CHAPTER 07

Toxicology Implications of Endocrine Disrupting Chemicals on Reproduction

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SUMMARY

Endocrine disrupting chemicals (EDCs) have received significant attention because of their detrimental effect on the reproductive system in recent years. In vitro and animal studies have revealed that Endocrine disrupting chemicals interfere with hormonal pathways essential for the development of female and male gonads. This particular disruption can occur via epigenetic/receptor mediated interactions or through non-receptor mediated modes of action. A strong correlation has been shown between EDC exposure and certain reproductive disorders in the epidemiological studies of human populations such as endometriosis, infertility, poor sperm quality and testicular cancer. Thus, in order to assess the toxicity of EDCs on the reproductive system, biomarkers have emerged as valuable tools, but precise differentiation requires advanced techniques. To mitigate these harmful effects various international strategies and therapeutic approaches have been implemented. Despite this, challenges are still persisting while addressing these issues effectively. This book chapter will delve into future directions in order to combat EDC induced reproductive toxicity and suggest innovative approaches for improved management of these toxicants.

INTRODUCTION

Theo Colborn and associates conducted a workshop at the beginning of the 1990s, during which they coined the term "endocrine disruptor" and released a statement regarding the influence of Endocrine Disrupting Chemicals on health of humans and environment (Colborn & Clement, 1992). Thus, the United States Environmental Protection Agency (EPA) first defined endocrine disruptors in 1996 as an exogenous substance that disrupt body's natural hormones, necessary for homeostasis, reproduction, development, and behavior. Additionally, they can also interfere with the production, emission, binding, transport, action, and removal of these hormones. In a statement issued by the Endocrine Society, the term "endocrine disruptors" was later redefined as "an exogenous chemical, or mixture of chemicals, which can interfere with any aspect of hormone action." They were thought to be caused by a wide range of chemicals, both natural and synthetic, including dioxins, medications, organochlorinated pesticides, plasticizers, and polychlorinated biphenyls. Furthermore, numerous common items, such as flame retardants, plastic bottles, pesticides, metal food cans, food, detergents, toys, and cosmetics contain endocrine disrupting chemicals (Zoeller et al., 2012).

Significance of reproductive health

According to International Conference on Population and Development (ICPD), reproductive health is not only an absence of sickness or illness, but it is "a state of complete social, mental, and physical welfare in every aspect of reproductive system, its activities and procedures" (Ortayli et al., 2014).

Brief overview of key EDC's

In the past couple of decades, there has been a significant growth in production of many chemicals such as triclosan, parabens, phthalates, PCBS, and bisphenol A which have the potential to affect human health and the environment adversely (Yueh & Tukey, 2016).

One well-known EDC that is frequently utilized in the food sector and personal care goods is triclosan (TCL). It is an endocrine disruptive substance used as an antibacterial agent in toothpaste and soaps and has an impact on homeostasis of thyroid and sex hormones strongly imply that TCL may disrupt the physiology of human endometrium which affects fertility and pregnancy (Weatherly & Gosse, 2017). According to Dodge et al. (2015b), there is a correlation between likelihood of decreased live birth after IUI (intrauterine insemination) and paternal concentrations of methyl paraben.

A group of synthetic compounds called phthalates found in different consumer goods are categorized into two groups: High molecular weight phthalates (i.e. Plastics) and low molecular weight phthalates (i.e. cosmetics). They are present in different items, including vinyl floor tiles, adhesives,

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lubricants, detergents, medical equipment, pharmaceuticals (used in the coating of some oral pills) toys and food packaging (Shaffer et el., 2019). There is an association between phthalate metabolites in urine and decreased meiosis II (MII) oocyte yield at retrieval, a higher risk of implantation failure, a drop in clinical pregnancy, and a decreased chance of a live birth after *in vitro* fertilization (Dodge et al., 2015a).

PCBs are blends of distinct congeners with varied chlorine atoms (1–10) and locations (ortho, meta, para) around biphenyl rings. Because of their inflammability and insulating qualities, they are therefore frequently utilized as insulators in capacitors, transformers, hydraulic fluids, paints, and related items. As a result, Anti-Mullerian hormone concentrations, fertilization rates, implantation rates were shown to be lower after exposure to PCBs and polychlorinated pesticides (Meeker et al., 2011),

Bisphenol A, a synthetic chemical utilized in the production of materials found everyday including water bottles, baby polycarbonate plastic bottles, epoxy resins used to line food and beverage cans, water pipes, and some dental sealants and composites (Machtinger & Orvieto, 2014). Additionally, studies have shown a dose-response relationship between BPA exposure and changes to the meiotic maturation and chromosomal alignment of human oocytes (Fig 1).

Sources and route of exposure

Humans are exposed to EDCs through different routes mainly by ingestion, inhalation and dermal uptake. Over 90% of the entire amount of chemical exposure occurs through dietary consumption, which serves as the primary pathway for EDCs to enter the human body. Thus, it is widely recognized that these substances can bioaccumulate in the body's fatty tissue, contaminate fish, meat, dairy, and poultry products and then ingested by humans (Cornelis et al., 2012).

Substances such as EDC found in environment have the potential to volatilize and infect humans by inhalation. Therefore, an important way for human contamination is occupational exposure to EDCs through inhalation. Moreover, EDCs can also enter into the human body through dermal absorption due to their fat-soluble ability. Although it accounts for a minor portion of total exposure, but skin contact with indoor organic chemical exposure can have significant effects (Cornelis et al., 2012).

REPRODUCTIVE SYSTEM: A VULNERABLE TARGET

Anatomy and physiology of male reproductive system

Male reproductive system consists of internal organs like testis, epididymis, vas deferens and accessory glands (seminal vesicles, bulbo-uretheral glands and prostate glands) provide fluids for nourishment of sperm cells and lubrication of duct system whereas scrotum and penis made external organs (Rosenfel, 2007).

The testes involve the production of sperm (spermatogenesis) while Leydig cells of seminiferous tubules

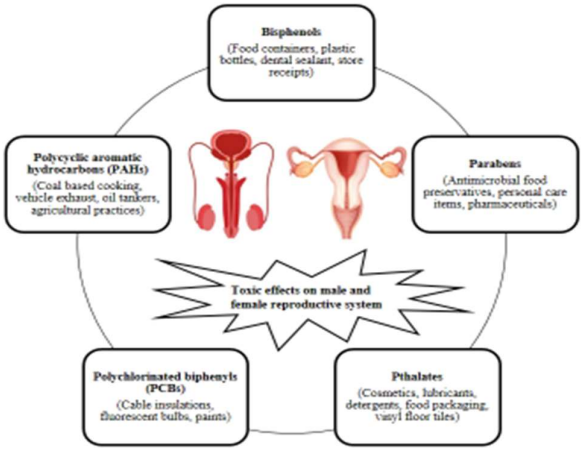

Fig 1. Male and female reproductive toxicity of edisrupting chemicals

in an interstitial compartment (regulate and maintain reproductive functions) includes production of testosterone. Furthermore, epididymis plays a significant role in maturation of sperm and store until its transportation through vas deferens. Additionally Accessory glands supply fluids that nourish the sperm cells and lubricate the duct system (Weinbauer et al., 2010).

Anatomy and physiology of female reproductive system

Female reproductive system consists of external genitalia and internal organs. External genitalia referred to as vulva located between perineum and pubis including labia majora, labia minora, urethra, clitoris, vestibule, mon pubis and vaginal opening. Furthermore, Skene's glands, vestibular glands, vestibular bulbs, and hymen are not visible externally but considered as part of external genitalia (Puppo, 2011). Internal organs comprised paired ovaries anchored by ligaments, oviduct or fallopian tube receives ovum after ovulation and are site of fertilization, uterus situated between urinary bladder and rectum composed of three layers (myometrium, endometrium and epithelial layer), cervix a narrow muscular canal connects vagina to uterus and vagina that undergo changes histologically during menstrual cycle (de Ziegler et al., 2016).

A menarche, or woman's first menstrual cycle, is indicated by her first menstrual bleeding period. During puberty, axillary and pubic hair, a growth spurt, breast, and numerous primordial follicles grow in the female ovary in which one become dominant and continue to grow while other stop developing and become atretic at the start of each menstrual cycle (Parker et al., 2010). Following the development of the dominant follicle into a Graafian follicle, meiosis I is ended, and the ovum is no longer in prophase I arrest thereby expelling the ovum from surrounding tissue during ovulation leading to menstrual bleeding due to decreased level of progesterone and unsuccessful fertilization. But if fertilization takes place, implantation of the fertilized egg takes place in the endometrial wall, and progesterone released (initially) by corpus luteum maintains endometrial lining until the placenta formation (Rimon-Dahari et al., 2016).

EFFECT OF EDCs ON MALE REPRODUCTION

Testicular development and function

A progressive decline in testicular volume and seminal parameters has been reported due to the exposure of environmental contaminants. For instance, in experimental studies BPA binds to Androgen receptor (AR), thyroid hormone receptor, and peroxisome proliferator-activated receptor (PPAR)-γ or ER-α and -β inhibits 5α-reductase and aromatase activities which interfere with testicular function and may not only impair testes development or testosterone production either but also reduce sperm counts and motility and worsen DNA damage. Furthermore, evidence suggests that DDT metabolite and PCB's exposure is one of primary causes for 2–4-fold rise in incidence of Testicular germ cells cancer (TGCC) over the last 50 years (Kabir et al., 2015).

Sperm quality and infertility

Semen parameters are crucial as they are used to assess quality of sperm and male infertility. At the same time, EDC levels have been rising and their exposure leading to reduced semen quality and thus increases male infertility. For example, Phthalates have an antiandrogenic impact on males through the androgen receptor (agonist and antagonist) lowers blood testosterone concentration and, as a result, lowers the number of sperm because of decreased androgen synthesis. Moreover Jurewicz et al. (2009) discovered that men exposed to pesticides, dioxins, and PCBs had a higher proportion of abnormal sperm, low linear motility, and normal morphology. In addition, exposure to organophosphates raised pH and decreased semen volume.

EFFECT OF EDCS ON FEMALE REPRODUCTION

Ovarian development and function

According to previous studies, exposure to EDCs like BPA mimics the action of estrogen by binding with ERs even at low doses, changing morphology of granulosa cells result low level of gonadotropins, estrogen, progesterone, and testosterone. This results an alteration in expression of ERs and, subsequently, of their target genes leading to dysfunctional female fertility, alterations in ovarian development and impairment of steroidogenesis and folliculogenesis. Further observations in rats revealed that ovarian follicles experienced atresia and modification causing shrinked oocyte nucleus and changed shape, thus affecting oocyte differentiation and folliculogenesis. These changes ultimately led to impaired ovarian development and sterility. Moreover, ALAN, an environmental endocrine modulator diminishes melatonin secretion, oocyte oxidation and estrogen/progesterone signaling (Souter et al., 2013).

Menstrual cycle and fertility

Endometrium experiences immunological and endocrine signaling in a cyclic pattern vital for controlling growth and function throughout reproductive years. Consequently, it is especially vulnerable to toxicants interfere with endocrine system and result in endometriosis, a gynecological illness marked by presence of endometrial tissue outside the uterus and a persistent inflammatory state (Signorile et al., 2010; Hayat et al., 2024). Thus, caused by immune response to oxidative stress brought on by menstruation. For Example, according to Xue et al. (2021) it has been hypothesized that Bisphenol A exposure causes endometriosis by upregulation of ERβ expression in eutopic endometrium through an H3K4me3-related epigenetic mechanism. Furthermore, research at cellular level focuses on high-affinity binding of TCDD with AhR receptor, consequently, forms a heterodimeric complex that is activated with structurally related protein ARNT leading to risk of endometriosis (Bruner-Tran et al., 2017).

Pregnancy and developmental implications

Pregnancy is a sensitive period because of increased susceptibility to toxic environmental contaminants like endocrine disrupting chemicals (EDCs). According to National Health and Nutrition Examination Survey (NHANES) women are frequently exposed to more chemicals present in personal care products because of greater use than men (Braun & Clarke, 2014). Numerous epidemiological research has reported possible association between GDM and non-persistent EDCs. For instance, presence of monoisobutyl phthalate and di-2- ethylhexyl phthalate metabolites in women have reduced glucose tolerance and elevated blood glucose concentrations cause GDM (James-Todd et al., 2016).

Women with elevated serum BPA concentrations cause abnormal placental vascular remodeling and disruption of trophoblast cell invasion, resulting in preeclampsia-like symptoms between 16 and 20 weeks. Moreover, throughout the gestational period butylbenzyl phthalate (BBzP) metabolite was positively correlated with diastolic blood pressure resulted in an increased risk of preeclampsia, eclampsia, hypertension, and HELLP syndrome (Ye et al., 2017).

Transgenerational effects

According to recent research, developmental exposure to EDCs can have deleterious effects on not only the exposed individual but also that individual's progeny and subsequent generations. This phenomenon is known as transgenerational inheritance (Wolstenholme et al., 2012).

Epigenetic mechanisms

The impact of environmental toxicants on structure and function without altering the gene sequence is satisfactorily explained by epigenetics. Most common epigenetic mechanisms are DNA methylation, histone modifications and micro RNAs.

DNA methylation

DNA methylation takes place when a methyl group binds to CpG dinucleotide at the cytosine residue. According to studies, a few substances alter an animal's methylation pattern led to heritable abnormalities in the progeny. For instance, experiment on rat indicated that DEHP affected male

reproductive system by altering the expression of DNA methyl transferase enzyme leading to a variety of inheritable methylation patterns, which cause their offsprings to have undescended testes. Moreover, Methoxychlor pesticide that has been proven to generate epimutations in parent sperm because of different methylated regions passed on to the progeny, resulting in obesity and ovarian problems in females (Xiong et al., 2016).

Histone modification

A family of positively charged proteins present inside DNA is known as histones. Acetylation, methylation, phosphorylation, and ubiquitination are histones modification. Evidence suggests that involvement of multiple EDCs cause different histone modifications result an abnormal gene expression by altering histone coding. Thus, EZH2 can be phosphorylated by diethylstilbestrol (DES) and bisphenol A (BPA) lead to reduction in trimethylation at lysine 27 Histone 3 through P13K/AKT pathway resulting uterine cancers. Additionally, it has been demonstrated that DES negatively affects steroidogenesis of Leydig cells by deacetylation at P450scc promoter site, lowering mRNA expression (Bredfeldt et al., 2010).

Micro RNAs

The family of non-coding RNAs known as micro RNAs (miRNAs) is typically made up of 18– 25 nucleotides. During development, miRNAs regulate gene transcription and have a significant role since abnormalities in the miRNA profile can cause developmental problems in the female and male reproductive tracts. Thus, Prolonged exposure to the mixture of EDCs in male humans may alter the expression of miRNA, which may dysregulate mRNA targets involved in testicular cell death post-transcriptionally therefore leading to spermatogenic failure (Bunay et al., 2019; Akbar & Ijaz, 2024). Moreover, Differential patterns of miRNA expression during oocyte/embryo development suggest that miRNAs have key regulatory roles, and EDCs like BPA seem to be involved in disruption of their activity by changing gene expression (Sabry et al., 2019).

MODE OF ACTION OF EDC

EDCs may change endocrine system by means of receptor mediated mechanisms or non-receptor mediated mechanisms (Zoeller et al., 2014).

Receptor mediated mechanisms

When EDCs bind to hormone receptors, they activate inappropriately thus having detrimental impacts on human health. During the embryonic stage, some EDCs incorrectly activate the estrogen receptor, leading to infertility in both sexes. Dichloro-diphenyl-tricloroethane (DDT), for instance, binds to both ERα and ERβ affects stimulation of ER-dependent transcriptional activation and proliferation (Munier et al., 2016). Furthermore, DDT also increases the synthesis of cAMP via binding to G protein coupled receptors (GPCR) and follicle-stimulating hormone receptor (Lee et al., 2013).

The physio-temporal pattern of expression of hormone receptors dictates their sensitivity to hormone signals as they mimic the effects of hormones. Hormone receptor expression, internalization, and degradation can all be regulated by EDCs. For instance, in the testis of adult mice di (2-ethylhexyl) phthalate reduces expression of mineralocorticoid receptor (MR) which functions as a positive modulator of testosterone production under normal circumstances (Martinez-Arguelles et al., 2009).

EDCs function as receptor antagonists to reduce or block an effect of endogenous hormones. In human and rat prostate cells, organochlorine pesticide dichloro-diphenyl-dichloroethylene prevents androgen binding to (AR) thus prevents transactivation of AR. Furthermore, Dihydrotestosterone binding to AR is also inhibited by other organochlorine pesticides, including lindane and dieldrin, closely related to aldrin (Walker, 2016). Although androgens perform a crucial role in regulating male sexual differentiation throughout fetal development, disrupting androgen action during this time through AR antagonistic interactions might cause persistent remasculinization of male fetuses as well as genital tract abnormalities (Gore et al., 2015).

Non-Receptor mediated Mechanisms

Endocrine feedback systems, both remote and intracellular, influence the synthesis of hormones. Thus, hormone synthesis has been known to be disrupted by certain EDCs. For example, Phthalates can cause testosterone deficiency by reducing the amount of testosterone synthesized in fetal rat testis. Experimental evidence indicates that herbicide atrazine promotes estrogen production in peripubertal male mice, decreasing serum testosterone levels accompanied by a rise in circulating estrogen levels and activity of enzyme aromatase (converts testosterone into estrogen) (Jin et al., 2013).

Hormones such as steroid hormones— progesterone, androgen, estrogen and adrenal have liphophilic nature, thus transport passively via membranes. Therefore, transportation of these hormones can be disturbed through endocrine disrupting chemicals. For instance, BPA at a lowest dose inhibited the entry of calcium into pancreatic β-cells thus the conjugative protein may or may not be present when they bind. In these situations, the hormones are displaced from their transport protein by EDCs, resulting in hormones that are not effective in the respected target tissue (Zhang et al., 2016).

When hormones are broken down by the enzyme proteases, they lose their active state. EDC also affects this process, resulting in different concentrations of hormones in blood due to degradation of hormones (Bansal & Zoeller, 2008). Polychlorinated biphenyls, or PCBs are one of the well-known EDC that may disrupt thyroid hormone signaling which result in an irregular shape of endocrine organ (Fig 2).

ASSESSMENT AND DETECTION OF REPRODUCTIVE TOXICITY

Currently, hormonal quantities and semen characteristics (morphology, motility, and sperm counts) are used to

determine the quality of male gametes and human testes whereas infertility due to toxicity in females is indicated by the presence of nuclear factors and hormone levels.

Biomarkers of reproductive toxicity

Dr. Gary Klinefleter of the US Environmental Protection Agency (EPA) has studied SP22, a sperm protein that has reduced after exposure to testicular and epididymal toxicants and has advocated potential value of assessing a sperm molecular biomarker to observe testicular toxicity (Klinefelter, 2008).

Sperm contains about 40% of testicular mRNAs, suggesting that the transcriptome of sperm can be utilized to assess gene expression during spermatogenesis. Numerous research examining the relationship between decreased testicular function and sperm mRNA transcript content discovered that: Men who are infertile have i) changed sperm protamine mRNA levels and ii) increased sperm Bcl2 mRNA (Steger et al., 2008). Transcription factor like nuclear factor-kappa B (NF-kB) is activated throughout inflammatory process in women with endometriosis. To gain understanding of NF-kB-implicated pathways, p65 and p50 subunits of active NF-kB dimers were also investigated in endometriotic lesions (Agarwal & Subramanian, 2010).

Women during *in vitro* fertilization were identified with implantation failure because of serum β- hCG level less than 6 mIU/mL. Although it is true that low hCG levels are biomarkers of early miscarriages but in contrast, elevated levels of hCG are associated with pre-eclampsia, a serious condition that develops in the latter stages of pregnancy. Measuring serum β-hCG is useful for diagnosis and has a strong predictive value for the reproductive outcome (Tuuli & Odibo, 2011).

INTERNATIONAL REGULATORY FRAMEWORK

Committee on Food Safety, Public Health, and Environment of European Parliament proposed a resolution in 2012 [2012/2066(INI)] in response to mounting calls for taking action to protect public from Endocrine disrupters. Thus, resolution focused on requirement to lessen human exposure to these chemicals, particularly among most vulnerable groups, while acknowledging challenge of establishing safe exposure levels.

European Food Safety and European Food Safety Authority released a regulation document in 2018 that proposed an EDC in response to scientific debate. This criterion is closely aligned with a hazard-based approach; even if accomplished, permission for pesticide usage may still be granted if there is proof that exposure is minimal or that adverse influence is not relevant to non-target organisms or humans (Slama et al., 2016).

Registration, evaluation, authorization, and restriction of chemicals— REACH is a European initiative from 2006 regulates chemicals in EU in multiple sectors with the exception of chemicals used in medical devices, biocides, cosmetics, pharmaceuticals, and plant protection products. Thus, the European Chemicals Agency must approve them, and approval is obtained only after arduous processes. However, authorizations and restrictions are determined after the risk resulting from exposure is evaluated (Wilson & Schwarzman, 2009).

CURRENT RISK ASSESSMENT STRATEGIES

For screening purposes, *in vitro* bioassays can be used in addition to chemical analysis to detect biological endpoints in a material. This accomplishment makes it possible to identify new contaminated locations using techniques like high throughput screening assays, reporter gene assays, receptor binding assays, and enzyme-linked receptor assays, among others, and to disclose the existence of active substances that are not identifiable by compositional analysis.

Substances are assessed using high-throughput screening techniques for a variety of endocrine modalities. For thorough coverage across endpoints, these assays evaluate the agonist as well as antagonist properties of a wide variety of receptors and receptor-independent processes. Instead of concentrating on a small number of receptor systems, high-throughput method can enable assessment of entire receptor systems amenabling *in vitro* screens. Thus, through ToxCast and Tox21 programs, efforts are being made to deal with high throughput testing of various compounds in various mechanism tests; nevertheless, concerns about the interpretation and quality control of all these efforts still exist (Hsieh et al., 2015). To ensure a wider biological foundation of potential EDC-induced disruption, these tests should combine with more functional *in vitro* assays to evaluate outcomes like spermatogenesis, adipocyte formation, and steroidogenesis (Jacobs et al., 2013).

ADVANCEMENT IN DIAGNOSTIC TOOL

Significant progress has been made in detecting EDCs, clearly identifying their structures, and estimating their quantities in recent years due to advancements in diagnostic tools. Since hyphenated chromatography-mass spectrometry techniques have developed into preferred methods for determination of trace amounts of organic analytes in biological and environmental samples, several analytical methods with varying degrees of sensitivity have been reported for the analysis of target compounds in recent years (Sosa-Ferrera et al., 2013). Therefore, it can be stated that the most popular methods for determining EDCs are liquid chromatography coupled with tandem mass spectrometers (LC-MS/MS) and GC-MS. These methods allow fragmentation of ions required for precise and accurate determination of analytes and provide information on molecular structure of compounds. Thus, advances in mass-analyser technology have been greatly accelerated by enormous interest in application of LC-MS techniques (Tseng et al., 2015).

Triple quadrupole mass spectrometry (MS) is utilized when examining extremely complex matrices to accurately identify the target molecules. However, more sophisticated MS methods, like linear ion trap and time-of-flight, have recently been introduced and are effective techniques

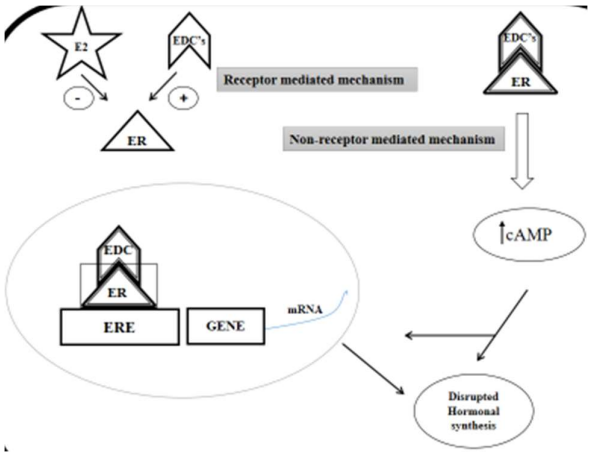

Fig 2. Mode of action of endocrine disrupting chemicals

(Antignac et al., 2009). Therefore, accurate mass of product ion can be obtained by acquiring full-scan product-ion spectra using new hybrid quadrupole-time-of-flight mass spectrometry. Meanwhile, three modern techniques in HPLC methods allow reduced analytical time without conceding resolution and isolation effectiveness such as utilization of monolith columns, ultra-high pressure liquid chromatography (UHPLC) and high temperature liquid chromatography (Singh et al., 2014).

TARGETED THERAPEUTIC APPROACHES

Antioxidants are different molecules that inhibit the oxidation or overproduction of reactive oxygen species in cells and tissues, hence preventing oxidative stress. Although, various studies conducted over past few decades have exposed how various antioxidants, including vitamins C, ginger extract, N-acetylcysteine, garlic, gallic acid and lipoic acid can prevent or lessen the damage caused by EDCs in a number of organs (Mohammed et al., 2020). Thus, advantages of taking antioxidant supplements include the improvement in spermatozoa's morphology, quality, viability, and motility through the reduction of oxidative stress. To mitigate the harmful effects of EDC on the reproductive systems of both men and women, several antioxidants—either in isolation or in combination—are examined (Kooti et al., 2015).

It has been reported that vitamins C, E, and glutathione inhibited the ROS generation, hence preventing immobility and unusual acrosomal reaction in spermatozoa treated with BPA. In addition, vitamin E and C (50 mg/kg) synergistically prevented apoptosis in ovarian cells of rats treated with selected dosage of BPA (Amraoui et al., 2018). According to Mou et al. (2018) detrimental effects of BPA on placental integrity were mitigated by a dietary methyl donor by acting on umbilical cord and trophoblastic cells via increasing the activity of various antioxidant (superoxide dismutase, catalase, and GSH-Px).

It has been reported that in 2014, trades of herbal nutritive supplements reached 6.4 billion whereas, majority of users were women, for a wide range of ailments, demonstrating the popularity of these supplements, especially for the health of women (Blumenthal et al., 2015). Moreover, scientific studies based on these plants indicate that medicinal herbs may be able to prevent the reproductive damage caused by EDCs by raising estrogen or progesterone levels therefore, through their antifertility and antioxidant actions, *F. vulgare* (Kooti et al., 2015), *P. dactylifera* (Moshtaghi et al., 2010) and *Lawsonia inermis*, or mehndi (Chaudhary et al., 2010) have influence on female reproductive hormones.

ONGOING CHALLENGES AND FUTURE DIRECTIONS

These assays are good for screening, but because they only measure binding properties, they cannot be used to categorize toxicants as agonists or antagonists. Thus, Research institutes globally should employ strategies that exploit validated techniques (e.g., technical and biological replicates, positive and negative controls, quality assurance and control) for chemical screening and testing in order to identify and quantify possible EDCs ascertain adverse impact, dose response, short- and long-term effects, assess risk, and ultimately achieve risk management in compliance with existing regulations Furthermore, main goals should be to establish a prioritized list of EDCs that are important for controlling environment, develop comprehensive protocols to identify EDCs using alternative analytical techniques, and provide an analytical model for behavior and fate of EDCs in the environment. Thus, to provide a more representative image of environmental quality, such evaluations require a thorough and reliable technique that can characterize level of pollution at appropriate spatial scales with respect to its eco-effects (Scognamiglio et al., 2016).

Hyphenated mass spectrometry-based chromatography and other chromatographic techniques are best options for screening of laboratories because they offer excellent sensitivity and selectivity for both qualitative and quantitative determinations, as well as other benefits like specificity, commercial availability, reuse and standardization (Wille et al., 2012).

CONCLUSION

Widespread uses of endocrine disrupting chemicals in an extensive array of daily products have resulted an environmental contamination and have significant influence on male and female reproductive health. These toxicants have the ability to accumulate in biological tissues thus disrupting the normal functioning of hormones leading to reproductive disorders. EDC's have visible effects on male reproductive system including impaired sperm quality, inhibition of testosterone synthesis thus leading to abnormal testicular development and function whereas females have shown preeclampsia, high blood pressure and gestational diabetes during pregnancy. Moreover, EDC's effects have also been seen in their offsprings through epigenetic inheritance. To assess risk, different assays have been used but for sensitivity measurement certainty analytical techniques are in practice. In addition to this, public awareness campaigns through media, health care practitioners, and education systems have been used to address EDC related issues for public awareness and

health. Various regulatory frameworks have developed strategies for regulations and risk management associated with Endocrine disrupting chemicals. Thus, to prevent reproductive abnormalities efficient therapeutic agents such as antioxidants can be used.

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