogens. The estrogenresponsive cancers including breast, endometrial, ovarian, and prostate cancers are caused due to several chemical xenoestrogens and phytoestrogens (88). EDC exposure during the critical periods of mammary gland development like gestation, puberty, and pregnancy may predispose to carcinogenesis. Dioxin exposure, especially TCDD has been found to increase the incidence of breast cancer (89). Inconsistent results have been obtained with regards to pesticide exposure and breast cancer risk, possibly due to individual chemicals studied whereas in real life, humans are often exposed to a mixture of them. Breast cancer patients present more frequently with a combination of aldrin, DDE, and DDD, and this mixture has not been found in healthy women (90). Exposure to diethyl phthalate, the parent may be associated with a 2-fold increase in breast cancer risk (91). EDCs may influence other estrogen dependent cancers as well. In women previously exposed to chlorotriazine herbicides, there was a significant 2.7-fold increased risk for ovarian neoplasms (92). Higher PFOA levels are associated with ovarian cancer (93). In males, those EDCs that can interfere with androgen and estrogen signaling pathways can increase the risk of prostate cancer. A classic example of developmental exposure and onset of latent disease is the progeny of mothers exposed to DES during pregnancy. Although abnormalities prostatic structural have been documented in this cohort (94), the exact effect on

prostate cancer is yet to be ascertained as the cohort is still being followed up. Pesticide exposure and carcinogenesis has garnered much interest after the Agricultural Health Study (AHS) in the United States. Specific organophosphate insecticides like fonofos, malathion, terbufos, and aldrin) have been associated with increased risk of aggressive prostate cancer (95). Certain organophosphates like coumaphos and organochlorine (aldrin) pesticides increase prostate cancer risk in men with a family history of the disease (96). Compounds like chlorpyrifos, coumaphos, fonofos, and phorate strongly inhibit the hepatic CYP1A2 and CYP3A4 enzymes that metabolize testosterone, estradiol, and estrone (97) and thereby act as EDCs apart from causing DNA damage by oxidative stress. TCDD, the most toxin dioxin in the Agent Orange herbicide spray has been found to have a strong positive association in the incidence and aggressiveness of prostate cancer in the Vietnam veterans (98). Trace elements like arsenic and cadmium, have been classified as EDCs due to their ability to act as a ligand and/or interact with members of the steroid receptor superfamily and have been implicated in prostate cancer although more conclusive studies are needed.

Effect on The Adrenals

The adrenal gland is probably one of the most ignored glands in toxicology, despite it being very sensitive to toxins. By virtue of its intense vascularity, its capacity for uptake and storage of lipophilic agents and high local concentrations of enzymes of CYP family with potential for bioactivation of toxins, the adrenals are very susceptible to the toxic effects of EDCs. The results of toxicological research on adrenals may not always be straightforward because of the dynamic nature of the HPA axis. Thus, even in the face of compromised adrenal steroidogenesis, it is not surprising to find relatively normal levels of circulating cortisol, albeit with an increased ACTH drive. Hence, scientists studying the toxic effect of EDCs on the adrenals, need to take into account the ACTH and

cortisol levels as well as the adrenal weight. One of the earliest evidences for an adrenal disruptor was the use of the anesthetic, etomidate, which inhibits CYP11B1, leading to adrenal insufficiency. Another direct inhibitor of adrenal steroidogenic enzymes is a derivative of the pesticide DDD, mitotane (o,p'-DDD), which is used to treat Cushing's syndrome. Polychlorinated biphenyl 126 (PCB126) causes an increase in aldosterone biosynthesis by increasing expression of CYP11B2, the enzyme which catalyzes the final step of aldosterone biosynthesis. High concentrations PCB126 has been shown to increase expression of the Angiotensin 1 (AT1) receptor, enhancing angiotensin II responsiveness of adrenal cells. Lead has also been reported to increase aldosterone synthesis by a mechanism consistent with upregulation of CYP11B2. It has also been reported that a class of herbicides (2-chloro-s-triazine herbicides) increase the expression of CYP19, which encodes aromatase, raising the possibility of increased adrenal estrogen secretion (99). The lack of a clear understanding of the adrenal toxicology can be overcome by the use of sophisticated endocrine studies, which take into account the dynamicity of the HPA axis.

EFFECT OF EDCs DURING PREGNANCY

Studies on animals have shown that EDCs can affect germ cell lines. In a cohort study of 47,540 women with history of exposure to diethylstilbestrol (DES) during pregnancy and ADHD diagnosis were followed up to three generations (F0, F1, F2) to know consequences of exposure to DES. This study revealed that the progeny of mothers who used DES in the 1st trimester of pregnancy had higher risk of developing ADHD. BPA is another EDC which can lead to neuroendocrinal problems (100). This highlights the ill effects of EDCs in vertical transmission. EDCs like perfluorooctanoic acid have been implicated in pregnancy induced hypertension. There have been some pointers towards an association between BPA and preterm birth but it has not been conclusively proven in experimental animal studies (101).

Phthalate exposure during pregnancy may be associated with increased odds of prematurity (102). The possible mechanisms are interference with the placental function via effects on trophoblast differentiation and placental steroidogenesis which could increase the risk of preterm birth. Similar genetic effects of pesticides have also been shown to result in increased prematurity and preterm birth. This risk has been shown to be magnified in those with certain genetic mutations, highlighting the gene- environment interaction (103). Environmental contaminants like TCCD exert pro-inflammatory effects on the placenta, leading to infection-mediated preterm birth (104). EDCs have also been implicated in adverse birth outcomes. In the Generation R study in The Netherlands, prenatal BPA exposure was associated with reduced fetal weight and head circumference (105). The same study also showed that maternal phthalate exposure was associated with an increased time-to-pregnancy (106) and impaired fetal growth during pregnancy and decreased placental weight (107). In a similar Japanese study, maternal urinary MEHP levels were negatively associated with anogenital distance (AGD) in male offspring (108). Pesticide exposure during the second trimester of pregnancy have been negatively associated with birth weight, birth length, and head circumference as shown in the data from Center for Health Assessment of Mothers and Children of Salinas (CHAMACOS) (109). Increased incidence of infants being born as small for gestational age has also been reported in mothers who were exposed to pesticides (110). A sex dependent nature of these adverse birth outcomes has been demonstrated in a Chinese study with a decrease in gestational duration in girls but not boys (111). Similarly, in the Hokkaido Study on Environment and Children's Health, an ongoing cohort study in Japan, PCDF and PCDD exposures were negatively associated with birth weight and infant development, with males being more susceptible than females (112). However, not all studies are shown

these consistent adverse effects of EDCs. Hence future studies should confirm these preliminary findings and also study certain EDCs which have never been studied so far in experimental and epidemiological studies.

DETECTION OF EDCs

EDCs may be in complex forms or in trace amounts in biological fluids or environment which makes it difficult to identify or detect them. The methods used for the detection of these compounds should be highly sensitive and specific. These include liquid chromatography, gas chromatography and capillary electrophoresis. The bioassay techniques (Receptor binding assay, Receptor gene assay, DNA binding assay) are either qualitative or quantitative and can be helpful to know the biological effects of the complex samples. Due to the complexities and trace amount of the EDC, preconcentration is required (5). However, the limitations in sensitivity, reproductivity, difficulty in separation, and affordability still remain.

FUTURE TRENDS

Newer methods are being explored to predict the effect of chemical disruptors using artificial intelligence (AI). Combining artificial neural network (ANN) and chemical similarity approaches, a significant role of AI in chemical endocrine receptor disruption prediction has been demonstrated. For example, isoflavone genistein, a phytoestrogen from soy was found to be active or disruptive whereas isoflavone daidzein from the soy was predicted to be inactive or non-disruptive (113). ANN can be used to predict chemical activity against estrogen and androgen receptors. Machine learning and ANN can more accurately and precisely predict EDCs in future.

Biosensors are newer devices which can detect chemicals up to femtomolar limit of detection. Aptasensors, Nanotubes, Molecularly imprinted polymer (MIP)-based sensors are the emerging EDC detectors (114). Recently a device called 'Tethys' has been invented to detect presence of lead in water. Lead is known to affect the hormone signaling and central nervous system. This device works on the basis of nanocarbon tubes and could send water quality information via Bluetooth (115).

Among several computer aided approaches, invitro and in silico predictions are now used to predict large number of chemical disruptors in the environment (116). Also the ligand-based models, like QSAR models which can predict biological activities of EDC and structure-based models can be combined with Artificial Intelligence technology for more accurate EDC predictions (117).

EDCs IN THE TROPICS

Pesticide use has increased over the years due to intensification of agricultural practices in the tropical countries. While the developed countries do have a well-established legal framework for pesticide environmental risk assessments, such requirements are either not available or inadequately implemented in tropical countries. Added to these woes are the fact that cheap compounds that are environmentally persistent and highly toxic, banned from agriculture use in developed countries, still remain popular in developing countries (118). These may lead to soil and water contamination with pesticide residues. The effect of these compounds on the applicators as well as the consumers are manyfold. In a multi-centric study to assess the pesticide residues in selected food commodities (Surveillance of Food Contaminants in India, 1993), DDT residues were found in about 82% of the 2205 samples of bovine milk. Data on 186 samples of 20 commercial brands of infants' formulae showed the presence of residues of DDT and Hexachlorocyclohexane (HCH) isomers in about 70

and 94% of the samples with their maximum level of 4.3 and 5.7 mg/kg respectively (119). The average daily intake of HCH and DDT by Indians was reported to be 115 and 48 mg per person respectively, which were higher than those observed in most of the developed countries (120). Over these continuous levels of exposure through food, water and soil are the occasional spillovers and accidents that lead to greater exposure. Although these exposures have been documented well in literature, there are sparse studies from the tropical areas on the long-term effects, especially in relation to the endocrine system. Although there are compelling social and economic benefits for the rampant use of EDCs, the policymakers need to be made aware of the long term and sometimes transgenerational effects of these molecules.

CONCLUSION

EDCs are an emerging global health problem that requires urgent attention and action. The most common EDCs that we encounter in our day-to-day life are BPA, PCBs, paraben etc. This results in endocrinological problems in all the age groups. There is an urgent need of novel biomarkers, detectors or assays using novel technologies for the early detection of EDCs. The novel technologies like Artificial Intelligence, OMICS (Genomics, Epigenomics, Mitochondriomics) and Nano technology are the new-way forward in this regard. Food and Health authorities play a vital role in curbing this problem. Food and safety laws should be more stringent and higher throughput screening for EDCs should be done prior to approval of any products. BPA free, paraben free products should be encouraged. Industrialists and others manufacturers must make sure not to pollute the water with the industrial wastes. All these measures will help in eliminating EDCs related health problems.

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APPENDIX- RECENT UPDATES ON ENDOCRINE DISRUPTING CHEMICALS (EDCs)

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PRENATAL EXPOSURE AND FETAL DEVELOPMENT

Recent studies have shown that prenatal exposure to disrupting chemicals (EDCs) endocrine can significantly impact fetal development. The HPP-3D (Human Placental Plasticity-3D) study found a negative association between maternal phthalate levels and fetal liver volume, with changes comparable to a 5 kg/m² difference in parental Body Mass Index suggesting early structural alterations with potential lifelong metabolic consequences (1). In the Ko-CHENS (Korean Children's Environmental Health Study) study, personal care product use was linked to higher levels of monoethyl phthalate (MEP), and cooking with plastic was associated with increased mono-n-butyl phthalate (MNBP) levels (2). The Let's R.O.A.R (Let's Reclaim Our Ancestral Roots) pilot intervention demonstrated that culturally tailored strategies could reduce low-molecular weight phthalate metabolites by over 5% in Black women, particularly dibutyl phthalate (3).

Neurodevelopment and Behavioral Outcomes

EDCs have implicated also been in neurodevelopmental and behavioral disorders. The PELAGIE (Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de Grossesse, l'Infertilité et l'Enfance) cohort from France found that exposure to perfluorinated compounds such as perfluorooctanoic acid (PFOA), (perfluorononanoic acid) PFNA, and perfluorodecanoic acid (PFDA) was associated with externalizing and internalizing behaviors in children (4). Bisphenol A (BPA) was found to be associated with aromatase gene methylation and autism spectrum disorder (ASD) traits in boys, with reversibility shown in mouse models

using !0-hydroxy-2-decenoic acid(10HDA), suggesting a potential therapeutic pathway (5). Another study identified BPA interaction with 35 of 77 ASD-related genes in transcriptomic analysis (6). A systematic review concluded that EDC exposure, especially to metals, phthalates, and PFAS is linked to poorer cognitive, language, and motor development in children, with girls being more susceptible (7).

FEMALE REPRODUCTIVE HEALTH AND OVARIAN FUNCTION

The Study of Women's Health Across the Nation (SWAN) found that exposure to heavy metals like arsenic, cadmium, and mercury was associated with lower anti-Müllerian hormone (AMH) levels and a faster premenopausal decline (8). A human ovarian model exposed to diethylstilbestrol (DES) and ketoconazole (KTZ) showed altered follicle survival and steroidogenesis, with upregulation of stearoyl-CoA desaturase (SCD) and 7-dehydrocholesterol reductase, indicating potential biomarkers for ovarian toxicity (9). Microplastics (MPs) have been detected for the first time in human ovarian follicular fluid, in 14 out of 18 women undergoing IVF, with an average of 2,191 particles/mL. A significant correlation has been observed between MP levels and FSH, suggesting potential effects on ovarian function. While no link has been found with fertilization or pregnancy outcomes, the findings highlight a concerning new avenue for understanding the reproductive impact of microplastic exposure (10). In a rat model, di(2-ethylhexyl) phthalate (DEHP) exposure induced polycystic ovary syndrome (PCOS)-like changes, insulin resistance, and oxidative stress via the PPARy pathway (11).

COGNITIVE AGING

EDC exposure may also affect cognitive aging. Analysis of NHANES data (2011–2014) linked exposure to 47 EDCs, including PFNA, PCB-199, and PCB-206, with worse verbal fluency and global cognition, though delayed recall effects were mixed (12).

PUBERTY AND HORMONAL PATHWAYS

In vitro analysis using the Tox21 10K library identified musk ambrette and methacholine analogs as agonists of KISS1R and GnRHR, suggesting that they may promote early puberty through hormonal activation (13).

TOXICOLOGY AND RISK ASSESSMENT

Regulatory and technological advancements in EDC detection and safety evaluation are ongoing. The European Food Safety Authority (EFSA) revised the tolerable daily intake for BPA from 4 μ g/kg/day to 0.2 ng/kg/day, indicating increased concern over low-dose effects (14). New Approach Methods (NAMs), including in vitro and in silico tools, were used to prioritize over 200 low-data chemicals for further study

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(15). An electrochemical sensor using a 2D-Al quasicrystal structure detected PFOA with high sensitivity (16). Concerns have been raised regarding the toxicity and potential endocrine disrupting effects of UV filters used in sunscreens. Six commonly used organic UV filters were assessed using the ToxCast/Tox21 database and found that they exhibited low biological activity, with most effects occurring at concentrations above cytotoxic levels. Except for oxybenzone, human plasma levels were significantly lower than those causing activity in assays. Overall, these UV filters showed weak or negligible endocrine-disrupting potential, supporting their low risk to human health(17).

CONCLUSION

The growing body of evidence highlights the pervasive impact of EDCs on female reproductive and metabolic health across the life course. From fetal development to menopause, EDCs such as phthalates, bisphenol A, perfluoroalkyl substances, and heavy metals disrupt hormonal pathways, with long-term health implications. Advances in biomonitoring, mechanistic studies, and NAMs are enhancing our understanding and risk assessment of these exposures. Continued interdisciplinary research and policy actions are critical to mitigate risks and safeguard public health.

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